TITLE PAGE

Division: Worldwide Development
Information Type: Worldwide Epidemiology Study Protocol

Title:	A retrospective observational chart review study to evaluate the clinical effectiveness of treatment with zanamivir 10 mg/ml solution for infusion in a cohort of intensive care unit-treated (ICU) patients with complicated influenza infection.

Compound Number: GR121167

Development Phase: IV

Effective Date: 18-MAY-2020

Subject: Effectiveness of zanamivir 10 mg/ml solution for infusion

Author(s):
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PASS information

Title	A retrospective observational chart review study to evaluate the clinical effectiveness of treatment with zanamivir 10 mg/ml solution for infusion in a cohort of intensive care unit-treated (ICU) patients with complicated influenza infection.
Protocol version identifier	208165
Date of last version of protocol	Not applicable
EU PAS (ENCEPP) register number	Study not registered
Active substance	Zanamivir
Medicinal product	Zanamivir 10 mg/mL solution for infusion
Product reference	Not applicable
Procedure number	Not applicable
Marketing authorisation holder(s)	GlaxoSmithKline Trading Services Ltd Currabinny Carrigaline County Cork Ireland
Joint PASS	No
Research question and objectives	This study aims to gain an understanding of the clinical management of complicated influenza in ICUs in Europe and to investigate the clinical effectiveness of IV zanamivir in the treatment of patients with complicated influenza illness in this setting.
Country(-ies) of study	European Union, UK, Norway & Iceland
Author	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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PPD

From: PPD
Sent: Monday, May 18, 2020 5:03 PM
To: PPD
Subject: FW: 208165 IV Zanamivir effectiveness protocol amendment approval

Hi PPD

Please see below!

Many thanks,

PPD

From: PPD
Sent: 18 May 2020 12:23
To: PPD
Subject: RE: 208165 IV Zanamivir effectiveness protocol amendment approval

I approve.

Regards,

PPD

From: PPD
Sent: 18 May 2020 10:53
To: PPD
Subject: 208165 IV Zanamivir effectiveness protocol amendment approval
Importance: High

Hi PPD

Dear Sponsor,
To approve the clinical protocol indicated below, reply to this email and state your approval.
PROTOCOL NUMBER: 208165
DOCUMENT IDENTIFIER: 2017N346119_01
AMENDMENT NUMBER: 01PROTOCOL TITLE: A retrospective observational chart review study to evaluate the clinical effectiveness of treatment with zanamivir 10 mg/ml solution for infusion in a cohort of intensive care unit-treated (ICU) patients with complicated influenza infection.

Name of Sponsor Signatory:	Iain Gillespie
Title of Sponsor Signatory:	Therapy Area Leader

Many thanks,

PPD
Associate Clinical Development Scientist

PPD

From: PPD
Sent: Monday, May 18, 2020 3:48 PM
To: PPD
Subject: FW: IV Zanamivir effectiveness amendment approval

Hi PPD

Please see below!

Many thanks,

PPD

From: PPD
Sent: 18 May 2020 11:17
To: PPD
Subject: RE: IV Zanamivir effectiveness amendment approval

I approve

From: PPD
Sent: Monday, May 18, 2020 5:55 AM
To: PPD
Subject: IV Zanamivir effectiveness amendment approval

Hi PPD

Please see below for approval of the IV Zanamivir effectiveness protocol.

Dear Sponsor,
To approve the clinical protocol indicated below, reply to this email and state your approval.
PROTOCOL NUMBER: 208165
DOCUMENT IDENTIFIER: 2017N346119_01
AMENDMENT NUMBER: 01PROTOCOL TITLE: A retrospective observational chart review study to evaluate the clinical effectiveness of treatment with zanamivir 10 mg/ml solution for infusion in a cohort of intensive care unit-treated (ICU) patients with complicated influenza infection.

Name of Sponsor Signatory:	Robert Reynolds
Title of Sponsor Signatory:	VP, Epidemiology

Many thanks,

PPD
Associate Clinical Development Scientist
Real World Study Delivery
VEO, Global Medical

SPONSOR INFORMATION PAGE

WWEpi Project Identifier: 208165

Sponsor Legal Registered Address:

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UK

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Brentford
Middlesex, TW8 9GS
UK
Telephone: PPD

Regulatory Agency Identifying Number(s): N/A

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

1. LIST OF ABBREVIATIONS

AE	Adverse Event
ARDS	Acute Respiratory Distress Syndrome
BMI	Body Mass Index
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CRO	Contract Research Organisation
CUP	Compassionate Use Program
EC	Ethics Committee
ECDC	European Centre for Disease Prevention and Control
eCRF	Electronic Case Report Form
EEA	European Economic Area
EMA	European Medicines Agency
EU	European Union
GCSP	Global Clinical Safety & Pharmacovigilance
GSK	GlaxoSmithKline
HA	Haemagglutinin
HDU	High Dependency Unit
ICU	Intensive Care Unit
ILI	Influenza-like illness
IPCW	Inverse Probability of Censoring Weighting
IPTW	Inverse-probability of treatment weighting
IRB	Institutional Review Boards
IV	Intravenous
NA	Neuraminidase
NAI	Neuraminidase Inhibitor
OM	Otitis Media
OR	Odds Ratio
PSM	Propensity Score Matching
PRAC	Pharmacovigilance Risk Assessment Committee
sPVP	Study-specific Pharmacovigilance Plan
UK	United Kingdom
WHO	World Health Organization

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2. ABSTRACT

Title
A retrospective observational chart review study to evaluate the clinical effectiveness of treatment with zanamivir 10mg/ml solution for infusion in a cohort of intensive care unit-treated (ICU) patients with complicated influenza infection.

Rationale and background
Despite annual vaccination campaigns, other prevention strategies and available treatments, seasonal influenza accounts for approximately 3-5 million severe infections and 250,000-500,000 deaths worldwide annually. Due to limited treatment options, antiviral drug resistance remains a public health concern. There is an unmet medical need for effective intravenous formulations of antivirals to treat complicated influenza. This proposed study will be implemented at the beginning of the seasonal influenza season following the granting of the marketing authorisation.

Research question and Objective(s)
This study aims to gain an understanding of the clinical management of complicated influenza in ICUs in Europe and to investigate the clinical effectiveness of IV zanamivir in the treatment of patients with complicated influenza in this setting.

Primary objective:

- To compare all-cause in-hospital mortality in a group of ICU-admitted patients with complicated influenza who receive treatment with IV zanamivir as part of their clinical care with all-cause in-hospital mortality in a propensity score-matched group of ICU patients who did not receive this therapy during the same influenza seasons and/or pandemic(s).

Secondary objectives:

- To compare all-cause in-hospital mortality at 7, 10 and 14 days after IV zanamivir treatment initiation/matching in the two groups.
- To understand, through the analysis of historical data, treatment patterns for ICU-admitted influenza patients and factors associated with NAI treatment.
- To estimate, in a time-dependent manner, the crude IV zanamivir treatment effect on all-cause in-hospital mortality in a group of ICU-admitted patients with influenza.

Study Design
The collection of data in this study will be triggered by completion of the first seasonal influenza season following the grant of the marketing authorisation for IV zanamivir in the European Union (EU), the United Kingdom (UK), Norway and Iceland. The collection of historical data from for periods prior to the marketing authorisation for IV zanamivir (henceforth 'historical cohort'), designed to gain an understanding of the clinical management of complicated influenza in European ICUs will run in parallel to a retrospective, observational, comparative chart review. Both will be conducted in patients infected with influenza and admitted to ICU. Patients treated with IV zanamivir will be propensity score-matched to patients who have not received this treatment, with both

patient groups followed up until they experience the event of interest (within-hospital mortality) or are censored.

Population
The study population will consist of ICU patients with severe influenza in various tertiary hospitals in the European Union, UK, Norway and Iceland.

Study Variables to be Captured

- Season/pandemic
- Country/centre
- Influenza strain/sub-type
- Age & Sex
- Body mass index (BMI)
- Smoking status (Current, ex-smoker, never smoked)
- Vaccination status, other antiviral treatments, antibiotics
- Underlying co-morbidities
    - Asthma
    - Chronic obstructive pulmonary disease (COPD)
    - Other pulmonary diseases
    - Other chronic conditions
    - Immunocompromised
    - Pregnancy
    - Obesity
    - Prematurity
- Duration of symptoms prior to hospitalisation/treatment
- Presentation at admission (Influenza-like illness [ILI], pneumonia, otitis media [OM], sepsis etc.)
- Requiring supplemental oxygen
- Mechanical ventilation in ICU
- Days from hospital admission to ICU/critical care admission
- In-hospital corticosteroid administration
- In-hospital antibiotic administration
- Reason why patient has limited treatment options

Data sources
This study will only make use of medical records.

Study size
For the comparative cohort, it has been estimated that a minimum of 450 patients in each exposure arm would be sufficient to detect an odds ratio of 0.5 with 80% power at the 5% significance threshold, assuming a baseline mortality of 12%. Depending on the number of untreated patients in the participating ICUs, the sample size estimation may need to be revisited after the analysis of the historical cohort.

Data analysis

A detailed statistical analysis plan will be written before data collection for the comparative study. Propensity scores will be derived from the predicted probability of IV zanamivir treatment estimated in a multivariable pooled logistic regression model with treatment/no treatment fitted as the binary outcome and the covariates above specified as explanatory variables. Treatment and exposure data will be captured separately for the pre- and post-ICU periods and models will be stratified by season (to control for differences in severity) and by time since illness onset (to facilitate appropriate matching).

The primary analysis will consist of a matched Cox regression model to estimate all-cause in-hospital mortality, presented as a hazard ratio for IV zanamivir treatment vs. matched control. A similar regression analysis will be performed to estimate in-hospital survival on Day 7, 10 and 14 after treatment initiation/matching, and a proportional odds regression model will be fitted to analyse the ordinal scale data on the same days.

Milestones

A study report will be filed with the European Medicines Agency (EMA) within 6 months of the required sample size being achieved. As it is challenging to predict the time required to complete the study, an update report will be filed with the EMA each year, providing details of the number of treated and untreated patients enrolled and guidance on the likely study end date.

3. AMENDMENTS AND UPDATES

Amendment number	Date	Section of the study protocol	Amendment/Update	Reason
01	18-May-20	Sponsor Information Page	The UK sponsor contact address has been updated	Following the change of the sponsor address.
01	18-May-20	7.3.3 Confounders and effect modifiers	Clarification on the co-morbidities has been added as well as additional collection of co-infecting viruses	To take into account the COVID-19 pandemic and any other co-infecting viruses.

4. MILESTONES

Milestone	Planned date
Start of data collection	After grant of the marketing authorisation
End of data collection	After intended study size is reached
Final report of study results	Within 6 months after electronic case report form (eCRF) completion for last subject

5. RATIONALE AND BACKGROUND

5.1. Background

Influenza A is the most common type of circulating seasonal influenza viruses in humans, and can be further sub-typed by its viral surface proteins haemagglutinin (HA) and neuraminidase (NA). Influenza B only circulates in humans but infections occur less commonly. Each year, 5-10% of adults and 20-30% of children will be infected by the influenza virus, with illness generally characterized by fever, myalgia, rhinorrhoea, cough, sore throat and headache. Children aged <2 years, adults over 65 years, pregnant women and people with certain chronic illnesses are at higher risk of serious illness due to influenza, including bronchitis, pneumonia, acute respiratory distress syndrome, myocarditis, encephalitis, and exacerbation of underlying chronic diseases [Fiore, 2011; WHO, 2014]. This in turn leads to a higher risk of hospitalisation. For these reasons, it is advised that high risk groups receive an annual influenza vaccination. Additionally, neuraminidase inhibitors (NAI) are most effective if administered within 48 hours of onset of symptoms in uncomplicated influenza illness and, based on real world observational data, may be effective if administered beyond 48 hours from symptom onset in complicated/severe influenza [Adisasmito, 2010; Louie, 2012; Muthuri, 2013; Muthuri, 2014]. Treatment with NAIs was associated with reduced mortality risk by 19%-87% in complicated influenza patients [Hanshaoworakul, 2009; Lee, 2010; Muthuri,

2014], while treatment within 2 days of symptom onset was associated with a reduced mortality risk by 52% compared with later treatment [Muthuri, 2014]. In a meta-analysis pooling data from many studies, treatment was associated with a significant reduction in mortality (Odds Ratio [OR] 0.61, 95% CI 0.41-0.90, I^2 5%) in the sub-group of patients in intensive care units (ICU). Similar results have been published for patients hospitalised in ICUs with pandemic influenza. Fifty-eight percent of untreated patients survived versus 75% of patients treated with NAIs [Louie, 2012]. Despite annual vaccination campaigns, other prevention strategies and available treatments, seasonal influenza accounts for approximately 3-5 million severe infections and 250,000-500,000 deaths worldwide each year [WHO, 2014].

Effectiveness of vaccinations and treatments depends on the most common circulating (sub)type of influenza virus in a particular season. Small genetic changes to the influenza virus (antigenic drift) occur constantly and result in a slightly altered influenza virus, against which existing antibodies are still effective. When the genetic composition has drifted sufficiently far away from the original virus for which there is pre-existing immunity, exposure may lead to infection again. Beyond antigenic drift, antigenic *shift* describes an abrupt change in the influenza virus and only occurs in influenza A. It results in a new influenza A virus for which there is no or very little population immunity [CDC, 2014] and can result in a pandemic. The last occurrence was in 2009, when the novel H1N1 virus spread quickly and led to a pandemic influenza outbreak, which affected at least 11,275 cases in the first 23 weeks in the European Economic Area (EEA) alone [ECDC, 2010].

When the H3N2, H1N1 seasonal and 2009 H1N1 pandemic influenza virus demonstrated complete resistance to adamantanes, health agencies recommended using NAIs for treatment of influenza [Fiore, 2011]. The most common NAIs are oral oseltamivir and inhaled zanamivir. However, the H275Y mutation, which is the most common resistance mutation in H1N1 viruses, has been proven resistant against oseltamivir [Takashita, 2015]. The seasonal H1N1 influenza virus that preceded the 2009 pandemic H1N1 strain carried the H275Y resistance mutation and was nearly 100% resistant to oseltamivir [Fiore, 2011], leaving only inhaled zanamivir as an effective treatment option. The occurrence of the H257Y mutation in the H1N1 pandemic in 2009-2010 strain was much less frequent, averaging 1-3%. Therefore, the pandemic influenza virus in 2009 could be treated with both oseltamivir and zanamivir.

In addition to seasonal epidemics and intermittent pandemics, zoonotic strains primarily of avian origin have emerged in recent years and have demonstrated very severe illness in humans, with reported mortality rates of 53% for the H5N1 strain [WHO, 2017] and 41% for H7N9 [Iuliano, 2017]. These strains cause respiratory failure due to lower respiratory tract viral pneumonia progressing to acute respiratory distress syndrome (ARDS), multi-organ dysfunction and cytokine storm. Should these viruses, or future novel re-assortment influenza A viruses, acquire the capacity to transmit from human to human, a severe pandemic could ensue. In addition, NAI resistance has been reported for both H5N1 and H7N9, highlighting the need for multiple treatment options in this scenario [De Jong, 2005; Hu, 2013].

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 an unmet medical need for patients who are unable to take 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. Similarly, some pathogenic strains may require systemic exposure beyond the respiratory tract, and therefore an intravenous formulation may offer benefit beyond that achieved by inhaled zanamivir. Peramivir is the only NAI provided as an intravenous formulation, however it is only approved in the United States, Korea, Japan and Israel as a single infusion for the treatment of acute uncomplicated influenza in patients who have been symptomatic for no more than two days with influenza [Komeda, 2014]. In 2018 peramivir was granted a marketing authorisation the EU. The approved indication is for the treatment of uncomplicated influenza in adults and children from the age of two years. It is not indicated in severe or complicated influenza. Peramivir is also cross-resistant to influenza viruses with the H275Y mutation [Memoli, 2010].

In 2009 GlaxoSmithKline (GSK) initiated the clinical development of an IV formulation of zanamivir (zanamivir 10mg/ml solution for infusion) in response to the influenza A/H1N1 pandemic. A global compassionate use program (CUP) was initiated in May 2009 at the onset of the influenza A/H1N1 pandemic to provide zanamivir aqueous solution 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. Over 3000 patients worldwide have received treatment within this program and, with some limitations, no safety signals were identified that would impact negatively on the benefit-to-risk balance for zanamivir 10 mg/mL solution for infusion (henceforth referred to as IV zanamivir).

The pivotal Phase III study was the largest randomized controlled trial of antiviral treatment in hospitalised patients with severe influenza illness. It enrolled 626 subjects from 26 countries, including 488 who were confirmed to have influenza and 190 who were in intensive care and/or on mechanical ventilation at baseline. The study did not meet its pre-specified primary endpoint (superiority to oseltamivir or IV zanamivir 300 mg in time to clinical response).

The clinical safety data from the IV zanamivir program are consistent with a hospitalised patient population with serious influenza illness and the known safety profile of zanamivir. No safety signals were identified that would impact negatively on the benefit-to-risk balance for IV zanamivir.

The proposed indication for the product 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 study is being proposed as a post-authorisation efficacy study to demonstrate clinical effectiveness and a positive benefit-risk assessment in the approved indication.

5.2. Rationale

This proposed study would be ready for implementation following the granting of the marketing authorisation in the European Union (EU), United Kingdom (UK), Norway and Iceland. The study population will be limited to patients in ICU. A study in ICU patients will assess a more homogeneous group of patients who have a higher risk of fatal outcome and who are likely to benefit from an effective IV antiviral formulation and is likely to reflect the target indication.

This observational, retrospective, medical records review study will compare clinical outcomes of complicated influenza patients admitted to ICU who were treated with IV zanamivir as part of their routine medical care with a concurrent cohort of ICU patients who did not receive this therapy. A propensity score matched approach will be used to compare the primary endpoint of all-cause mortality during the influenza hospital stay between treatment groups. A modified ordinal scale of clinical outcomes will be investigated as an exploratory endpoint.

6. RESEARCH QUESTION AND OBJECTIVE(S)

This study aims to:

i) gain an understanding of the clinical management of complicated influenza in ICU in Europe, including treatment patterns, monitoring the entry of new anti-influenza treatments and utilisation of diagnostic tests including resistance testing.

ii) investigate the clinical effectiveness of IV zanamivir treatment in ICU patients with complicated influenza illness. Specifically:

Primary objective:

- To compare all-cause in-hospital mortality in a group of ICU-admitted patients with complicated influenza who receive treatment with IV zanamivir as part of their clinical care with all-cause in-hospital mortality in a propensity score-matched group of ICU patients who did not receive this therapy during the same influenza seasons and/or pandemic(s).

Secondary objectives:

- To understand, through the analysis of historical data, treatment patterns for ICU-admitted influenza patients and factors associated with NAI treatment.

- To estimate, in a time-dependent manner, the crude IV zanamivir treatment effect on all-cause in-hospital mortality in a group of ICU-admitted patients with influenza.

- To compare all-cause in-hospital mortality at 7, 10 and 14 days after IV zanamivir treatment initiation/matching in the two groups.

Exploratory objectives:

- To explore, through inverse-probability of censoring weighting (IPCW) analysis, the effect of non-persistence to exposure status in the analysis of the primary objective, above.

- To define the clinical course of disease for the IV zanamivir and comparator groups, categorized in 6 categories on an ordinal scale as described in Section 7.3.2.

    - The category of each patient on day 7, 10, 14 after IV zanamivir treatment initiation/matching

    - The change in category over time of each patient, from Day 1 to Day 14 after IV zanamivir treatment initiation/matching

- To compare the length of hospitalisation between the two groups
- To compare the length of ICU stay between the two groups
- To summarize associated complications of influenza (bacterial pneumonia, sepsis, myocarditis, encephalitis, acute respiratory distress syndrome, respiratory failure, bronchitis) in both groups.

7. RESEARCH METHODS

7.1. Study Design

The study will be a retrospective, observational, comparative chart review study conducted in ICU-admitted influenza patients in Europe. The collection of these data will be triggered by completion of the first seasonal influenza season following the grant of the marketing authorisation for IV zanamivir. There will be two parts to the study. The first stage (Part I) will involve the collection of historical data on patients from those influenza seasons which occurred prior to marketing authorisation. This part of the study, which aims to improve understanding of treatment patterns and to validate the assumptions for the comparative cohort, is timed to reflect current medical practice and to generate the most relevant data for comparison to the period following the grant of the marketing authorisation for IV zanamivir. If there are insufficient untreated patients, these historical data will assess whether the use of propensity score stratification or inverse-probability of treatment weighting (IPTW) would be appropriate. Similarly, if exposure to IV zanamivir is low, Disease Risk Score matching will be employed, as this technique has particular advantages when investigating newly marketed treatments with few exposures [Glynn, 2012]. Additionally, these historical data will serve to monitor the entry of new anti-influenza treatments, diagnostic tests and the regular use of resistance testing in future clinical practice. The second part (Part II) is the main comparative study with collection of data from ICU patients who were treated with IV zanamivir (IV zanamivir cohort) and those who did not receive this therapy at the point of matching (untreated cohort) during the same seasons/pandemic.

PART I: Historical Cohort

The data will be collected from a subset of eligible identified study sites (see Section 7.2). A dedicated research nurse(s) at each participating study site will complete study-specific electronic case report forms (eCRFs) for influenza patients who were admitted to ICU each year (see Section 7.3 for variables). Data collection will be for a pre-specified number of patients according to a pre-specified sampling frame (e.g. first 10 consecutive patients, based on admission date, per site and season).

PART II: Comparative Cohort

The collection of the comparative cohort data in this study will be triggered by completion of the first seasonal influenza season after the grant of the marketing authorisation for IV zanamivir in the EU. Once initiated, a dedicated research nurse(s) at each participating study site (see Section 7.2) will identify eligible patients from the hospital records and complete an eCRF for each patient (see Section 7.3 for variables).

7.2. Study Population and Setting

Study population

PART I: Historical Cohort

Inclusion criteria:

- Adults, adolescents, children and infants of all ages who were admitted to ICU with influenza illness.

Exclusion criteria:

- No informed consent given in countries where informed consent for retrospective chart reviews is mandated by local ethics/regulatory requirements.
- Prior treatment (within 30 days) with an investigational influenza drug therapy.

PART II: Comparative Cohort

Inclusion criteria:

- Adults, adolescents, children and infants of all ages who were admitted to ICU with influenza illness and treated with IV zanamivir as part of their routine medical care, treated with inactive antivirals or not treated at all.
    - Treatment may be initiated before or during ICU admission

Exclusion criteria:

- No informed consent given in countries where informed consent for retrospective chart reviews is mandated by local ethics/regulatory requirements.
- Prior treatment (within 30 days) with an investigational influenza drug therapy.

Setting

Hospitals are eligible to participate in this study if they fulfil all of the following criteria:

- Tertiary centre with ICU
- Ability to provide the variables of interest as described in Section 7.3.
- Ability for in-house testing for influenza type and sub-type by approved diagnostics

Hospitals in the European Union, UK, Norway and Iceland that participated in the Phase II and Phase III clinical trials, and the compassionate use program that meet the above criteria may be invited to join this study. These sites are situated in Belgium, the Czech Republic, Denmark, France, Germany, Greece, Hungary, Latvia, the Netherlands, Norway, Poland, Portugal, Slovakia, Spain and the UK. Additionally, ICU networks in France, Italy and the UK were identified through a literature search. A brief description of the networks can be found in the table below. If necessary, further hospitals will be identified through existing hospital networks that were set up for influenza surveillance or for post-pandemic data analyses. In the same literature review, networks in Spain [Cuevas Gonzalez-Nicolas, 2010] and the UK [Nguyen-Van-Tam, 2010] were identified as potentially interesting for follow-up.

Country	**Network**	**Description**
France	REVA-SRLF [Richard, 2012]	Network of 89 ICUs (25% of all ICUs in France) that reported ICU admissions (influenza vs non-influenza)
Italy	GiviTI [Bertolini, 2016]	Network of Italian 526 ICUs that report number of cases and reason for being in ICU, of which 359 are potentially relevant.
UK	USISS [Health Protection Agency, 2011]	Sentinel network of hospitals around the UK (from 36 randomly selected Acute Trusts) who report number of confirmed influenza cases hospitalised, and number of ICU admissions. Additionally, it includes a network of all Acute Trust ICUs in England who report admissions.

In addition to networks with ongoing reporting, two research networks that are not part of ongoing influenza surveillance were also identified at the time of writing this protocol. The first is a network of 13 university hospitals in Spain that was set up to investigate the relationship between oseltamivir and outcomes in hospitalised adults [Viasus, 2011]. The second is a European consortium (PRIDE) to perform an individual participant data meta-analysis on the effectiveness of antiviral use during the 2009 pandemic [Muthuri, 2014], which included data from 6,782 patients from European countries of which 90% originated from France, Spain and the United Kingdom.

7.3. Variables

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

7.3.1. Exposure definitions

PART I: Historical Cohort

The aim of the historical cohort is to understand treatment patterns for ICU-admitted influenza patients and factors associated with treatment. Therefore, included patients will be those hospitalised with influenza and admitted to ICU.

PART II: Comparative Cohort

All subjects in the IV zanamivir treatment cohort are exposed to at least 1 dose of IV zanamivir. Subjects in the untreated comparator arm are not treated with IV zanamivir at the time of matching. In this approach, which is analogous to the intention-to-treat analyses employed in clinical trials, matched patients will retain their exposure status during the analysis regardless of future treatment status (IV zanamivir discontinuation/initiation in cases/matched comparators respectively). The effect of this potential exposure misclassification will be investigated (exploratory analysis; Section 7.7.2).

7.3.2. Outcome definitions

PART I: Historical Cohort

The aim of the historical cohort is to understand treatment patterns for complicated influenza patients admitted to ICU and factors associated with treatment. Therefore, the outcome will be Neuraminidase Inhibitor treatment versus no Neuraminidase Inhibitor treatment.

PART II: Comparative Cohort

Clinical outcomes – primary endpoint:

- All-cause in-hospital mortality up to end of follow-up (defined in Section 7.7.1).

Clinical outcomes – secondary endpoints:

- All-cause in-hospital mortality up to end of follow-up
- All-cause in-hospital mortality at Day 7, 10 and 14 after hospital admission
- Ordinal scale for clinical course of influenza disease
    1. Discharged from hospital
    2. Not requiring supplemental oxygen
    3. Requiring supplemental oxygen
    4. In ICU, not on mechanical ventilation
    5. In ICU, on mechanical ventilation
    6. Death

Analyses will consider the ordinal scale at Day 7, 10 and 14 after treatment initiation/matching.

Clinical outcomes - exploratory

- All-cause in-hospital mortality up to end of follow-up
- Length of stay in hospital and in critical care unit/ICU
- Summary of associated complications of influenza (bacterial pneumonia, sepsis, myocarditis, encephalitis, acute respiratory distress syndrome, respiratory failure, bronchitis)

7.3.3. Confounders and effect modifiers

Outcomes will be summarised according to the following risk factors:

- Season/pandemic
- Country/centre
- Influenza strain/sub-type
- Age
- Sex
- Body mass index (BMI)
- Smoking status (Current, ex- smoker, never smoked)
- Vaccination status, other antiviral treatments, antibiotics
- Underlying co-morbidities including but not limited to:
    - Asthma
    - Chronic obstructive pulmonary disease (COPD)
    - Other pulmonary diseases
    - Other chronic conditions (e.g. Cardiovascular Disease, Chronic Kidney Disease, Diabetes, Neurological Disease and Obesity)
    - Immunocompromised
    - Pregnancy
    - Obesity
    - Prematurity
- Co-infecting viruses
- Duration of flu-specific symptoms prior to hospitalisation/treatment
- Presentation at admission (Influenza-like illness [ILI], pneumonia, otitis media [OM], sepsis etc.)
- Requiring supplemental oxygen
- Mechanical ventilation in ICU
- Days from hospital admission to ICU/critical care admission
- In-hospital corticosteroid administration (timing, drug, dose, frequency etc.)
- In-hospital antibiotic administration (timing, drug, dose, frequency etc.)
- Reason why patient has limited treatment options

7.4. Data sources

This study will only make use of hospital medical records.

7.5. Study size

The following assumptions are made with regard to the sample size estimation for the comparative cohort:

- There is no other difference between the IV zanamivir cohort and untreated cohort, except the treatment;
- The baseline mortality in the untreated group ranges between 5% and 25% representing differences in pathogenesis of potential circulating strains;
- The mortality odds ratio (treated vs. untreated) ranges between 0.20 and 0.80
- α=0.05 and β=0.20
- A continuity correction was applied [Fleiss, 1980]

Based on the assumptions above, the sample sizes required to detect various odds ratios with 80% power at the 5% statistical level are described in Table 1. For example,assuming mortality of 12% in unexposed patients and assuming a 1:1 treated vs untreated ratio, a minimum of 450 patients in each exposure arm would be required to demonstrate a statistically significant reduction in mortality with 80% power, assuming a true odds ratio of 0.5. Depending on the number of untreated patients in participating ICUs, the sample size estimation may need to be revisited after the feasibility study.

Table 1 Estimated sample size corresponding with varying treated/untreated ratio, mortality and odds ratios (OR)

Treated: Untreated	Mortality untreated	OR=0.20		OR=0.40		OR=0.50		OR=0.80	
		Treated	Not*	Treated	Not*	Treated	Not*	Treated	Not*
1:1	5%	343	343	686	686	1044	1044	7565	7565
	12%	142	142	292	292	450	450	3352	3352
	25%	68	68	148	148	233	233	1835	1835
2:1	5%	473	236	977	488	1502	751	11207	5595
	12%	198	99	419	209	651	325	4975	2484
	25%	96	48	214	107	341	170	2734	1365
3:1	5%	597	199	1263	421	1956	652	14823	4941
	12%	249	83	543	181	849	283	6585	2195
	25%	123	41	279	93	447	149	3624	1208

* Untreated

7.6. Data management

A separate Data Management Plan will be written before the start of this study outlining the procedures in more detail.

7.6.1. Data handling conventions

The eCRFs used to collect the data will include specific error checks to minimize data entry errors (formatting and range checks). Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data.

7.6.2. Resourcing needs

The implementation, management and closure of this study will be outsourced to a contract research organisation (CRO). The study will be overseen at GSK by a PhD level Epidemiologist.

Biostatistical and methodological issues will be addressed by a senior level statistician at GSK with expertise in observational data.

7.6.3. Timings of Assessment during follow-up

The final data collection time for both the historical and comparative cohorts of the study is at hospital discharge, the latest available date before study withdrawal or loss to follow-up, or at day 28 after hospital admission if a patient has not been discharged or has been re-admitted to hospital within the 28-day study period.

The dedicated research nurse(s) at each site will check medical charts of discharged patients to identify eligible patients. Table 2 below outlines for which times each (group of) variable(s) of interest will be collected.

Table 2 Proposed exposure and outcome assessment intervals

Data variable	At hospital admission	Before ICU admission	At/after ICU admission	Hospital discharge OR Day 28 post-treatment
Demographics	X			
Influenza diagnostics/details (e.g. influenza strain/type, diagnostic test)	X			
Other risk factors (confounders/effect modifiers from Section 7.3.3)	X	X	X	
In-patient IV zanamivir treatment	X	X	X	X
Admission to critical care facilities (e.g. ICU/high dependency unit [HDU])	X		X	X
Ordinal scale clinical outcomes	X	X	X	X
Mortality in hospital		X	X	X

7.7. Data analysis

7.7.1. Essential analysis

All analyses will be performed in SAS 9.4. Descriptive analyses will be performed with continuous variables expressed as means with 95% confidence intervals or medians and ranges, as appropriate for the data distribution. Categorical variables will be expressed as frequency or proportion of patients in each category.

The sub-sections below are an outline of the types of analyses that are currently being considered. A detailed statistical analysis plan will be written before data collection for the comparative cohort starts.

PART I: Historical Cohort

A logistic regression analysis will be performed to identify factors associated with anti-influenza treatment versus no anti-influenza treatment. If sufficient data are available, the analysis will be repeated for IV zanamivir.

PART II: Comparative Cohort

Propensity scores will be derived from the predicted probability of IV zanamivir treatment estimated in a multivariable pooled logistic regression model with treatment/no treatment fitted as the binary outcome and the covariates listed in Section 7.3.3 above specified as explanatory variables. Treatment and exposure data will be captured separately for the pre- and post-ICU periods as per Section 7.6.3, and models will be stratified by season (to control for differences in severity) and by time since illness onset to facilitate appropriate matching. Standardised differences will be calculated to assess the balance achieved in the matched sample [Austin, 2011a]. If an insufficient number of matched pairs are obtained, alternative approaches e.g. propensity score stratification or inverse-probability of treatment weighting (IPTW) will be considered and the analysis modified accordingly [Cullen, 2009; Austin, 2011a]. Similarly, if only a small number of patients are exposed to IV zanamivir then a Disease Risk Score-match approach will be applied [Glynn, 2012]. For analysis of within-hospital mortality fitted as the binary outcome, the same method will be applied.

If there are sufficient data, propensity score-matched samples will be created to compare: early (≤2 days from symptom onset to treatment initiation) versus late IV zanamivir treatment (>2 days from symptom onset to treatment initiation); early IV zanamivir treatment versus no treatment; late IV zanamivir treatment versus no treatment. Analyses will also be conducted in the subset of mechanically-ventilated patients, and, if sufficient data are available, an analysis will be conducted on patients infected with influenza viruses where resistance is confirmed. If numbers are sufficient, further stratified analyses will be performed for adults and children (aged <16 years) as well as for immunocompromised patients.

Following matching, patients will accrue time-at-risk from ICU admission (for IV zanamivir patients who initiated prior to ICU admission), treatment initiation (for IV zanamivir patients who initiated in the ICU) or ICU admission (comparator patients); as the study is conducted among ICU-admitted patients, person-time prior to ICU admission is immortal. Patients will be followed up until they experience the event of interest (death) or they are censored (the earlier of hospital discharge or 28 days post treatment/matching [as applicable]). For the secondary objectives described below censoring will be modified as appropriate (7, 10 or 14 days post treatment/matching).

Primary objective: all-cause in-hospital mortality to end of follow-up

A matched Cox regression analysis will be performed to estimate the association between IV zanamivir treatment and mortality during hospital stay. The treated vs. untreated groups will be compared to obtain the hazard ratio for in-hospital survival. Kaplan-Meier plots will be produced for graphical comparison of survival in the two groups.

Secondary objective: crude all-cause in-hospital mortality to end of follow-up

A crude estimate of the hazard ratio, based on the unmatched sample, will also be obtained using a time-dependent Cox regression model stratified by season, to control for differences in severity.

Secondary objective: All-cause in-hospital mortality at Day 7, 10 and 14

A regression analysis, similar to the primary analysis, will be performed on available mortality data at Day 7, 10 and 14 post treatment/matching.

7.7.2. Exploratory analysis

Inverse Probability of Censoring Weighted (IPCW) Analysis

The proposed matching strategy seeks to minimise bias by not utilising future information to define exposure status [Hernan, 2016]. Accordingly, patients who are matched as controls may go on to receive IV zanamivir and treated patients may discontinue IV zanamivir. To examine the effect of this potential exposure misclassification, if observed to some (≥10%) degree, (IPCW) analysis will be performed for the primary objective analysis. Patients who do not persist to their exposure status will be censored at the time of non-persistence, and stabilised weights – generated from a pooled logistic regression model with non-persistence fitted as the outcome variable and the parameters described in Section 7.3.3 included as explanatory variables – will be utilised in a weighted pooled logistic regression analysis of the effect of IV zanamivir treatment on all-cause within-hospital mortality.

Ordinal Scale at Day 7, 10 and 14

A proportional odds regression model will be fitted to estimate the odds of different categories of the ordinal scale at Day 7, 10 and 14, and their 95% confidence intervals, in the IV zanamivir group compared with the untreated group. Results will be presented for two levels of adjustment: (i) unadjusted (i.e., crude comparison) and (ii) using propensity score stratification with additional adjustment for ICU ventilation on Day 1, inpatient antibiotics and systemic corticosteroids. Patients will be assigned to the point on the ordinal scale based on the information for that day and not for the period up to and including that day (e.g. 0-7, 0-10, 0-14 days).

Length of hospital/ICU admission

Matched t-tests, or alternative non-parametric tests, will be performed to compare length of hospital stay and length of ICU admission between IV zanamivir and no IV zanamivir treatment patients (and, if sufficient data exist, by early/late treatment).

Associated complications

Descriptive analyses of the proportion of each treatment group with associated complications of influenza (bacterial pneumonia, myocarditis, encephalitis, sepsis, acute respiratory distress syndrome, respiratory failure, bronchitis) during ICU stay will also be reported.

For optimal comparability, the primary and secondary analyses will be repeated using the following definitions, which are similar to what was used in the Phase 3 clinical trial:

- Early treatment: ≤4 days after symptom onset to treatment initiation;
- Late treatment: >4 days after symptom onset to treatment initiation.

7.7.3. General considerations for data analyses

Missing data

It is anticipated that missing data will be minimal given the source of the information on patients (e.g. medical chart review). Accordingly, missing data will be recorded as such (e.g. coded as 99), but with those records retained (e.g. propensity score calculations) or excluded (e.g. T tests to compare admission/ICU length) as appropriate. Patients for whom details on potential risk factors are missing will not be included in the sensitivity analyses.

7.8. Quality control and Quality Assurance

As part of data cleaning efforts, all eCRFs will be checked for completeness. In case of missing data, the CRO will contact the relevant research nurse for further details. Ideally, the eCRF would be built to prevent the entry of impossible answers (e.g. body temperature of 375 degrees C instead of 37.5 degrees C). Additionally, automated logical checks will be put in place to identify possible data entry errors (e.g. body temperatures below 32 degrees Celsius, or age younger than 0 or older than 100). Findings will be queried with the relevant research nurse for confirmation or correction.

There will be no systematic data quality check against the original medical records, as it is very unlikely access to medical records will be granted for third party oversight without patient consent. However, if many data cleaning queries occur for a particular site, additional training will be provided to prevent future data entry errors. Monthly telephone calls with the research nurses will be considered as an additional method to identify or preempt potential issues with data collection.

7.9. Limitations of the research methods

Medical records may not always be complete, potentially leading to incomplete data for specific patients (historical and not captured in the clinical history). The historical cohort will inform on completeness of data and may promote increased data capture for the main comparative study. To further minimise missing data, identified hospitals will be asked if they can provide a minimum dataset from their medical records. Training will also be provided to ensure that all participating health care providers understand the importance of complete medical records. The minimum dataset requirements will also help prevent any major differences between countries, with regard to which variables are recorded.

Although measures are in place to ensure the collected hospital records are fairly complete, they are not linked to other databases capturing patient health post-discharge. Therefore, this study design does not include any collection of mortality data after

hospital discharge. It is possible that Day 28 survival data will not be available for some patients, unless the patient is readmitted to the same hospital.

The proposed propensity score matching in this planned study aims to minimize channeling bias whereby patients who receive IV zanamivir may be sicker than those who do not. The feasibility phase will inform on changes in treatment patterns over time, including the potential to assess impact of approval of new antiviral treatments and advances in influenza diagnostics. It will also allow an assessment of the feasibility of obtaining data from untreated ICU patients and of implementing the propensity score approach (i.e. whether there will be sufficient overlap between propensity strata of untreated and treated patients). It is possible that the proposed comparative study is not deemed feasible following Part I of this protocol. This will most likely be due to a very limited number of patients that are eligible for inclusion in the untreated comparator group, or due to lack of overlap between the IV zanamivir and comparator groups. If this is the case advice will be sought from the European Medicines Agency (EMA) and the Committee on Human Medicinal Products (CHMP) on the appropriate way forward. It is also important to note that PSM will only reduce bias with regard to measured confounders, meaning that the potential for uncontrolled confounding by indication might exist if important factors which dictate treatment or which are related to the study outcome are not recorded in chart records. It is unlikely that such information would be absent, however, as it is likely that such information would to be pertinent to the effective management of influenza patients in the ICU setting.

Another limitation is related to the observational nature of this study, which does not allow for any additional testing beyond that obtained during standard clinical practice. Although some (mostly academic) hospitals are able to perform resistance testing in-house, it is usually done for research purposes instead of clinical decision making. Therefore, it will be very unlikely that this study will obtain sufficient if any data on resistance from medical records and will be reliant on global patterns of influenza resistance through European surveillance networks. Additionally, this study will assume that zanamivir is the only active treatment for all patients with a specific influenza A strain that has been identified as highly drug-resistant, while it is possible that some of these patients are susceptible to other treatments because they do not possess the resistant mutation. Likewise, some patients may be infected with influenza B. Such misclassification is likely to be non-differential as treating physicians will not know the strain and will not treat to strain type, with resulting treatment effect estimates biased towards the null. If possible, this study will include a sensitivity analysis based on available resistance data to investigate this particular group of non-resistant influenza patients. Finally, the proposed analyses for this study will be amended accordingly if resistance testing becomes more common and widely available in clinical practice before the current protocol is triggered.

7.9.1. Study closure/uninterpretability of results

Whilst it is unlikely that this study would be terminated due to low enrolment as it will only be conducted in situations when higher levels of IV zanamivir exposure is

anticipated, it is possible that the proposed comparative study (part II) is not deemed feasible based on the findings from part I. If this is the case advice will be sought from the EMA and the CHMP on the appropriate way forward.

7.10. Other aspects

Not applicable.

8. PROTECTION OF HUMAN SUBJECTS

8.1. Ethical approval and subject consent

This study is designed as a non-interventional, anonymized, retrospective medical record review. Relevant local Ethics Committees (ECs)/Institutional Review Boards (IRBs) will be contacted to determine if a full submission of the study protocol is required, or if notification only of the study to the EC/IRB is sufficient. Regulatory submissions/notifications will be performed according to national and local requirements for non-interventional studies. Patient consent requirements will be assessed and obtained according to national consent procedures for non-interventional, observational, retrospective medical record reviews.

8.2. Subject confidentiality

Direct patient identifiers linked to personal identifiable information (e.g., name, address, medical record number) will not be collected in the study. Patients will be identified using an assigned unique study participant number only.

9. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

All serious and non-serious adverse events (AEs), pregnancy exposures, or incidents related to any GSK product will be collected and reported as described in the study-specific pharmacovigilance plan (sPVP). This plan will include the following elements to ensure a comprehensive approach to safety event collection and reporting presented in ANNEX 2:

- Supplier pharmacovigilance training
- Safety-specific roles
- AEs, pregnancy exposures, and incidents collection and reporting processes
- AE, pregnancy exposure, and incident collection forms
- Frequency of data review
- Reporting process and timelines
- Study-specific PVP monitoring process
- Provision of final study report

10. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

10.1. Target Audience

The EMA, the CHMP and the Pharmacovigilance Risk Assessment Committee (PRAC) will be the primary audience for this study. It will also be of interest to infectious disease, pulmonary and critical care clinicians, as well GSK stakeholders such as IV zanamivir project team members and the Global Safety Board. Additionally, this study will contribute novel data to the published literature.

10.2. Study reporting and publications

As the patient population will include paediatric patients it will fall under Article 46 of Regulation (EC) No 1901/2006 (the 'Paediatric Regulation') a study report will be filed with the EMA within 6 months of the required sample size (Section 7.5) being achieved. As the required sample size is dictated by underlying mortality amongst other factors, it is challenging to predict the time required to complete the study. Accordingly, an update report will be filed with the EMA by each year, providing details of the number of treated and untreated patients enrolled and guidance on the likely study end date. Final study results will be submitted for publication in a suitable peer-reviewed journal and presented at relevant conferences or meetings where possible.

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ANNEX 1: LIST OF STAND-ALONE DOCUMENTS

N/A

ANNEX 2. PVP ELEMENTS AND REQUIREMENTS TABLE

PVP Element	How the SAP will address the PVP element	Minimum Requirement (In certain circumstances, advice for specific requirements will be provided by GCSP representative (see above)
Vendor PV training	• Standard Pharmacovigilance training. GSK Training function would be responsible for its conduct • PV training provided by Vendor will also be considered if comparable to internal GSK training	• Pharmacovigilance training for Epidemiology and Health Outcomes vendors (example(s) available at Templates - HO and Epi Research)
Investigator and site staff PV training	• No PI or site staff to be trained	• Pharmacovigilance training for Epidemiology and Health Outcomes vendors (example(s) available at Templates - HO and Epi Research)
Safety-specific roles	• Exposures in pregnancy will be collected as part of this protocol • Routine PV will cover all other safety-related activities	• Roles defined in the protocol and tailored to the research
AEs, pregnancy exposures, and incidents collection and reporting processes	• Pregnancy exposures will be actively collected as part of this study and will be presented as proportions in the study report.	• All serious and non-serious AEs, pregnancy exposures, and incidents related to GSK medicines will be collected and reported
AE, pregnancy exposure, and incident collection forms	• There will not be any follow-up	• AE, Pregnancy, and Incident Reporting Form for Epidemiology and Health Outcomes Research (example(s) available at Templates - HO and Epi Research)
Frequency of data review	• Pregnancy exposure will be reviewed as data are collected	• Review of data review defined in the protocol and tailored to the research
Reporting process and timelines	• All serious and non-serious AEs, pregnancy exposures, and incidents related to GSK medicines will be reported to GCSP within 24 hours of recognition	• All serious and non-serious AEs, pregnancy exposures, and incidents related to GSK medicines will be reported to GCSP within 24 hours of recognition
Interim reports	• There will be no interim report	• Requirement defined in the protocol and tailored to the research
Reconciliation process	• There will be no reconciliation process as part of this study.	• Reconciliation process defined in the protocol and tailored to the research • Reconciliation form for Epidemiology and Health Outcomes (example(s) available at Templates - HO and Epi Research
PVP monitoring process	• PVP monitoring will be according to routine	• Requirement defined in the protocol

PVP Element	How the SAP will address the PVP element	Minimum Requirement (In certain circumstances, advice for specific requirements will be provided by GCSP representative (see above)
	pharmacovigilance processes	and tailored to the research
Provision of final study report	• Any AEs, pregnancy exposures, and incidents reported during the course of this study will be described in the final study report (as frequency or proportion), using standard shell tables	• Requirement defined in the protocol and tailored to the research

GlaxoSmithKline

Study-Specific Pharmacovigilance Plan (sPVP)

Unique Identifier	208165
Full title of protocol	A retrospective observational chart review to evaluate the clinical effectiveness of treatment with intravenous zanamivir in a sentinel cohort of intensive care (ICU) patients with severe influenza
Abbreviated title of protocol	PRJ2956 - IVZ post-marketing effectiveness
Department	Pharma-EPI
Study Accountable Person	PPD
Type of Study (tick type of study that applies)	☐ Interventional (interaction) study with data collection - face-to-face or phone-based interviews
	☐ Interventional (interaction) study with data collection - digital or paper surveys
	☒ non-interventional study with data collection where data source includes identifiable patient information (e.g., data extraction from medical records, existing registry)
	☐ other, please describe:
Study-Specific Pharmacovigilance Plan Approval Date	*22 July 2019*
SMG Pharma Safety Approver(s)	PPD

Revision Chronology:

Version Date	Document Type	Change(s) since last version
22-July-19	Original	n/a

sPVP Element	**Study-Specific Pharmacovigilance Plan (sPVP)** (tick applicable statements)
Supplier/ Vendor PV training	☐ N/A – No supplier/vendor involved that could be in receipt of serious and/or non-serious AEs, pregnancy exposures, and/or incidents related to any GSK product
	☒ Supplier/vendor PV training will be conducted using the agreed method and current, approved content, prior to beginning the study. Training will be completed annually and documented.
Investigator and site staff PV training	☐ N/A – No Investigator and/or site staff involved that could be in receipt of serious and/or non-serious AEs, pregnancy exposures, and/or incidents related to any GSK product
	☒ Investigator and/or site staff PV training will be conducted using the agreed method and current, approved content, prior to beginning the study. Training will be completed annually and documented.
Safety-specific roles	☐ SAP is responsible for identifying, collecting, reporting and reconciling AEs, pregnancy exposures, and/or incidents related to any GSK product
	☒ Supplier/vendor is responsible for identifying, collecting, reporting and reconciling AEs, pregnancy exposures, and/or medical device incidents related to any GSK product
AEs, pregnancy exposures, and incidents collection and reporting processes	The following will be identified, collected, and reported to GSK central safety (for multiple country studies) or local safety (for single country studies): • serious and/or non-serious AEs, **related** to any GSK product • pregnancy exposures to any GSK product (*note: in the case of a pregnancy registry, the registry will manage exposures*) • incidents **related** to any GSK product
	For studies that evaluate a GSK product, consult with SMG Pharma Safety SERM to determine if additional data is required and complete the information below: ☐ Study does not evaluate a GSK product - No additional study-specific safety data is to be collected ☒ Study evaluates a GSK product - No additional study-specific safety data is to be collected ☐ Study evaluates a GSK product - additional study-specific safety data is to be collected
AE, pregnancy exposure, and incident collection forms	☒ GSK Global Adverse Event, Pregnancy Exposure, and Incident Reporting Form for Epidemiology and Health Outcome studies
	☐ Alternative collection form(s) will be utilized
Frequency of data review	☒ N/A – No batch reviewing of the data.
	☐ Batch review will be conducted

sPVP Element	**Study-Specific Pharmacovigilance Plan (sPVP)** (tick applicable statements)
Reporting process and timelines for AEs, pregnancy exposures and medical device incidents	All adverse events, pregnancy exposures, and/or incidents related to any GSK product will be reported to SMG Pharma Safety within 24 hours of awareness of the event.
Interim study reports	☐ N/A – No interim study reports are planned.
	☒ Interim study reports will be shared with the SERM product specialist / physician for review of the interim report safety data
Reconciliation process	☒ A log of all AEs, pregnancy exposures, and incidents identified during the research will be provided to GSK central safety (for multiple country studies) or local safety (for single country studies) on a Reconciliation Form. Central or local safety will confirm all reports listed on the log are included on the GSK Safety Database.
Study-specific PVP monitoring process	☒ SAP will review the sPVP elements and discuss during regular study team and/or supplier meetings to ensure the plan is working effectively.
	☐ Other, please describe
Provision of final study report	A summary of AEs, pregnancy exposures, and/or incidents related to any GSK product will be included in the final study report. The final draft study report will be provided to the SERM product specialist / physician for review and approval where a specific asset is involved.