Study Protocol
Sponsor:
GlaxoSmithKline Biologicals
Rue de l'Institut 89
1330 Rixensart, Belgium

1. PASS INFORMATION

Title	Fluarix®/ FluLaval®/ Fluarix® Quadrivalent/ FluLaval® Quadrivalent Pregnancy Registry: a prospective, exploratory, cohort study to detect and describe abnormal pregnancy outcomes in women intentionally or unintentionally vaccinated with Fluarix® or Fluarix® Quadrivalent or FluLaval® or FluLaval® Quadrivalent during pregnancy or within 28 days preceding conception.
Protocol version identifier	201476 (EPI-FLU-039 VS US PR)
Date of last version of the protocol	Final Version 1: 13 May 2014
EU PAS Register No:	Not applicable
Active substance	J07BB02, Influenza Virus Vaccines
Medicinal products:	Fluarix®, FluLaval®, Fluarix® Quadrivalent, FluLaval® Quadrivalent, Inactivated Influenza Virus Vaccines
Product reference:	Not applicable
Procedure number:	Not applicable
Marketing Authorization Holder	GlaxoSmithKline Biologicals Rue de l'Institut 89 1330 Rixensart, Belgium
Joint PASS	No
Research question and objectives	**Co-primary objectives** • To describe the characteristics of prospectively reported pregnancies (women vaccinated with *Fluarix* or *FluLaval* or *Fluarix Quadrivalent* or *FluLaval Quadrivalent* during pregnancy or within 28 days preceding conception) with abnormal pregnancy outcomes.

	• To assess the proportion of prospectively reported pregnancies (women vaccinated with *Fluarix* or *FluLaval* or *Fluarix Quadrivalent* or *FluLaval Quadrivalent* during pregnancy or within 28 days preceding conception) with abnormal pregnancy outcomes.
Country of study	United States
Authors	Coordinating author: • [redacted] XPE Pharma & Science, contractor for GSK Biologicals GSK contributors: • [redacted] Director, Safety Evaluation & Risk Management, Vaccine Clinical Safety and Pharmacovigilance • [redacted] Director, Safety Evaluation & Risk Management, Vaccine Clinical Safety and Pharmacovigilance • [redacted] Director and Head, Clinical Safety Sciences, Vaccine Clinical Safety and Pharmacovigilance • [redacted] VP, Head Vaccine Clinical Safety and Pharmacovigilance • [redacted] Director, Global Clinical R&D • [redacted] Senior Manager, Vaccine Value & Health Science Epidemiology • [redacted] Director, Vaccine Value & Health Science Epidemiology • [redacted] Senior Manager, Regulatory Affairs

2. MARKETING AUTHORIZATION HOLDER

Marketing authorization holder	GlaxoSmithKline Biologicals Rue de l'Institut 89, 1330 Rixensart, Belgium

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LIST OF ABBREVIATIONS

ACIP	Advisory Committee on Immunization Practices
AE	Adverse Event
BLA	Biologics License Application
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
EDD	Estimated Date of Delivery
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GSK	GlaxoSmithKline
HA	Hemagglutinin
HCP	Healthcare Professional
ICH	International Conference on Harmonization
IM	Intramuscular
IND	Investigational New Drug
LMP	Last Menstrual Period
MACDP	Metropolitan Atlanta Congenital Defects Program
PASS	Post Authorization Safety Study
PI	Prescribing Information
sIIV(s)	seasonal Inactivated Influenza Vaccine(s)
US	United States
VCSP	Vaccine Clinical Safety and Pharmacovigilance

3. RESPONSIBLE PARTIES

GlaxoSmithKline (GSK) Biologicals has the overall responsibility for the conduct of the study.

4. ABSTRACT

Title

Fluarix®/ FluLaval®/ Fluarix® Quadrivalent/ FluLaval® Quadrivalent Pregnancy Registry: an exploratory prospective, cohort study to detect and describe abnormal pregnancy outcomes in women intentionally or unintentionally vaccinated with Fluarix® or Fluarix® Quadrivalent or FluLaval® or FluLaval® Quadrivalent during pregnancy or within 28 days preceding conception.

201476 (EPI-FLU-039 VS US PR), Final Version 1: 13 May 2014

Main author

[redacted] Director, Safety Evaluation & Risk Management, Vaccine Clinical Safety and Pharmacovigilance, GSK Biologicals

Rationale and background

The four seasonal Inactivated Influenza Vaccines *Fluarix*, *FluLaval, Fluarix Quadrivalent* and *FluLaval Quadrivalent* (collectively referred to as GSK seasonal Inactivated Influenza Vaccines [GSK sIIVs]) are approved in the United States (US) for prevention of disease caused by influenza A subtype viruses and type B viruses contained in the vaccine in persons 3 years of age and older. Pregnant women may inadvertently be vaccinated with GSK sIIVs during the first trimester, before pregnancy is known. In general, the women are closely monitored throughout the remainder of the pregnancy.

The purpose of this pregnancy registry study is to detect and describe abnormal pregnancy outcomes in women intentionally or unintentionally vaccinated with GSK sIIVs. The combination of the large number of women who are of reproductive capacity in the indicated age range for vaccination with these vaccines and the lack of data concerning vaccination with GSK sIIVs during pregnancy makes such a Registry an important component of the ongoing program to assess the safety of these four vaccines. The intent of the Registry is to prospectively collect data such as vaccination with GSK sIIVs during pregnancy or within 28 days preceding conception, potential confounding factors (such as exposure to other medications) and information related to the outcome of the pregnancy.

Research question and objectives	**Co-primary objectives** • To describe the characteristics of prospectively reported pregnancies (women vaccinated with *Fluarix* or *FluLaval* or *Fluarix Quadrivalent* or *FluLaval Quadrivalent* during pregnancy or within 28 days preceding conception) with abnormal pregnancy outcomes. • To assess the proportion of prospectively reported pregnancies (women vaccinated with *Fluarix* or *FluLaval* or *Fluarix Quadrivalent* or *FluLaval Quadrivalent* during pregnancy or within 28 days preceding conception) with abnormal pregnancy outcomes.
Study design	• This study is a transition of existing ongoing pregnancy registries for *Fluarix*, *FluLaval* and *Fluarix Quadrivalent* and an ongoing PASS for *FluLaval Quadrivalent* into a combined PASS for these four GSK sIIVs. • This is an exploratory prospective, observational, cohort study. The GSK sIIVs pregnancy registry study requires voluntary, prospective* reporting of eligible pregnancies by patients and healthcare professionals (HCPs). Data such as vaccination with GSK sIIVs during pregnancy or within 28 days preceding conception, potential confounding factors (such as exposure to other medications) and information related to the outcome of the pregnancy will be collected prospectively. **Some pregnancy exposures may be reported when the outcome is unknown (prospective reports).* *Some pregnancy exposures may be reported after pregnancy outcome has been identified (retrospective reports). The Registry will capture retrospective reports, but these reports will not be included in the analyses of prospective reports.* • This study is a post-marketing commitment in the US. • Study population: pregnant women, vaccinated with GSK sIIVs during pregnancy or within 28 days preceding conception volunteering to take part in the study. • Type of study: self-contained. • Data collection: initial and follow-up data will be collected using questionnaires (Registration form and Outcome form). Follow-up of cases is performed within 3 months of the estimated date of delivery (EDD) to ascertain outcome and approximately 6 months and 12

months after the EDD (for all live births) to ascertain the presence of birth defects not diagnosed before.

- After transition of the ongoing pregnancy registries into one combined PASS for GSK sIIVs, data will be collected for a minimum of 5 years starting Q2 2014

Population, including the setting and study population

In the US, GSK sIIVs are indicated for prevention of disease caused by influenza A subtype viruses and type B viruses contained in the vaccine. GSK sIIVs are approved for use in persons 3 years of age and older.

Size of the potential "at-risk" population

In the year 2012, the fertility rate in the US was 63.2 births per 1000 women aged 15-44 years and there were 3.96 million births [CDC, 2012].

Number of pregnant vaccinees

Although the number of pregnant women who will be vaccinated with GSK IIVs is impossible to predict, experiences with other vaccine pregnancy registries indicate that it is likely that fewer than 100 pregnancies per year will be registered for each of the vaccines.

Variables

Primary endpoint

Occurrence of abnormal pregnancy outcomes in women intentionally or unintentionally vaccinated with GSK sIIVs during pregnancy or within 28 days preceding conception.

Data sources

Reporting of vaccine-exposed pregnancies to the Registry is voluntary. Registration can be initiated from a HCP or from a consumer; in the latter case permission is requested to obtain confirmation and follow-up from their HCP. A toll-free telephone number for reporting adverse events (AEs) and vaccine-exposed pregnancies to the Registry are listed in the product information leaflet and on the GSK Registry website. Retrospective post-marketing reports and relevant scientific publications are potential sources of additional information.

Study size

No minimum sample size is required for this descriptive, exploratory study.

Please refer to Abstract Section "Study population" above for the size of the potential "at-risk" population and the number of pregnant vaccinees.

Data analysis

Pregnancy outcomes include spontaneous abortion (pregnancy loss before 20 weeks gestation), fetal deaths/stillbirths (loss

at or after 20 weeks gestation), elective/therapeutic abortions and live births. The presence or absence of birth defects or other abnormalities is evaluated within each of the preceding outcome categories.

Pregnancy outcomes are stratified by the trimester of exposure, with an additional stratum for preconception exposure with no subsequent administration of vaccine during pregnancy. Reports of multiple exposures during a pregnancy are classified by the earliest trimester of exposure. The calculations of risk for birth defects are made by dividing the number of infants with birth defects by the total number of infants with and without birth defects. An exact 95% confidence interval is calculated using standard statistical software. The outcomes of the study will be assessed against known rates from an external reference group for the likelihood of a safety signal warranting further investigation.

Spontaneous abortions without birth defects are excluded from the risk calculations.

All defects regardless of trimester of vaccine exposure will be included in the periodic summary reports of this Registry and stratified by trimester of exposure.

A section of each periodic summary report, separate from the analysis of prospective reports, will describe all abnormal outcomes of retrospectively reported cases.

Milestones

Summary reports will be written annually. A final report will be written and submitted 18 months after the last annual report.

After submission of the final report, GSK will continue the Registry pending Center for Biologics Evaluation and Research (CBER) review of the report and determination whether the Registry can be discontinued.

References

Centers for Disease Control and Prevention (CDC). Recent Trends in Births and Fertility Rates Through December 2012. Available at http://www.cdc.gov/nchs/data/hestat/births_fertility_december_2012/births_fertility_december_2012.htm Accessed 29 August 2013.

5. AMENDMENTS AND UPDATES

None.

6. MILESTONES

Milestone	Planned date [a]
Start of data collection	01 June 2014 [b]
End of data collection	31 May 2019 [c]
Annual report 1 (2014-2015 influenza season)	30 June 2015
Annual report 2 (2015-2016 influenza season)	30 June 2016
Annual report 3 (2016-2017 influenza season)	30 June 2017
Annual report 4 (2017-2018 influenza season)	30 June 2018
Annual report 5 (2018-2019 influenza season)	30 June 2019
Final report	06 March 2020

[a] The *Fluarix* and *FluLaval* Registries were originally initiated on 02 Sep 2011. The *Fluarix Quadrivalent* and *FluLaval Quadrivalent* Registries were originally initiated on 30 Aug 2013 and 30 Nov 2013, respectively. The ongoing Registries will be combined and converted into a PASS. GSK plans to continue the Registry for a minimum of 5 years, starting Q2 2014.

[b] Women vaccinated with GSK sIIVs during pregnancy or within 28 days preceding conception, reported before the planned date of start of data collection (01 June 2014) but for which the pregnancy outcome is not yet known, may be enrolled retroactively in the Registry.

[c] After submission of the final report, GSK will continue the Registry pending Center for Biologics Evaluation and Research (CBER) review of the report and determination whether the Registry can be discontinued.

7. RATIONALE AND BACKGROUND

7.1. Background

Both *Fluarix* and *Fluarix Quadrivalent* vaccines are manufactured by GSK Biologicals, in Dresden, Germany.

Both *FluLaval* and *FluLaval Quadrivalent* vaccines are manufactured by ID Biomedical Corporation of Quebec, a subsidiary of GSK; in Quebec City, Canada.

GSK currently has 4 Pregnancy Registry protocols that have been submitted to Investigational New Drug (IND) and Biologics License Applications (BLAs). These were submitted either as a postmarking commitment or as voluntary pharmacovigilance activities in a Risk Management Plan for the GSK sIIVs. See Table 1 for information on these registries.

Table 1 Current Pregnancy Registry Protocols being conducted for *Fluarix*, *FluLaval, Fluarix Quadrivalent* and *FluLaval Quadrivalent*

Product Name	File Number	Submission Date of Pregnancy Registry Protocol	Registry Starting Date
Fluarix	125127	31 August 2010 (Sequence No. 0065)	02 September 2011
FluLaval	125163/181	10 August 2010 (Sequence No. 0027)	02 September 2011
Fluarix Quadrivalent	125127 BB-IND 114473	15 April 2013 (Sequence No. 0181) 13 June 2013 (Sequence No. 0036)	30 August 2013
FluLaval Quadrivalent	125163 BB-IND 14466	29 October 2013 (Sequence No. 0157) 28 October 2013 (Sequence No.0032)	30 November 2013

7.1.1. Trivalent influenza vaccines

Fluarix and *FluLaval* are both split virion, inactivated influenza vaccines consisting of equal amounts of three monovalent viral antigen bulks prepared from influenza strains A/H1N1, A/H3N2 and one B strain. One dose of the split inactivated vaccine contains 15 µg hemagglutinin (HA) for each of the three influenza virus strains, for a total of 45 µg HA/0.5 mL dose.

7.1.1.1. Animal studies

Animal reproduction studies were performed in female rats using 0.1 mL (approximately 56 times the human dose based on average weight) of *Fluarix* administered 28 days before mating and on Days 6, 8, 11 and 15 of gestation. There were no adverse effects on mating performance or fertility of the female rats, and no adverse effects on embryo/fetal survival, growth or development, or the pre- or post-natal survival, growth or development of the offspring up to 25 days of age [Fluarix Prescribing Information (PI), 2013].

In a reproductive and developmental toxicity study, the effects of *FluLaval* on embryo-fetal and pre-weaning development were evaluated in pregnant rats. Animals were administered *FluLaval* by intramuscular injection, once prior to gestation and on gestation days 6, 8, 11, and 15 during the period of organogenesis, at a dose of 0.1 mL/rat/occasion (approximately 40-fold excess relative to the projected human dose on a body weight basis). No adverse effects on mating, female fertility, pregnancy, parturition, lactation parameters, and embryo-fetal or pre-weaning development were observed. There were no vaccine-related fetal malformations or other evidence of teratogenesis [FluLaval PI, 2013].

7.1.1.2. Post marketing exposure in pregnant women

Fluarix:

Overall, as of 31 August 2013, GSK had received 243 reports of exposure to *Fluarix* during pregnancy since its launch on 04 July 1991. The outcomes of the 243 pregnancies are summarized in Table 2.

Table 2 Outcomes of pregnancy exposed to *Fluarix*

Outcome	Number of Cases since launch (n)
Live infant, no apparent congenital anomaly *	55
Live infant with congenital anomaly	4
Elective termination, no apparent congenital anomaly *	1
Elective termination with congenital anomaly	2
Spontaneous abortion, no apparent congenital anomaly *	12
Spontaneous abortion with congenital anomaly	0
Stillbirth, no apparent congenital anomaly *	2
Stillbirth with congenital anomaly	1
Ectopic pregnancy	0
Molar pregnancy	0
Pregnancy ongoing, lost to follow-up or unknown	166
Total	243

* Pregnancy outcome categories stating no apparent congenital anomaly include outcomes where it is unknown whether a congenital anomaly occurred.

FluLaval:

Overall, as of 17 December 2013, GSK had received 128 reports of exposure to *FluLaval* during pregnancy since launch on 18 December 1992. The outcomes of the 128 pregnancies are summarized in Table 3.

Table 3 Outcomes of pregnancy exposed to *FluLaval*

Outcome	Number of Cases since launch
Live Infant, no apparent congenital anomaly *	26
Live infant with congenital anomaly	2
Elective termination, no apparent congenital anomaly *	0
Elective termination with congenital anomaly	0
Spontaneous abortion, no apparent congenital anomaly *	3
Spontaneous abortion with congenital anomaly	0
Stillbirth, no apparent congenital anomaly *	0
Stillbirth with congenital anomaly	0
Ectopic pregnancy	0
Molar pregnancy	0
Pregnancy ongoing / Unknown / Lost to Follow-up	97
Not applicable	0
Total	128

* Pregnancy outcome categories stating no apparent congenital anomaly include outcomes where it is unknown whether a congenital anomaly occurred.

7.1.2. Quadrivalent influenza vaccines

Fluarix Quadrivalent and *FluLaval Quadrivalent* are split virion, inactivated influenza vaccines consisting of equal amounts of four monovalent viral antigen bulks prepared from influenza strains A/H1N1, A/H3N2 and two B strains (one B/Yamagata lineage and one B/Victoria lineage). One dose of the split inactivated vaccine contains 15 µg HA for each of the four influenza virus strains, for a total of 60 µg HA/0.5 mL dose.

7.1.2.1. Animal studies

Reproductive and developmental toxicity of *Fluarix Quadrivalent* and *FluLaval Quadrivalent* has been studied in female rats at doses approximately 80 times the human dose (on a mg/kg basis) and no evidence of impaired female fertility or harm to the fetus was observed.

In reproductive and developmental toxicity studies, the effect of *Fluarix Quadrivalent* and *FluLaval Quadrivalent* on embryo-fetal and pre-weaning development was evaluated in rats. Animals were administered *Fluarix Quadrivalent* or *FluLaval Quadrivalent* by intramuscular (IM) injection twice prior to gestation, during the period of organogenesis (gestation days 3, 8, 11 and 15) and during lactation (day 7), 0.2 mL/rat/occasion

(approximately 80-fold excess relative to the projected human dose on a body weight basis). No adverse effects on embryo-fetal or peri- and post-natal development, no maternal toxicity and no impact on F_0 female clinical condition, food consumption, body weight, mating performance, fertility or ability to produce a live litter were observed during these studies [Fluarix Quadrivalent PI, 2013; FluLaval Quadrivalent PI, 2013].

7.1.2.2. Post marketing exposure in pregnant women

Fluarix Quadrivalent:

Overall, as of 19 February, 2014, GSK had received 25 reports of exposure to *Fluarix Quadrivalent* during pregnancy since launch on 5 August 2013. Of the 25 pregnancy reports, 22 were ongoing at the time of reporting and 3 were considered lost to follow-up.

FluLaval Quadrivalent:

Overall, as of 17 December 2013, GSK had received 5 reports of exposure to *FluLaval Quadrivalent* during pregnancy since launch on 15 August 2013. At the time of the reporting, all 5 pregnancies were ongoing

7.1.2.3. GSK sIIVs

Animal studies did not reveal any developmental or reproductive safety issue for GSK sIIVs. There are, however, no adequate and well-controlled studies of these vaccines in pregnant women. Review of the collective post marketing exposure experience of GSK sIIVs does not suggest a safety signal. It is not known whether GSK sIIVs can have negative effects on human reproductive capacity or pregnancy outcomes. It is generally accepted that inactivated vaccines pose no risk to the pregnant or lactating women (Centers for Disease Control and Prevention [CDC, 2002]).

7.1.3. Medical conditions for use

The GSK sIIVs are approved by the US Food and Drug Administration (FDA) for prevention of disease caused by influenza A subtype viruses and type B viruses contained in the vaccines (Table 4). In the US, the GSK sIIVs are approved for use in persons 3 years of age and older.

Table 4 Year of initial US approval for GSK sIIVs

GSK sIIV	Initial US Approval
Fluarix	2005
FluLaval	2006
Fluarix Quadrivalent	2012
FluLaval Quadrivalent	2013

7.1.4. Characteristics of exposure

Pregnant women may inadvertently be vaccinated with GSK sIIVs during the first trimester, before pregnancy is known. In general, the women are closely monitored throughout the remainder of the pregnancy.

Refer to Section 9.2.1.2 for potential annual exposure in pregnant women.

7.1.5. Potential benefits of product

Because of the increased rate of hospitalization for serious complications of influenza among pregnant women, particularly in the third trimester [Neuzil, 1998], the CDC Advisory Committee on Immunization Practices (ACIP) recommends that any woman who will be pregnant during the influenza season should be vaccinated for influenza [CDC, 2011] and the American College of Obstetrics and Gynecology guidelines indicate that pregnant women may be vaccinated with IIV during any trimester [ACOG, 2004].

7.2. Rationale

The purpose of this pregnancy registry study is to detect and describe abnormal pregnancy outcomes in women intentionally or unintentionally vaccinated with any of the four GSK sIIVs. The combination of the large number of women who are of reproductive capacity in the indicated age range for vaccination with GSK sIIVs, and the lack of data concerning vaccination during pregnancy, makes such a Registry an important component of the ongoing program to assess the safety of these vaccines. This study is a transition of existing ongoing pregnancy registries for *Fluarix*, *FluLaval*,and *Fluarix Quadrivalent* and an ongoing PASS for *FluLaval Quadrivalent* into a combined PASS for GSK sIIVs. Timelines for collection of follow-up data will be adapted in order to correspond to the follow-up timelines of other GSK pregnancy registries.

The Registry requires voluntary, prospective reporting of eligible pregnancies by patients and healthcare professionals (HCPs). Patient confidentiality is strictly maintained. The intent of the Registry is to prospectively collect data such as vaccination with any of the four GSK sIIVs during pregnancy or within 28 days preceding conception, potential confounding factors (such as exposure to other medications) and information related to the outcome of the pregnancy.

The GSK sIIV pregnancy registry study will be maintained by GSK's Vaccine Clinical Safety and Pharmacovigilance (VCSP) department.

8. RESEARCH QUESTION AND OBJECTIVES

8.1. Co-primary objectives

- To describe the characteristics of prospectively reported pregnancies (women vaccinated with *Fluarix* or *FluLaval* or *Fluarix Quadrivalent* or *FluLaval Quadrivalent* during pregnancy or within 28 days preceding conception) with abnormal pregnancy outcomes.
- To assess the proportion of prospectively reported pregnancies (women vaccinated with *Fluarix* or *FluLaval* or *Fluarix Quadrivalent* or *FluLaval Quadrivalent* during pregnancy or within 28 days preceding conception) with abnormal pregnancy outcomes.

Refer to Section 9.3.1 for the definition of the primary endpoint.

9. RESEARCH METHODS

9.1. Study design

9.1.1. Overview

- This study is a transition of existing ongoing pregnancy registries for *Fluarix*, *FluLaval*,and *Fluarix Quadrivalent* and an ongoing PASS for *FluLaval Quadrivalent* into a combined PASS for GSK sIIVs.
- This is an exploratory, prospective, observational, cohort study. The GSK sIIV pregnancy registry study requires voluntary, prospective* reporting of eligible pregnancies by patients and HCPs. Data such as vaccination with a GSK sIIV during pregnancy or within 28 days preceding conception, potential confounding factors (such as exposure to other medications) and information related to the outcome of the pregnancy will be collected prospectively.

  **Some pregnancy exposures may be reported when the outcome is unknown (prospective reports).*

  Some pregnancy exposures may be reported after pregnancy outcome has been identified (retrospective reports). The Registry will capture retrospective reports, but these reports will not be included in the analyses of prospective reports.
- This study is a post-marketing commitment in the US.
- Study population: pregnant women, vaccinated with GSK sIIV during pregnancy or within 28 days preceding conception, volunteering to take part in the study.
- Type of study: self-contained.
- Data collection: initial and follow-up data will be collected using 2 questionnaires. Follow-up of cases is performed within 3 months of the estimated date of delivery (EDD) to ascertain outcome and approximately 6

months and 12 months after the EDD (for all live births) to ascertain the presence of birth defects not diagnosed before.

- After transition of the ongoing pregnancy registrations into one combined PASS for GSK sIIVs, data will be collected for a minimum of 5 years starting Q2 2014.

9.1.2. Rationale for study design

This study is designed as a Registry. After market authorization, adverse events (AEs) that occur after administration of the vaccine can and should always be reported. In that case, however, there is no clear group in which the events occur and so a proper rate of occurrence cannot be estimated. In this pregnancy registry, participants are recruited between administration of the vaccine and the potential occurrence of an AE (i.e., a teratogenic effect in the offspring). This allows for a more proper estimation of the rate of occurrence of these events. Nevertheless, the results of this study still need to be regarded with caution as the exact number of women exposed during pregnancy is unknown. Incidences of events cannot therefore be calculated from the study data.

Furthermore, it is likely that pregnant women who accept vaccination may differ from those who refuse vaccination in underlying health status, propensity to seek medical care, propensity to report AEs and differences in access to medical care in general. The differential response/participation by vaccinated versus unvaccinated pregnant women in a pregnancy registry could significantly bias risk estimates and possibly in unpredictable ways, because of the inability to collect adequate data to characterize the non-responders. Therefore, the risks of any identified birth defects will be compared to those in the general population, such as that defined by the Metropolitan Atlanta Congenital Defects Program (MACDP).

9.2. Setting

9.2.1. Study population

9.2.1.1. Patient population

In the US, the GSK sIIVs are indicated for prevention of disease caused by influenza A subtype viruses and type B viruses contained in the vaccine. GSK sIIVs are approved for use in persons 3 years of age and older.

The study population includes women vaccinated with any of the four GSK sIIVs during pregnancy or within 28 days preceding conception.

9.2.1.2. Potential annual exposure

Size of the potential "at-risk" population

In the year 2012, the fertility rate in the US was 63.2 births per 1000 women aged 15-44 years and there were 3.96 million births [CDC, 2012].

Number of pregnant vaccinees

The four GSK sIIVs are classified as Pregnancy Category B. Although the number of pregnant women who will be vaccinated with GSK sIIV is impossible to predict, experiences with other vaccine pregnancy registries (e.g., smallpox vaccine [CDC, 2003], varicella vaccine [Shields, 2001] and *Twinrix*) indicate that it is likely that fewer than 100 pregnancies per year will be registered for each of the vaccines.

9.2.2. Patient recruitment

Reporting of vaccine-exposed pregnancies to the Registry is voluntary. Reporters become aware of the Registry through the US Prescribing Information (PI) and the GSK Registry website. The PIs for each of the sIIVs and GSK website each give a brief summary of the purpose and intent of the Registry, along with telephone and fax contact information. Additionally, GSK has requested that information regarding GSK pregnancy registries be posted directly on the FDA website.

9.2.3. Selection of a comparison group

This registry study is a prospective cohort study. Active enrollment of a valid internal comparison group is not possible. The outcomes of the study will be assessed against known rates from an external reference group for the likelihood of a safety signal warranting further investigation. Background risks from existing, external systems (e.g., the National Birth Defects Prevention Network and the National Center for Health Statistics) will be used.

9.2.4. Study period

GSK proposes to continue the Registry for a minimum of 5 years (5 influenza seasons), starting in Q2 2014. Enrollment is planned to take place during the following Northern Hemisphere influenza seasons: 2014-15, 2015-16, 2016-17, 2017-18 and 2018-19. After submission of the final report, GSK will continue the Registry pending CBER review of the report and determination whether the Registry can be discontinued.

9.2.5. Inclusion criteria

A subject will be included in the Registry if all of the following criteria are met:

- Exposure to GSK sIIVs occurs during pregnancy or within 28 days preceding conception.
- Subject is a US resident.
- A HCP is identified (name, address and phone number).
- Subject can be identified (by GSK or HCP).

Data from registered subjects will be included in the analyses if the following criterion is met:

- Pregnancy is ongoing and the outcome is unknown at the time of initial report.

9.2.6. Exclusion criterion

Data from registered subjects will not be included in the analyses if the following criterion is met:

- Outcome of pregnancy is known at the time of initial report. Types of known outcomes include prenatal testing reports in which the results are abnormal or outside the reference range, indicating possible abnormality in the fetus. Pregnancies in which prenatal testing indicates a normal pregnancy would also be excluded because inclusion of such pregnancies could potentially bias results toward a lower overall estimate of risk for defects [Honein, 1999]. Typically pregnancies > 16 weeks gestation will have undergone prenatal testing that can identify whether a child has congenital abnormalities.

9.3. Variables

9.3.1. Primary endpoint

- Occurrence of abnormal pregnancy outcomes in women intentionally or unintentionally vaccinated with *Fluarix* or *FluLaval* or *Fluarix Quadrivalent* or *FluLaval Quadrivalent* during pregnancy or within 28 days preceding conception.

9.3.2. Data to be collected

Data will be collected using 2 questionnaires; one for initial data and one for follow-up data.

9.3.2.1. Questionnaire for initial data collection

The following initial data will be collected using the questionnaire for initial data collection:

- Patient identifier.
- Maternal medical and family history including date of birth, date of last menstrual period (LMP), EDD, ethnicity.
- Type of conception.
- Prenatal testing.
- Number and outcome of previous pregnancies, including details of birth defects if applicable.
- Maternal/paternal history which may have an impact on the outcome of this pregnancy.
- *Fluarix*, *FluLaval*, *Fluarix Quadrivalent* or *FluLaval Quadrivalent* vaccination including lot number and date of administration.
- Other drug/vaccine exposure including drug/vaccine name, route of administration, dose, lot number, indication and date of administration.

- Occurrence of AEs (if any), including onset/end date, outcome and relationship to GSK products.
- HCP name and contact information.
- Any additional data that seems relevant for this study.

9.3.2.2. Questionnaire for follow-up data collection

The following follow-up data will be collected using the questionnaire for follow-up data collection:

- Pregnancy outcome.
- Method of delivery.
- Fetal/neonatal status, including description of birth defects if applicable.
- Infant information including gestational weeks at birth/miscarriage/termination, gender, length, weight, Apgar score.
- Additional drug/vaccine exposure including drug/vaccine name, route of administration, dose, lot number, indication and date of administration.
- AEs experienced by the fetus/infant or the mother.
- HCP name and contact information.
- Any additional data that seems relevant for this study.

9.4. Data sources

Reporting of vaccine-exposed pregnancies to the Registry is voluntary. Registration can be initiated from a HCP or from a consumer; in the latter case permission is requested to obtain confirmation and follow-up from their HCP. A toll-free telephone number for reporting AEs and vaccine-exposed pregnancies to the Registry are listed in the product information leaflets and on the GSK Registry website. Retrospective post-marketing reports and relevant scientific publications are potential sources of additional information.

9.5. Study size

No minimum sample size is required for this descriptive study.

Refer to Section 9.2.1.2 for the size of the potential “at-risk” population and the number of pregnant vaccinees.

9.6. Data management

9.6.1. Data collection

Initial and follow-up data will be collected using 2 questionnaires. Initial data will be collected before the outcome is known. Follow-up of cases is performed at the following timepoints, with each follow-up independent from the others:

- Within 3 months of the EDD, to ascertain outcome. At least three attempts to obtain outcome information will be made before any case is considered lost to follow-up.
- An additional follow-up will be done for all live births approximately 6 months after the EDD to ascertain the presence of birth defects not diagnosed at the time of the initial follow-up.
- The last follow-up will be done approximately 12 months after the EDD to ascertain the presence of birth defects not diagnosed at previous follow-ups.

9.6.2. Processing of reports

Initial reports are entered into the GSK safety database by Client Response Center staff using existing mechanisms and practices. Follow-up is conducted by the Case Management Group. The HCP is contacted if she/he requests or if initial information is insufficient or needs clarification. The HCP is encouraged to keep a copy of the initial completed form in the patient's chart.

9.6.2.1. Solicitation of outcomes

Within three months after the EDD and if the HCP has not already provided the outcome, she/he is sent an outcome form (questionnaire), along with a copy of the initial completed pregnancy form. The mode of communication is the one through which the initial information was received (telephone, fax, or postal mail).

At least three attempts are made to secure the outcome information from the HCP. The second and third attempts utilize all modes of contact available (mail, fax, telephone). If outcome is not received from the HCP and contact information is available for the patient, she is then contacted by mail or fax.

In the event of an abnormal outcome and with the mother's permission, attempts are made to solicit information from the pediatrician and/or other specialists who have provided healthcare/consultation to the child.

9.6.2.2. Classification of outcomes

This Registry uses the term 'birth defects' for outcomes sometimes referred to as 'congenital anomalies'. For purposes of analysis, pregnancy outcomes are dichotomized according to the presence or absence of birth defects. The latter group is

further categorized as: 1) live births, 2) spontaneous abortions (i.e., pregnancy losses) and 3) induced abortions.

This Registry adopts a definition of a child with a birth defect as any live or stillborn neonate with a structural or chromosomal abnormality diagnosed before 6 years of age. The Registry employs a conservative approach of including all morphologic anomalies, including minor ones, as birth defects. To provide consistency in the definitions of major defects in this Registry, CDC MACDP criteria are used for the classification of defects [CDC, 2008; Correa-Villasenor, 2003]. Some of the conditions excluded from the MACDP criteria for major structural defects may actually have major clinical, functional, or genetic significance. Therefore, minor malformations not appearing in the CDC Inclusion List may be classified as birth defects in this Registry. In addition, CDC guidelines disqualify as defects those findings that are present in infants delivered at less than 36 weeks of gestation and are attributable to prematurity itself, such as a patent ductus arteriosus or inguinal hernias. Infants with infectious conditions (e.g., neonatal sepsis) or isolated biochemical abnormalities (e.g., hyperbilirubinemia) are classified as being without birth defects unless there is a possibility that the condition reflects an unrecognized congenital abnormality. All other congenital abnormalities are included in the 'birth defects' category, regardless of whether the neonate is delivered alive, including structural defects in neonates delivered prior to 20 weeks of gestation or weighing less than 500 g.

9.7. Data analysis

Pregnancy outcomes include spontaneous abortion (pregnancy loss before 20 weeks gestation), fetal deaths/stillbirths (loss at or after 20 weeks gestation), elective/therapeutic abortions and live births. Gestational weeks are counted from the date of the LMP. The second trimester is considered to begin at week 14 and the third trimester begins at week 28. The presence or absence of birth defects or other abnormalities is evaluated within each of the preceding outcome categories.

Pregnancy outcomes are stratified by the trimester of exposure, with an additional stratum for preconception exposure with no subsequent administration of vaccine during pregnancy. Receiving multiple administrations of GSK sIIV during a single pregnancy is unlikely; however, if this does occur, reports of multiple exposures during a pregnancy are classified by the earliest trimester of exposure. The calculations of risk for birth defects are made by dividing the number of infants with birth defects by the total number of infants with and without birth defects. An exact 95% confidence interval is calculated using standard statistical software. The outcomes of the study will be assessed against known rates from an external reference group for the likelihood of a safety signal warranting further investigation. In each periodic and the final reports, the data will be analyzed for all GSK sIIVs pooled and for each of the 4 vaccines separately. The analyses will also include data collected cumulatively in each individual registry up to the initiation of the combined Registry for GSK sIIVs.

The majority of spontaneous abortions occur early in pregnancy [Wilcox, 1981; Wilcox, 1983; Ellish, 1996]. If spontaneous abortions were to be evaluated as an outcome of interest, it would be essential to enroll pregnancies as soon as possible after

vaccination with GSK sIIV. Because enrollment and recognition of pregnancy would occur at various times, it would be virtually impossible to meaningfully evaluate the effects of GSK sIIV on pregnancy loss [Kennedy, 2004]. Therefore, spontaneous abortions without birth defects are excluded from the risk calculations.

The risk in the general population of all birth defects meeting CDC criteria is approximately 3% (1 of 33) of live births [CDC, 2013]. The estimated risk cited in the medical literature varies because of differences in case definitions, populations sampled and ascertainment methods. The Collaborative Prenatal Project, using a broader case definition and prospective ascertainment, reports a frequency of 5% to 7% [Chung, 1975]. Most major structural defects originate during the first trimester of pregnancy, which is the critical time for organogenesis [Niebyl, 2012]. For such defects, exposures occurring in the second or third trimester are not likely to be causally associated. However, for the sake of completeness and to enable the assessment of possible increases in the frequency of birth defects, all defects will be included in the periodic summary reports of this Registry and stratified by trimester of exposure.

Criteria for review of a specific individual report include:

- Is the timing of the vaccination with GSK sIIVs commensurate with the ontogenetic development of the organ(s) affected by the abnormalities?
- Is there another known or likely cause (e.g., pre-existing genetic or chromosomal defect or exposure to a known teratogen)?
- Is the congenital abnormality not previously described (i.e., is it new to medical science)?
- Is there a unique constellation of defects (i.e., is there a new syndrome)?

Criteria for review of aggregate data include:

- Is there a deviation from the expected frequency of all defects indicating an increase in the overall risk of defects?
- Is there a deviation from the expected frequencies of individual defects?
- Is there uniqueness (e.g., a pattern) of the abnormalities that is suggestive of a common etiology?

Studies have shown the risk of spontaneous abortion is high early in pregnancy and decreases substantially from week 8 to week 28, yielding a cumulative estimated risk of 10% to 22% [Wilcox, 1981; Wilcox, 1983; Wilcox, 1988; Fenster, 1997; Windham, 1997; Khattak, 1999; Anderson, 2000; Osborn, 2000].

While the Registry is to be limited to prospective reports, some pregnancy exposures are reported after pregnancy outcome has been identified (retrospective reports). The Registry will capture retrospective reports, but these reports will not be included in the analyses of prospective reports. In general, retrospective notification of outcomes following exposure to drugs or vaccines is biased toward reporting the severe and unusual cases and is not reflective of the general experience with the drug. Information

about the total number of exposed pregnancies, i.e., the pool of exposures from which the retrospective reports arise, is unknown; therefore, incidences of outcomes cannot be calculated from these data. A series of reported birth defects, however, can be analyzed to detect patterns of specific congenital abnormalities and can identify early signals of new vaccine-associated risks. A section of each periodic summary report, separate from the analysis of prospective reports, will describe all abnormal outcomes of retrospectively reported cases.

9.8. Quality control

Data will be recorded using questionnaires. Subject data necessary for analysis, follow-up and reporting will be entered/transmitted into a validated database or data system. Data management will be performed in accordance with applicable GSK standards.

To ensure compliance with Good Clinical Practice (GCP) and all other applicable guidelines and regulatory requirements, GSK may conduct a quality assurance audit. Regulatory agencies may also conduct a regulatory inspection of this study. Such audits/inspections can occur at any time during or after completion of the study.

9.9. Limitations of the research methods

This Registry is a prospective cohort study. Active enrollment of a valid internal comparison group is not possible. Therefore, background risks from existing, external systems (e.g., the National Birth Defects Prevention Network and the National Center for Health Statistics) are used. The potential limitations of comparisons between Registry and background data depends upon the event(s) being compared and will be discussed on an *ad hoc* basis in the relevant periodic Registry reports. In addition, variations in the year-to-year (or strain), resulting in differences in the safety profiles of the vaccines, remain a possible limitation.

Refer to Section 9.1.2 for other potential limitations of the study.

10. PROTECTION OF HUMAN SUBJECTS

10.1. Regulatory and ethical considerations, including the informed consent process

The study will be conducted in accordance with the International Conference on Harmonization (ICH) Guideline for GCP or other applicable guidelines, all applicable subject privacy requirements and the guiding principles of the Declaration of Helsinki.

The study has been designed and will be conducted in accordance with the ICH Harmonized Tripartite Guideline for clinical investigation of medicinal products in the pediatric population (ICH E11) and all other applicable ethical guidelines.

GSK will obtain favorable opinion/approval to conduct the study prior to study start or will document that neither a favorable opinion nor an approval to conduct the study is needed.

Conduct of the study includes, but is not limited to, the following:

- Institutional Review Board review and favorable opinion/approval of study protocol and any subsequent amendments;
- Institutional Review Board review and favorable opinion/approval of waiver for documentation of informed consent.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Reporting of vaccine-exposed pregnancies to the Registry is voluntary. All reports received by the Registry will be entered into the GSK safety database and reported to regulatory authorities according to applicable regulations.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Study information from this protocol will be posted on publicly available clinical trial registers following finalization of the protocol and, whenever possible, before initiation of the study.

GSK plans to continue the Registry for a minimum of 5 years. Summary reports will be written annually and will be submitted with the Periodic Benefit-Risk Evaluation Report for each GSK sIIV. Each report will summarize the adverse pregnancy outcomes that have been identified since the previous report and will also summarize cumulative results since the inception of the individual Registry. A final report will be written and submitted to CBER after the 5th annual report. In each periodic and the final reports, the data will be analyzed for all GSK sIIVs pooled and for each of the 4 vaccines separately. The analyses will also include data collected cumulatively in each individual registry up to the initiation of the combined Registry for GSK sIIVs. After submission of the final report, GSK will continue the Registry pending CBER review of the report and determination whether the Registry can be discontinued.

Summary results of observational studies that are designed to inform the safety or effectiveness, including cost-effectiveness, of GSK vaccines/products as used in ordinary clinical practice are publicly registered within 8 months of completion of the analysis. GSK also aims to publish the results of these studies in the searchable, peer reviewed scientific literature; manuscripts are submitted within 18 months of the completion of the analysis.

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ANNEX 1 List of stand-alone documents

No.	Document Reference No	Date	Title
1	201476 (EPI-FLU-039 VS US PR)	13-MAY-2014	List of stand-alone documents
2	201476 (EPI-FLU-039 VS US PR)	13-MAY-2014	ENCePP Checklist for study protocols
3	201476 (EPI-FLU-039 VS US PR)	13-MAY-2014	Glossary of terms
4	201476 (EPI-FLU-039 VS US PR)	13-MAY-2014	Trademarks
5	201476 (EPI-FLU-039 VS US PR)	13-MAY-2014	Protocol Sponsor Signatory Approval

ANNEX 2 ENCePP Checklist for study protocols

ANNEX 3 Glossary of terms

Adverse event:	Any untoward medical occurrence in a subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product, or temporally associated with a study procedure. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e., lack of efficacy), abuse or misuse.
eTrack:	GSK Biologicals' tracking tool for clinical/ epidemiological trials.
GSK seasonal Inactivated Influenza Vaccines (GSK sIIVs):	Fluarix®/ FluLaval®/ Fluarix® Quadrivalent/ FluLaval® Quadrivalent vaccines
Non-interventional (observational) Human Subject Research:	Studies where medicinal products, should they be administered, are prescribed in normal (routine) medical practice. No medical care or medical/scientific procedures as required in a research protocol are administered to participants except as part of routine medical care.
Post-Authorization Safety Study (PASS):	A pharmaco-epidemiological study or a clinical trial carried out in accordance with the terms of the marketing authorization, conducted with the aim of identifying or quantifying a safety hazard relating to an authorized medicinal product. This includes all GSK sponsored non-interventional studies and clinical trials conducted anywhere in the world that are in accordance with the terms of the European marketing authorization and where the investigation of safety is the specific stated objective. Note: The phrase 'In accordance with the terms of the European marketing authorization' means that the product is used according to the European label (e.g., within the recommended dose range, the approved formulation, indication etc.).
Prospective study:	A study that looks ahead for outcomes, e.g., the development of a disease, during the study period and relates this to other factors such as a potential risk due to exposure or protection factor(s). The study usually involves taking a cohort of subjects and watching them

	over a period for one or more common outcomes of interest.
Protocol amendment:	The International Conference on Harmonization (ICH) defines a protocol amendment as: 'A written description of a change(s) to or formal clarification of a protocol.' GSK Biologicals further details this to include a change to an approved protocol that affects the safety of subjects, scope of the investigation, study design, or scientific integrity of the study.
Research protocol:	A document that describes the objective(s), design, methodology, statistical considerations and organization of a study. The protocol usually also gives the background and rationale for the study, but these could be provided in other protocol referenced documents.
Retrospective study:	A study that looks backward in time (e.g., at events that occurred in the past; outcomes and exposure can no longer be influenced), usually using medical records, databases or interviews in order to address one or more study objectives.
Self-contained study:	Study with objectives not linked to the data of another study.
Study population:	Sample of population of interest.
Subject:	Term used throughout the protocol to denote an individual who has been contacted in order to participate or participates in the epidemiological study or a person about whom some medical information has been recorded in a database.

ANNEX 4 Trademarks

The following trademarks are used in the present study outline. Note: In the remainder of the document, the names of the vaccines will be written without the superscript symbol ™ or ®.

Trademarks of the GlaxoSmithKline group of companies	Generic description
Fluarix®	trivalent inactivated influenza virus vaccine
Fluarix® Quadrivalent	quadrivalent inactivated influenza virus vaccine
FluLaval®	trivalent inactivated influenza virus vaccine
FluLaval® Quadrivalent	quadrivalent inactivated influenza virus vaccine
Twinrix®	hepatitis A inactivated & hepatitis B (recombinant) vaccine

ANNEX 5 Protocol sponsor signatory approval

eTrack study number and Abbreviated Title	201476 (EPI-FLU-039 VS US PR)
Date of protocol	Final Version 1: 13 May 2014
Detailed Title	Fluarix®/ FluLaval®/ Fluarix® Quadrivalent/ FluLaval® Quadrivalent Pregnancy Registry: a prospective, exploratory, cohort study to detect and describe abnormal pregnancy outcomes in women intentionally or unintentionally vaccinated with Fluarix® or Fluarix® Quadrivalent or FluLaval® or FluLaval® Quadrivalent during pregnancy or within 28 days preceding conception.
Sponsor signatory	[redacted] VP, Head Vaccine Clinical Safety and Pharmacovigilance
Signature	_____
Date	_____