Title	BEXSERO® pregnancy registry: an observational study of the safety of BEXSERO exposure in pregnant women and their offspring.
Protocol version identifier	Version 2
Date of last version of protocol	12 AUG 2016
EU PAS Register No:	EUPAS 12183
Active substance	Recombinant *Neisseria meningitidis* group B NHBA/NadA/fHbp proteins (50/50/50 micrograms); outer membrane vesicles (OMV) from *Neisseria meningitidis* group B strain NZ98/254 measured as amount of total protein containing the PorA P1.4 (25 micrograms).
Medicinal product	BEXSERO suspension for injection in pre-filled syringe Meningococcal Group B Vaccine (rDNA, component, *adsorbed)*.
Product reference	Not applicable.
Procedure number	Not applicable.
Marketing authorisation holder(s)	GlaxoSmithKline Biologicals S.A
Joint PASS study	No
Research question and objectives	The objective of the BEXSERO Pregnancy Registry is to evaluate pregnancy outcomes among women immunized with the BEXSERO vaccine within 30 days prior to the last menstrual period or at any time during pregnancy. The primary outcomes of interest include major congenital malformation, preterm birth, and low birth weight.
Country(ies) of study	United States

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Marketing authorisation holder(s)

Marketing authorisation holder(s)	GlaxoSmithKline Biologicals S.A Rue de l'Institut 89 BE – 1330 Rixensart Belgium
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2. LIST OF ABBREVIATIONS

ACIP	Advisory Committee on Immunization Practices
AE	Adverse event
CBER	Center for Biologics Evaluation and Review
CEDD	Corrected estimated date of delivery
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CRF	Case report form
DSUR	Development Safety Update Report
EDC	Electronic data capture
EDD	Estimated date of delivery
ELISA	Enzyme-linked immunosorbent assay
FDA	Food and Drug Administration
GPP	Good Pharmacoepidemiological Practice
GSK	GlaxoSmithKline Biologicals S.A.
HCP	Health care provider
HIPAA	Health Insurance Portability and Accountability Act
HMO	Health maintenance organization
IAB	Induced abortion
ICH	International Conference on Harmonisation
ICSR	Individual Case Safety Reports
IMD	Invasive meningococcal disease
IRB	Institutional review board

LMP	Last menstrual period
LBW	Low birth weight
MACDP	Metropolitan Atlanta Congenital Defects Program
MAH	Market Authorisation Holder
MCM	Major congenital malformation
MSL	Medical science liaison
NVSS	National Vital Statistics System
PMC	Post-marketing commitment
PSUR	Periodic Safety Update Report
RCC	Registry Coordination Center
SAB	Spontaneous abortion
SAC	Scientific Advisory Committee
SAEs	Serious adverse events
SAP	Statistical analysis plan
SBA	Serum bactericidal assay
SOP	Standard operating procedure
STROBE	STrengthening the Reporting of OBservational studies in Epidemiology
US	United States

3. RESPONSIBLE PARTIES

3.1 Main Author(s) of the Protocol

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3.2 Principal Investigator

[redacted], MD, PPD

3.3 Coordinating Investigator(s)

Not applicable.

3.4 Advisory Committee

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

4. ABSTRACT

Name of MAH: GlaxoSmithKline Biologicals S.A.	**Protocol number:** V72_82OB	**Date of Protocol Abstract:** 12 AUG 16
Title of Study: BEXSERO pregnancy registry: an observational study of the safety of BEXSERO exposure in pregnant women and their offspring		
Study Period: Enrollment in the pregnancy registry will commence on 31 January 2016 and will continue for a period of 3 years or pending review by the Center for Biologics Evaluation and Research (CBER), and discussion of results with GlaxoSmithKline S.A. (GSK) will submit a full study report to CBER by 31 May 2020. The data collection process for each participant will begin at enrollment (post exposure to BEXSERO within 30 days of the last menstrual period or at any time during the pregnancy), and follow-up will occur at the end of the second trimester (approximately 24 weeks' gestation) and at pregnancy outcome (delivery or early termination).	**Study Type:** This study is designed to meet a post-marketing commitment (PMC) agreed upon with CBER to establish a pregnancy registry to prospectively collect data on pregnancy exposures to BEXSERO.	
Rationale and Background: The BEXSERO Pregnancy Registry is established to meet a CBER PMC and is designed to collect prospective data on pregnancy outcomes among pregnant women vaccinated with BEXSERO within 30 days prior to the last menstrual period (LMP) or at any time during pregnancy. BEXSERO was approved by the Food and Drug Administration (FDA) for use in individuals 10 through 25 years of age in January 2015. Subsequently, the Advisory Committee on Immunization Practices recommended that a serogroup B meningococcal vaccine should be administered to persons in the United States (US) aged ≥10 years who are at increased risk of meningococcal disease (those with persistent complement component deficiencies, anatomic or functional asplenia, microbiologists routinely exposed to isolates of *Neisseria meningitidis* and persons identified to be at increased risk because of a serogroup B meningococcal disease outbreak). BEXSERO is not contraindicated during		

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pregnancy, but should be used during pregnancy only if clearly needed. Inadvertent exposure during pregnancy may also occur because the age group targeted for vaccination includes young women of reproductive potential. The registry will add to the current clinical experience with BEXSERO®, supplementing data from animal toxicology studies and human exposure data. Pregnancy data will be collected at registry enrollment, at the end of the second trimester of pregnancy, and at pregnancy outcome for both mother and infant. GSK sponsors the registry in consultation with specialists from appropriate fields such as obstetrics, pediatrics, clinical research, genetics, epidemiology, and teratology from academic institutions, private practice, and/or government agencies. These individuals constitute the Scientific Advisory Committee (SAC) and will provide an independent review of registry data.

Research Question and Objectives: The objective of the BEXSERO Pregnancy Registry is to evaluate pregnancy outcomes among women immunized with the BEXSERO vaccine within 30 days prior to LMP or at any time during pregnancy. The primary outcomes of interest include major congenital malformation (MCM), preterm birth, and low birth weight (LBW). Other pregnancy outcomes will also be collected, including spontaneous abortions (SABs) and stillbirths.

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

Study Design: The BEXSERO Pregnancy Registry is a prospective, observational study of women immunized with the BEXSERO vaccine within 30 days prior to LMP or at any time during pregnancy as part of routine care. It is strictly observational; the schedule of office visits and all treatment regimens will be determined by the treating health care provider (HCP). This phase 4 pregnancy registry follows current FDA guidance for designing and implementing pregnancy exposure registries (FDA, 2002).

Population: The study population will include pregnant women within the US who received at least 1 dose BEXSERO vaccine within 30 days prior to LMP or at any time during pregnancy. BEXSERO is not contraindicated during pregnancy but should be used only if clearly needed and inadvertent exposure during pregnancy may occur, particularly during the early stages of pregnancy before pregnancy status is known. Enrollment and data collection will be coordinated through a registry coordination center (RCC). The registry will allow eligible pregnant women to self-enroll and also allow HCPs and/or health maintenance organizations (HMOs) to report de-identified

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data on pregnancy exposures and outcomes. An evaluable subject is a pregnant woman with data submitted and/or confirmed by an HCP that contains at least the minimum criteria for a report and is not lost to follow-up. The minimum criteria required for enrollment into the registry are as follows:

- Sufficient evidence to confirm that exposure to a meningococcal B vaccine (confirmed or possible BEXSERO exposure) occurred within 30 days prior to LMP or at any time during pregnancy
- Sufficient information to determine whether the pregnancy is prospectively or retrospectively registered (i.e., whether the outcome of pregnancy was known at the time of first contact with the registry)
- Date the pregnancy exposure is registered
- Full reporter (i.e., HCP) contact information to allow for follow-up (name, address, etc.)

In the event that it cannot be ascertained to which meningococcal B vaccine the woman was exposed, an unknown exposure cohort will be established and analyzed separately. Because registry enrollment is open to all eligible pregnant women, an active recruitment campaign will reach out to immunization providers and their patients in a broad variety of settings. The recruitment strategy will target HCPs who are known to immunize patients specifically with the BEXSERO vaccine. These providers could be identified through GSK BEXSERO distribution data and/or medical science liaisons, as well as HCP networks and HMOs. Recruitment strategies could include the distribution of informational kits to HCPs and their patients and ongoing awareness and educational activities via the internet and/or through other media.

The primary population for analysis will include prospectively enrolled pregnant women exposed to at least 1 dose of BEXSERO who are not lost to follow-up (i.e., with outcome information that meet the minimum criteria for evaluation). In the event that a fetal abnormality is identified on a diagnostic prenatal test prior to enrollment (i.e., that the pregnancy outcome is presumed known at enrollment), this will be considered a retrospective report and will also be included in this study. Retrospective reports can be biased toward the reporting of more unusual and severe cases and are less likely to be representative of the general population experience than cases reported prior to knowledge of the outcome. Therefore, retrospective reports will not be included in the primary analysis and statistical calculations. Retrospective reports with reported MCMs

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will be captured in the registry and reviewed to aid in detection of early signals and will be listed in registry reports.

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

Background prevalence estimates from external surveillance sources and estimates from published literature will be the primary comparators. Background estimates in the general population on pregnancy outcomes, such as preterm birth and LBW, are readily available from national vital statistics (Martin, 2015). Published prevalence estimates of MCMs are available from the Centers for Disease Control and Prevention's (CDC's) Metropolitan Atlanta Congenital Defects Program (MACDP), which is an ongoing population-based birth defects surveillance program (Correa, 2007). To the extent possible, comparator prevalence estimates will be age-adjusted to reflect the age distribution of the BEXSERO Pregnancy Registry population.

Variables:

Exposure(s) of interest

This pregnancy registry is strictly observational. Although not contraindicated during pregnancy, BEXSERO should be used during pregnancy only if clearly needed. Inadvertent exposure during pregnancy may also occur, particularly during the early stages of pregnancy before pregnancy status is known. When a pregnant woman self-enrolls in the registry, she will be asked when and where she was immunized with the BEXSERO vaccine, or any meningococcal B vaccine if the brand is unknown. She will then be asked to provide a medical release that allows the registry to confirm with the appropriate source the exposure to a meningococcal B vaccine occurred. The registry will contact the vaccine provider to confirm the vaccination date, brand, and lot number. If HCPs provide de-identified data to the registry, they must be able to verify the vaccination with BEXSERO and date of vaccination.

Outcome(s)

Major congenital malformation (MCM): The registry defines an MCM as any major

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structural or chromosomal defect or combination of 2 or more conditional defects in live-born infants, stillbirths, or fetal losses of any gestational age (including outcomes prior to 20 weeks' gestation or weighing <500 g). This definition is consistent with, but not restricted to, the CDC MACDP definition (which includes conditional defects only if they occur in the presence of a major defect) and thus increases the sensitivity of monitoring.

Preterm birth: An infant born at gestational age <37 weeks.

Low birth weight (LBW): An infant whose birth weight is <2500 g.

Outcome variables will be provided by the obstetric HCP and/or pediatrician attending the birth. The HCP will be asked to describe any congenital malformations observed in the infant or fetus and will also be asked to report the gestational age and birth weight. These 2 variables will be used to calculate preterm birth (gestational age <37 weeks at birth) and LBW (birth weight <2500 g).

A teratologist/geneticist will review all reported congenital anomalies and classify them using the CDC's MACDP system. Additionally, the teratologist/geneticist will provide an opinion regarding the possible temporal association of the BEXSERO exposure to the development of observed defects. The SAC will meet periodically to review the data and reach consensus on the coding and classification of MCMs and other outcomes of interest.

Other Variables

Maternal characteristics: Age, ethnicity, race

Prenatal data: LMP, estimated date of delivery (EDD), corrected estimated date of delivery (CEDD)

Obstetrical history: Previous pregnancies, live births, stillbirths, SABs, induced abortions (IABs), births with congenital malformations, family history of congenital malformations.

Concurrent medical conditions

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Concomitant medications and vaccines

Alcohol, tobacco, and illicit drug use

Pregnancy outcomes

Each pregnancy outcome will be classified in 1 of the following mutually exclusive categories:

- Live birth: an infant born alive
- Stillbirth: fetal death occurring at or after 20 weeks' gestation, or if gestational age is unknown, a fetus weighing 500 g or more.
- Spontaneous abortions (SABs): fetal death or expulsion of products of conception prior to 20 weeks' gestation, or if gestational age is unknown, weighing less than 500g. Terminology may include missed abortion, incomplete abortion, and inevitable abortion.
- Induced abortions (IABs): voluntary interruption of pregnancy, including pregnancy termination that occurs electively, to preserve maternal health, or due to fetal abnormalities
- Ectopic pregnancy: implantation of a conception outside of the uterus
- Molar pregnancy: a conception that results in a gestational trophoblastic tumor

Data Sources: The pregnant woman and/or appropriate members of her health care team will serve as data reporters to the registry. The registry is strictly observational; the schedule of office visits and all treatment regimens will be determined by the treating HCP. There are no additional laboratory tests or assessments required as part of this registry. Only data noted as part of routine care will be collected.

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Study Size: The pregnancy registry is a PMC agreed upon with the CBER to commence enrollment on 31 January 2016 and to continue for a period of 3 years or pending CBER review and discussion of results with GSK. GSK will submit a full study report to CBER by 31 May 2020.

The registry will prospectively enroll women with exposure to a meningococcal B vaccine 30 days prior to LMP or at any time during pregnancy. The primary population for analysis will be those vaccinated with BEXSERO only. In the event that it cannot be ascertained to which meningococcal B vaccine the woman was exposed, an unknown exposure cohort will be established and analyzed separately.

BEXSERO is not contraindicated during pregnancy, but should be used during pregnancy only if clearly needed. Under current ACIP recommendations, the CDC estimates that approximately 350,000 individuals will be advised to receive a meningococcal B vaccine (MacNeil, 2015), of whom it is likely that a small proportion will be exposed during pregnancy. There are uncertainties regarding the degree of market penetration and vaccine uptake that will be achieved in at-risk groups. A recent US study of the safety of Cervarix® in pregnancy was terminated due to low accrual of subjects attributed to low uptake of the vaccine in the US (GSK, 2015). To account for this, and that the proportion of clinically recognized pregnancies that can be expected to result in a live birth is approximately 62% (Martin, 2015), a range of sample size estimates was considered, from a minimum of 5 to 150 live births.

It is likely that the majority of exposures will occur inadvertently within 30 days prior to LMP or early in the first trimester before pregnancy status is known. If exposures occur later in pregnancy, results will be stratified by trimester of exposure, acknowledging that the power of stratified analyses to detect low prevalences will be limited by the sample size of each subgroup.

According to the CDC MACDP, the prevalence of MCMs for mothers <25 years of age in the US is 2.54% (Correa, 2007). According to the CDC National Vital Statistics System (NVSS), the prevalence of preterm birth and LBW for mothers <25 years of age are 11.71% and 8.50%, respectively (Martin, 2015).

The table below depicts sample sizes of 5, 20, 50, 100, and 150 live births and the associated effect sizes (i.e., the ratio of the registry-derived prevalence versus the reference prevalence) that would be detectable using a binomial distribution, a power of 80%, and a 1-sided Type I (false positive) error rate of 5% (Altman, 1991). For

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example, with a sample size of 100 live births, the study will have 80% power to detect a 1.79-fold increase in the prevalence of preterm birth compared with the reference of 11.71% (population prevalence). In other words, if the registry-derived prevalence estimate is at least 1.79 times higher than the reference prevalence of preterm birth, the 1-sided 95% confidence interval for the estimate will exclude 11.71% (i.e., will lie above 11.71%), with a probability of 80%.

Table 4.1 Detectable effect size assuming 80% power

Sample Size (N of live births)	Effect Size (ratio of the registry-derived prevalence versus the reference prevalence for mothers <25 years of age)		
	MCM [reference = 2.54%]	PTB [reference = 11.71%]	LBW [reference = 8.50%]
5	19.30	5.75	7.92
20	7.95	3.13	3.69
50	4.23	2.24	2.59
100	3.07	1.79	1.96
150	2.66	1.63	1.82

Abbreviations: LBW = low birth weight; MCM = major congenital malformation; PTB = preterm birth.

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

Demographic and baseline characteristics will be summarized with simple descriptive statistics and data listings for the evaluable populations of pregnant women and live births. Demographic and baseline characteristics will also be summarized for the population that is lost to follow-up and compared with the evaluable populations to assess potential differences. These data will be reviewed for potential confounding factors that could affect the interpretation of comparisons of registry outcome prevalence estimates with that of comparators.

Overall and stratum-specific point estimates and 95% confidence intervals will be calculated using the binomial distribution for prevalence estimates of MCMs, preterm birth, and LBW among pregnant women exposed to at least 1 dose of BEXSEROand their live births. For each prevalence estimate, both 1-sided and 2-sided 95% confidence intervals will be calculated and reported. One-sided confidence

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intervals are appropriate, as we are specifically interested in detecting outcome prevalence estimates greater than the respective reference prevalences, and 2-sided confidence intervals will provide further description of the accuracy of the estimates.

For MCM, the overall prevalence of MCM will be reported. Since most structural defects have their origins in the first trimester of pregnancy during the period of organogenesis, analyses of MCM will be stratified by trimester of exposure if applicable. It is expected that the vast majority (99%) of prenatal exposures will occur during the first trimester before the pregnancy is recognized. The prevalence of combined MCMs reported to the registry will be calculated as a proportion, with the number of MCMs as the numerator and the number of live births as the denominator. Fetal losses with reported MCMs occurring at or after 20 weeks' gestation will be included in the numerator of the estimate of risk for MCMs to increase sensitivity and to allow comparison with the CDC MACDP, which calculates prevalence by this convention. A secondary analysis will be conducted including fetal losses with reported MCMs occurring at less than 20 weeks' gestation in the calculation of prevalence. The prevalence of combined MCMs in exposed subjects will be compared with that of the CDC MACDP (Correa, 2007). The prevalence of preterm births and LBW will be calculated as proportions, with the number of live births as the denominator. These prevalence estimates in exposed subjects will be compared with those of the CDC NVSS (Martin, 2015).

Informed Consent and Ethical Approval: As a post-marketing safety reporting activity, this registry qualifies for exemption of US Health Insurance Portability and Accountability Act (HIPAA) authorization. It also qualifies for a waiver of documentation of informed consent (verbal consent) for adult women who self-enroll, and it qualifies for a waiver of informed consent for de-identified data reported to the registry. If a minor requests participation in the registry and all eligibility criteria are met, the registry will obtain assent from the minor and signed written consent from the parent or guardian. The protocol and informed consent waivers will be submitted to an institutional review board (IRB) for approval prior to registry implementation.

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Criteria for Study Termination

In accordance with FDA guidance (FDA, 2002), criteria for discontinuing the registry will include insufficient sample size recruitment, unacceptably low levels of exposure or enrollment, and/or the availability of more appropriate methods to gather relevant information. It is proposed that enrollment in the pregnancy registry will be reviewed by CBER on receipt of each annual report, and an appropriate course of action will be agreed upon after discussion with GSK. The registry acknowledges the challenges of enrolling exposed pregnancies in a young population of limited size in the US and will carefully monitor enrollment trends and outcomes. This is an open registry with initiation of patient recruitment from the time of launch.

Milestones:

Start of data collection: 31 January 2016.

End of data collection: The pregnancy registry will continue enrolling exposed pregnancies for a period of 3 years or pending CBER review and discussion of results with GSK.

Annual interim reports will be submitted to CBER per the PMC and GSK will submit a full study report to CBER by 31 May 2020.

5. AMENDMENTS AND UPDATES

Number	Date	Section of the study protocol	Amendment or update	Reason
1	12AUG16	Throughout the text of this protocol.	Amendment	To reflect the change of Sponsor from Novartis Vaccines and Diagnostics Inc. to GlaxoSmithKline Biologicals S.A.
1	12AUG16	page 1	Amendment	EU PAS register number has been added in the coversheet.
1	12AUG16	Throughout the text of this protocol.	Amendment	The name of the vaccine (BEXSERO) has been capitalized.
1	12AUG16	Annex 2 ENCEPP CHECKLIST	Amendment	ENCePP Checklist updated and attached to this protocol.

6. MILESTONES

Table 6-1 Overview of study milestones.

Milestone	Planned date
Start of data collection	31 January 2016
End of data collection	The pregnancy registry will continue enrolling exposed pregnancies for a period of 3 years (final enrollment: 31 January 2019) and subsequent follow-up of enrolled infants will continue until 30 November 2019 (maximum 10 months follow-up post enrolment) or pending CBER review and discussion of results with GSK.
Annual updates	Annual interim reports will be provided to CBER per the PMC.
Final report of study results	A final report will be produced approximately 6 months after all data have been collected and cleaned and will be submitted to CBER by 31 May 2020.

Abbreviations: CBER = Center for Biologics Evaluation and Review; IRB = institutional review board; GSK = GlaxoSmithKline Biologicals S.A.

7. RATIONALE AND BACKGROUND

The gram-negative bacterium *Neisseria meningitidis* is the most common cause of bacterial meningitis in children and young adults in developed countries (Khatami, 2010). For the majority, exposure results in asymptomatic nasopharyngeal carriage. For those who develop invasive meningococcal disease (IMD), the disease spectrum ranges in severity from mild influenza-like illness to meningoencephalitis, prostration, and death in 10% to 15% of patients. Long-term side effects including neurological deficit, limb amputation, hearing loss, blindness, and skin scarring can occur in up to 20% of cases (Edmond, 2010).

Six major meningococcal serogroups are associated with invasive disease: A, B, C, W, X, and Y (Stephens 2007a). Serogroup prevalence varies with geography, time of year, and age group. Serogroups B, C, and Y strains are currently the most prevalent in North America (Stephens, 2007b), while serogroup B and C strains are the most prevalent in Europe (ECDC, 2015); serogroup A strains (which have largely disappeared from Europe and North America) are responsible for large annual epidemics of bacteremia and meningitis in sub-Saharan Africa (WHO, 2014). Serogroups W and X meningococci have been responsible for epidemics in sub-Saharan Africa since 2002 (Stephens, 2007).

The incidence of IMD in the United States (US) has fluctuated cyclically since the early 1970s, ranging from 0.5 to 1.5 cases per 100,000 population. Since 1996, the incidence has declined sharply and in 2012 the incidence was 0.18/100,000, serogroup B accounting for 0.04/100,000 cases (Adams, 2014). The incidence is highest in infants aged <1 year, with a second peak occurring in adolescents and young adults (Cohn, 2013). Most IMD cases are sporadic, but between 2009 and 2015, there were 32 cases of serogroup B meningococcal disease associated with outbreaks at 5 US universities, including 1 fatality (MacNeil, 2015).

Since 2010, routine use of quadrivalent meningococcal conjugate vaccine covering serogroups A, C, W, and Y is recommended in the US for adolescents and others at increased risk for meningococcal disease (Cohn, 2013). More recently, vaccines against serogroup B disease have been approved by the Food and Drug Administration (FDA) for use in individuals 10 through 25 years of age (FDA, 2014; FDA, 2015). In February 2015, the Advisory Committee on Immunization Practices (ACIP) recommended that a meningococcal group B vaccine should be administered to persons in the US aged ≥10 years who are at increased risk for meningococcal disease. This includes persons with persistent complement component deficiencies (estimated at approximately 80,000 persons in the US), persons with anatomic or functional asplenia (approximately 100,000 persons), microbiologists routinely exposed to isolates of *Neisseria meningitides* (approximately 100,000 persons), and persons identified to be at increased risk because of a serogroup B meningococcal disease outbreak (approximately 60,000 between 2009 and 2013) (MacNeil, 2015).

BEXSERO was developed by to help confer protection against a broad range of meningococcal B strains causing disease. It is formulated with 3 major recombinant proteins (factor H binding protein, neisserial heparin binding antigen, and *Neisseria* adhesin A) combined with bacterial outer membrane vesicles derived from the New Zealand outbreak strain NZ98/254, containing PorA type P1.4 as the main antigen (Giuliani, 2006) and aluminium hydroxide as an adsorbent. In those aged 10 to 25 years, it should be administered in a 2-dose schedule (0.5 mL each), each dose at least 1 month apart (Bexsero® prescribing information, 2015).

GSK did not study vaccination in pregnancy as one of the objectives of clinical studies pre-licensure; pregnant women were excluded from enrollment, and the use of birth control, where appropriate, was an entry criterion. Well-controlled studies in pregnant women are otherwise not available; however, during participation in 1 of 6 Legacy Novartis (GSK) sponsored studies (V72P10, V72_29, V72_41 V102_03) and supportive studies (V72P4 and V72P5), 32 subjects became pregnant (Rastogi, 2015). Of these, 25 had received at least 1 dose of BEXSERO 20 gave birth to live-born infants with no abnormalities, 1 had a therapeutic abortion, and 1 had an ectopic pregnancy. Two women gave birth to live-born infants with congenital abnormalities: Prader-Willi syndrome and absence of second toe of 1 foot. The latter infant died at 2 months after birth from sudden infant death syndrome. Independent review of each pregnancy outcome found no association with BEXSERO vaccination (Rastogi, 2015). For 1 participant, the outcome is unknown because the subject was lost to follow-up. In response to outbreaks in universities in the US, the Centers for Disease Control and Prevention (CDC) sponsored 2 studies in which pregnant women were eligible to enroll. As of 27 June 2014, 5 pregnancies were reported in the CDC-sponsored studies at Princeton University and the University of California, Santa Barbara. For all 5 women, therapeutic abortion was planned (Baumblatt, 2015).

Reproduction studies have been performed in female rabbits at BEXSERO doses up to 15 times the human dose on a body weight basis and have revealed no evidence of impaired fertility or harm to the fetus due to BEXSERO. A summary of these studies is provided as follows:

The pilot embryofetal dose-range developmental toxicity study in rabbits (GLP Study No. UBA00041) tested 5 doses (3 prior to mating and 2 during gestation) at 1 to 2 times the highest anticipated human clinical dose of BEXSERO. No hazard of vaccination to maternal animals or the developing fetuses was identified. (Pilaro, 2004; cited by Ching-Long, 2014).The vaccine was immunogenic in maternal animals, and fetuses had circulating antibodies (enzyme-linked immunosorbent assay [ELISA] and serum bactericidal assay [SBA] with rabbit complement).

The definitive fertility, developmental, and perinatal/postnatal reproduction toxicity study in rabbits (GLP Study No. UBA00044) tested 5 doses of BEXSERO(3 prior to mating

and 2 during gestation) at a dose equivalent to the absolute human dose or 15 times the human dose on a body weight basis (4 kg in rabbits and 60 kg in humans). This study was designed to comply with FDA guidance on the testing of the developmental toxicity of vaccines, and according to International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline (ICH, 1996) (stages A through E of the reproductive process, with the exception of determination of effects on estrous cycle). Evaluation of the maternal animals, their developing fetuses, and offspring for up to 4 weeks after birth demonstrated that BEXSERO was not a reproductive or developmental toxicant (Ching-Long, 2014). The vaccine was immunogenic in the maternal animals; circulating antibodies were detected in their fetuses and persisted in offspring through day 29 of lactation (ELISA and SBA with rabbit complement).

BEXSERO is not contraindicated during pregnancy, but according to the vaccine label, BEXSERO should be used during pregnancy only if clearly needed. Inadvertent exposure within 30 days prior to last menstrual period (LMP) or early in the first trimester (before pregnancy status is known) might be expected to occur because the age group targeted for the vaccine includes young women of reproductive potential. The BEXSERO Pregnancy Registry is established to meet a Center for Biologics Evaluation and Research (CBER) post-marketing commitment (PMC) and is designed to collect prospective data on pregnancy outcomes among women immunized with the BEXSERO vaccine within 30 days prior to LMP or at any time during pregnancy. The registry will add to the current clinical experience with BEXSERO, supplementing existing data from animal toxicology studies and human exposure data. Pregnancy data will be collected at registry enrollment and, where accessible, at the end of the second trimester of pregnancy, and at pregnancy outcome for both mother and infant. GSK will sponsor the registry in consultation with specialists from appropriate fields such as obstetrics, pediatrics, clinical research, genetics, epidemiology, and teratology from academic institutions, private practice, and/or government agencies. These individuals constitute the Scientific Advisory Committee (SAC) and will provide an independent review of registry data.

8. RESEARCH QUESTION AND OBJECTIVES

The objective of the BEXSERO Pregnancy Registry is to evaluate pregnancy outcomes among women immunized with the BEXSERO vaccine within 30 days prior to the LMP or at any time during pregnancy. The primary outcomes of interest include major congenital malformations (MCMs), preterm birth, and low birth weight (LBW).

Other pregnancy outcomes will be collected, including stillbirths and spontaneous abortions (SABs). The probability of SAB varies greatly as a function of when the pregnancy is enrolled in the registry (Savitz, 2002). Because pregnancies will be reported to the registry at different and imprecise times during gestation, calculation of the prevalence of SAB from the registry is deemed inappropriate and could lead to erroneous conclusions. For example, if a woman enrolls in the registry at 16 weeks of pregnancy, only an SAB after this time could be detected and included in prospective reports. Similarly, SABs occurring earlier in gestation may not have been recognized and/or reported.

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

9. RESEARCH METHODS

9.1 Study Design

The BEXSERO Pregnancy Registry is a prospective, observational study of pregnant women immunized with the BEXSERO vaccine within 30 days prior to LMP or at any time during pregnancy. It is strictly observational; the schedule of office visits and all treatment regimens will be determined by the treating health care provider (HCP). The registry will collect data that are routinely documented in the patient's medical record in the course of usual care.

The design of this pregnancy registry follows current FDA guidance for designing and implementing pregnancy exposure registries (FDA, 2002).

9.2 Setting

Not applicable.

9.2.1 Study Period

The pregnancy registry will be implemented after approval by the applicable regulatory authority and central institutional review board (IRB). The data collection process for each participant will begin at enrollment (during pregnancy), follow-up will occur (pending ongoing cooperation by the woman and her HCP) at the end of the second trimester (approximately 24 weeks' gestation) and at pregnancy outcome (delivery or early termination).

9.2.2 Study Subjects

The study population will include pregnant women within the US who received at least 1 dose of BEXSERO vaccine (confirmed or possible exposure) within 30 days prior to LMP or at any time during pregnancy. BEXSERO should be used during pregnancy only if clearly needed, but inadvertent exposure during pregnancy might be expected because the age group targeted for the vaccine includes young women of reproductive potential.

9.2.3 Study Population Selection

The minimum criteria required for enrollment into the registry are as follows:

- Sufficient evidence to confirm that exposure to a serogroup B meningococcal vaccine (confirmed or possible BEXSERO vaccination) occurred within 30 days prior to LMP or at any time during pregnancy

- Sufficient information to determine whether the pregnancy is prospectively or retrospectively registered (i.e., whether the outcome of pregnancy was known at the time of first contact with the registry)
- Date the pregnancy exposure is registered
- Full reporter (i.e., HCP) contact information to allow for follow-up (name, address, etc.)

In the event that it cannot be ascertained to which meningococcal B vaccine the woman was exposed, an unknown exposure cohort will be established and analyzed separately.

Enrollment in the Registry

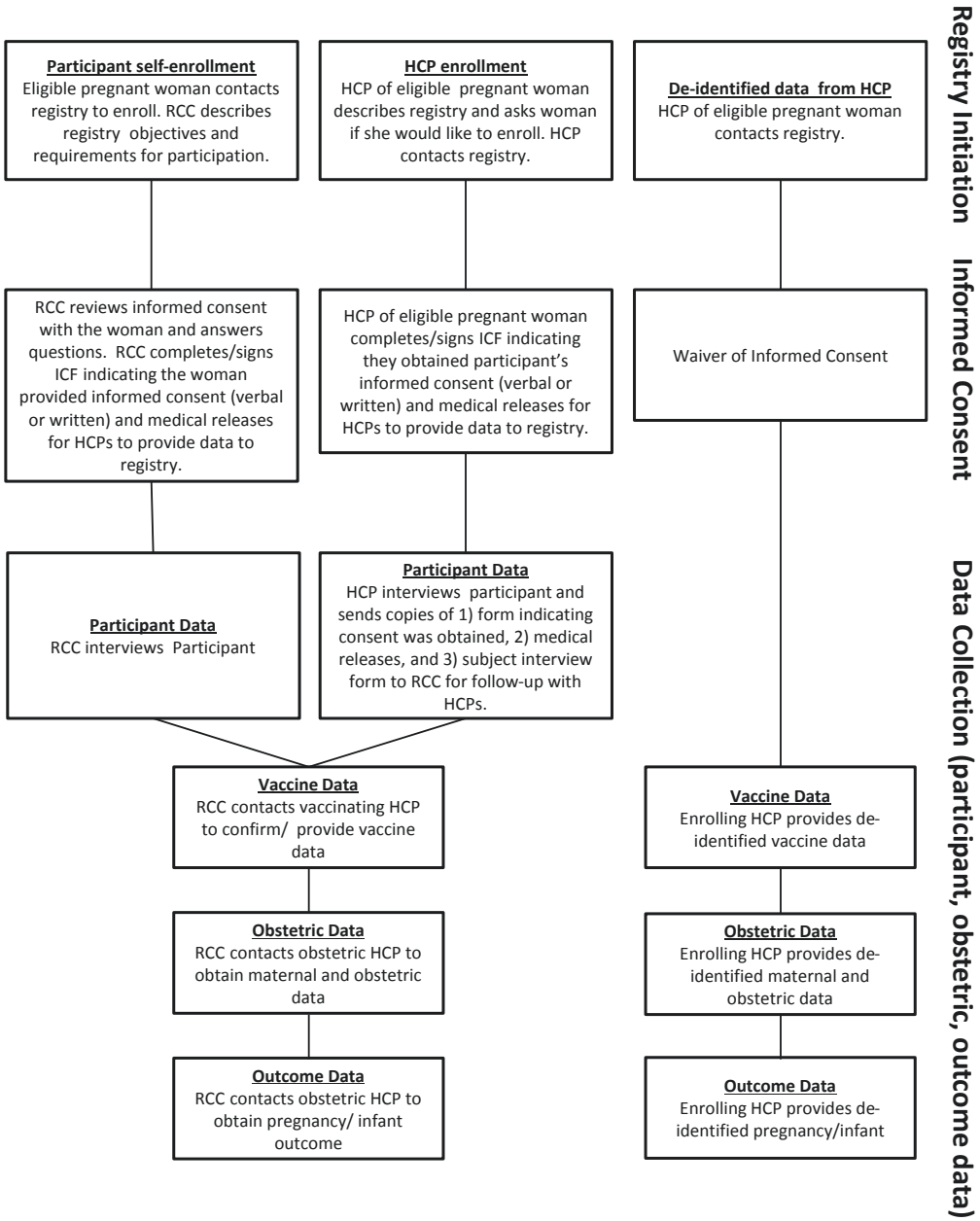
Enrollment and data collection will be coordinated through a registry coordination center (RCC) staffed by trained registry coordinators located in the US. These registry coordinators will be the first line of communication with participants and their HCPs. The coordinators are experienced in working directly with both patients and HCPs to establish a rapport with them and assist them in fulfilling registry requirements. The team will be formally trained in the appropriate methods for handling registry calls with scripts and decision trees in place. Please also refer to Section 10.3 for additional details of the RCC.

Eligible pregnant women may be enrolled in various ways. They may self-enroll in the registry by calling the pregnancy registry telephone number directly or their HCP can, with their consent, enroll them on their behalf. Alternatively HCPs may report de-identified data on pregnancy exposures and outcomes occurring within their network/health maintenance organization (HMO).

Figure 9.2.3-1 outlines the process flow for enrolling registry participants under the 3 models:

1. Self-enrollment with signed informed consent or verbal consent (waiver of documentation of informed consent)
2. HCP enrollment with signed informed consent or verbal consent (waiver of documentation of informed consent)
3. De-identified data provided by HCPs under the waiver of informed consent provision.

Figure 9.2.3-1 Registry enrollment, informed consent and data collection process



Abbreviations: HCP = health care provider; ICF = informed consent form; PI = principal investigator; RCC = registry coordination center.

Registry Awareness and Recruitment

Because registry enrollment is open to all eligible pregnant women, an active recruitment campaign will reach out to immunization providers and their patients in a broad variety of settings. The recruitment strategy will target HCPs who are known to immunize patients specifically with the BEXSERO vaccine. This might include OBGYN consultants and other specialists attending high-risk groups as defined by the ACIP recommendation (MacNeil, 2015). These providers could be identified through GSK BEXSERO distribution data and/or medical science liaisons (MSLs), as well as HCP networks and HMOs.

This targeted awareness will include the distribution of a comprehensive informational kit designed to solicit interest among pregnant women in registry participation. All messaging will be in line with product labeling.

The kit may include:

- Branded registry information sheet and/or brochure that will briefly describe the registry purpose and procedures
- Enrollment form and sample patient consent form
- Prescribing information
- Participant consent to contact card (this card enables the RCC to contact the potential patient and provide additional information about the registry)

Persistent awareness activities incorporating the above awareness materials as well as a variety of other approaches such as internet, product labeling, or messaging by MSLs may also be used, for example:

- Internet:
  - FDA listing of pregnancy registries on www.fda.gov
  - www.clinicaltrials.gov
  - Society for Maternal-Fetal Medicine listing of registries
  - PPD website
  - GSK website)
- Print:
  - BEXSERO prescribing information
  - BEXSERO medication guide
  - Medical journal advertising and/or direct to physician advertising

- Registry contact information in report(s)

- Education:
  - MSL outreach to treating HCPs
  - Scientific presentations and publications
  - Distribution of report(s) to HCPs

Reference Groups

Given the inherent difficulties in identifying a comparison group (Covington, 2009), several different methods may be used to review the data for safety signals. As described below, background prevalence estimates from external surveillance sources and estimates from published literature will be the primary comparators. To the extent possible, comparator prevalence estimates will be age-adjusted to reflect the age distribution of the BEXSERO Pregnancy Registry population.

Background Prevalence Estimates of Pregnancy Outcomes

Background prevalence estimates in the general population of pregnancy outcomes, such as premature birth and LBW, are readily available from national vital statistics or publications in the scientific literature (Martin, 2015).

Background Prevalence Estimates of Major Congenital Malformations (MCMs)

Published prevalence estimates of MCMs are available from the CDC's Metropolitan Atlanta Congenital Defects Program (MACDP), which is an ongoing population-based birth defects surveillance program (Correa, 2007). The primary objectives of MACDP are to regularly and systematically monitor births of malformed infants for changes in incidence or other unusual patterns suggesting environmental influences, and to develop a case registry for use in epidemiological studies. MACDP actively searches for MCMs among the 50,000 annual births to residents of metropolitan Atlanta's 5 counties and abstracts medical records at all Atlanta obstetric hospitals, Atlanta pediatric referral hospitals, genetics labs, and vital records (Correa-Villasenor, 2003). While there are inherent problems with comparing data from women exposed to specific vaccines in pregnancy with background prevalence estimates from the general population, this is not an unrealistic comparison (Honein, 1999), and background estimates may be the only practical comparator. MACDP has been used as a comparator by over 60% of pregnancy registries identified in a recent survey (Covington, 2009).

Background Prevalence Estimates from Literature or Other Studies

The registry is committed to identifying other appropriate comparison groups, and research of the literature and other sources, such as other pregnancy registries or observational studies, will continue in order to obtain appropriate background prevalence estimates.

9.3 Variables

The sections below describe the theoretical aspects of relevant variables. Data sources and operational definitions are discussed in Section 9.4.

9.3.1 Exposure of Interest

This pregnancy registry is strictly observational and confirmed exposure to a meningococcal B vaccine within 30 days prior to LMP or at any time during pregnancy is a condition of enrollment. The exposure of interest is exposure to at least 1 dose of the BEXSERO vaccine. In the event that it cannot be ascertained to which meningococcal B vaccine the woman was exposed, an unknown exposure cohort will be established and analyzed separately.

BEXSERO is not contraindicated during pregnancy, but should be used during pregnancy only if clearly needed. Inadvertent exposure within 30 days prior to LMP or early in the first trimester (before pregnancy status is known) may be expected to occur because the age group targeted for the vaccine includes young women of reproductive potential. Data to be collected include the date of vaccination, facility (e.g., HCP office, clinic, or commercial facility such as a pharmacy or other retail outlet), dose, and lot number if available. In the event that it cannot be ascertained to which meningococcal B vaccine the woman was exposed, an unknown exposure cohort will be established and analyzed separately.

9.3.2 Outcome(s) of Interest

Major Congenital Malformation (MCM): The registry defines, classifies, and codes MCMs with criteria specified by CDC MACDP (CDC, 2007). Newborn and infant conditions that are not necessarily considered MCMs appear in the Exclusion List for the MACDP. These conditions may be included under certain circumstances by CDC criteria and will be considered “conditional defects” in the registry (e.g., skin tags, webbed toes, etc.). Please see the following link for a listing of all MACDP MCMs and conditions on the Exclusion List:
http://www.cdc.gov/ncbddd/birthdefects/documents/macdpcode0807.pdf.

The registry defines an MCM as any major structural or chromosomal defect or combination of 2 or more conditional defects in live-born infants, stillbirths, or fetal losses of any gestational age (including outcomes prior to 20 weeks' gestation or birth weight <500 g). This definition is consistent with, but not restricted to, the CDC MACDP definition. Clusters of conditional abnormalities (as defined by CDC MACDP) and data from aborted fetuses of less than 20 weeks' gestation, when available, will be included to increase sensitivity of monitoring. The MACDP includes conditional defects only if in the presence of a major defect. This registry will consider reports of 2 or more conditional defects as a defect case, to increase signal sensitivity and to capture instances where a combination of conditional events might constitute a major defect or syndrome.

The registry conforms to the CDC MACDP guidelines in disqualifying as defects those findings that are present in infants born at less than 36 weeks of gestation, and are attributable to prematurity itself, such as patent ductus arteriosus, patent foramen ovale, or inguinal hernias. The CDC MACDP classification does include chromosomal defects. Though vaccine exposure is not likely to contribute to a risk for chromosomal defects, the registry includes these defects to maintain this consistency with the CDC MACDP.

Live-born infants with only transient or infectious conditions or with biochemical abnormalities will be classified as being without reported MCMs unless there is a possibility that the condition reflects an unrecognized MCM. Detected and reported transient or infectious conditions or biochemical abnormalities in infants without reported MCMs and defects that are excluded by the CDC guidelines will be noted in an appendix in the registry reports.

Preterm birth: An infant born at gestational age <37 weeks

Low Birth Weight: An infant whose birth weight is <2500 g

9.3.3 Other Variables

Maternal characteristics: Age, ethnicity, race

Prenatal data: LMP, estimated date of delivery (EDD), corrected estimated date of delivery (CEDD)

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

Obstetrical history: Previous pregnancies, live births, stillbirths, SABs, induced abortions (IABs), births with congenital malformations, family history of congenital malformations

Concurrent medical conditions

Concomitant medications and vaccines

Alcohol, tobacco, and illicit drug use

Pregnancy outcomes

Each pregnancy outcome will be classified in 1 of the following mutually exclusive categories:

- Live birth: an infant born alive
- Stillbirth: a fetal death occurring at 20 weeks' gestation or greater, or if gestational age is unknown, a fetus weighing 500 g or more
- Spontaneous abortion (SAB): fetal death or expulsion of products of conception prior to 20 weeks' gestation, or if gestational age is unknown, weighing less than 500g
  - Terminology may include missed abortion, incomplete abortion, and inevitable abortion.
- Induced Abortion (IAB): voluntary interruption of pregnancy, including pregnancy termination that occurs electively, to preserve maternal health, or due to fetal abnormalities
- Ectopic pregnancy: implantation of a conception outside of the uterus
- Molar pregnancy: a conception that results in a gestational trophoblastic tumor

Infant outcomes: Gestational age, birth weight, sex

9.4 Data Sources

The pregnant woman and appropriate members of her health care team will serve as data reporters to the registry. The registry is strictly observational; the schedule of office visits and all treatment regimens will be determined by the treating HCP. There will be no additional laboratory tests or assessments required as part of this registry. Only data noted as part of routine care will be collected. Data related to maternal characteristics will be provided by the pregnant woman or by her HCP (Section 9.4.3). Interim follow-up and outcome data will be provided by the obstetric HCP and/or pediatrician attending the birth, where accessible (Section 9.4 – Attempts to Obtain the Follow-up Information). Additionally, the teratologist/geneticist on the SAC will provide an opinion regarding the possible temporal association of the BEXSERO exposure to the development of observed defects. If additional information is needed to aid in classification or temporality assessment, the teratologist will request additional information using the targeted follow-up process outlined in Section 9.4.2. The SAC will meet periodically to review the data, discuss the MCM cases and their classification and temporality with the teratologist, and reach a consensus on the coding and classification of MCMs and other primary endpoints.

HCPs may also report de-identified data to the registry. The following table provides a summary of data that will be collected at specific time points and the source of data. See Figure 9.2.3-1 for the various enrollment and data collection options used by the registry.

Table 9.4-1 Summary table of evaluations

Information requested	Registration provided by participant and/or Ob HCP	Interim prenatal follow-up (end of 2nd trimester) provided by Ob HCP	Pregnancy outcome provided by Ob HCP and/or pediatrician attending birth	Targeted follow-up to collect information not previously obtained [b], provided by the Ob HCP and/or pediatrician attending birth
Maternal contact information, alternate contact information, HCP contact information	X	X [a]	X [a]	
Maternal characteristics (age, ethnicity, race, etc.)	X	X [a]		
Maternal prenatal information (LMP, EDD, CEDD, prenatal test results and timing)	X	X [a]	X [a]	
Obstetrical history	X	X [a]		X
Family history of MCMs	X	X [a]		X
BEXSERO exposure information	X	X [a]	X [a]	
Concurrent conditions, concomitant medications, alcohol & tobacco use during pregnancy	X	X [a]	X [a]	
Pregnancy status		X	X [a]	
Outcome information (live birth, still birth, SAB, gestational age, birth weight, infant/fetus sex)			X	
MCM noted and description			X	
Contributing factors			X	X

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

[a] Obtain updated information since the previous contact.

[b] Targeted follow up is designed to collect addition information (if necessary) to facilitate characterization of the fetal loss and/or MCMs.

Registration Process

Registry enrollment may be initiated by pregnant women or by their HCPs, who will act as data reporters to the registry. HCPs may also submit de-identified data to the registry. See Figure 9.2.3-1 for the various enrollment and data collection options used by the registry. After applicable subject informed consent is obtained from eligible women, the reporter will be asked to complete the ***Registration Form*** and submit it to the registry. HCPs may also report de-identified pregnancy and outcome data to the registry. The registry will provide a variety of convenient means for reporters to communicate with and submit data to the registry.

Information Collected at Registration

Reporter Information

- Contact information for the patient (if the patient self-enrolls), as well as alternate contact information, such as a permanent address and/or next of kin.
- HCP reporter contact information

Maternal Information

- Maternal demographics (age, ethnicity, race)
- LMP
- EDD determined from LMP
- CEDD (e.g., by ultrasound), if available
- Prenatal tests (diagnostic or screening) performed, date of test, and findings including the identification of congenital anomalies

Maternal Obstetrical History

- Number of previous pregnancies
- Outcome of previous pregnancies: live births, stillbirths, SABs, IABs, ectopic pregnancies, molar pregnancies
- History of offspring with congenital anomalies
- Maternal and paternal history of congenital anomalies

Maternal BEXSERO Exposure (may be provided initially by the pregnant woman at registry enrollment and confirmed by the vaccinating HCP)

- BEXSERO administration, including dose, timing, and lot number
- *Other Conditions and Exposures*

- Concurrent maternal conditions
- Concomitant medications or vaccinations during pregnancy
- Tobacco, alcohol, and illicit drug use during pregnancy

Pregnancy Follow-up

Around the end of the second trimester and in the month of the EDD, the ***Interim Pregnancy Follow-up Form*** and ***Pregnancy Outcome Form***, respectively, will be requested from the obstetric HCP.

Information Collected at Interim Pregnancy Follow-up and Pregnancy Outcome

Interim Pregnancy Follow-up at End of Second Trimester

Pregnancy Status

- Updates to EDD (i.e., CEDD)
- Subsequent prenatal tests (diagnostic or screening) performed and findings including the identification of congenital anomalies
- Pregnancy complications (preterm labor, eclampsia, placental abruption)
- Details of pregnancy outcome if pregnancy is not ongoing as described below

Other Exposures

- Concomitant medications and vaccinations
- Tobacco, alcohol, and illicit drug use during pregnancy

Additional Information Collected at Pregnancy Outcome

Fetal Outcome

- Pregnancy outcome (live birth, stillbirth, SAB, IAB, ectopic pregnancy, molar pregnancy)
- Date of outcome of pregnancy
- Gestational age at outcome
- Fetal/infant characteristics: sex, birth weight
    - MCM(s) and assessment of potential contributing factors
    - For a fetal loss (SAB, stillbirth), factors that may have had an impact on the fetal loss and attribution

Targeted Follow-up Process

If there is an MCM or other event of interest noted, in order to properly characterize the event, additional information may be requested from the reporting HCP on the ***Targeted Follow-up Form***:

- Details of the MCM/condition
- Etiology
- Outcome attribution
- Specific questions requested by GSK and/or the MCM evaluator

Attempts to Obtain the Follow-up Information

In the month that the follow-up is due, the HCP will be contacted and asked to provide follow-up information. Three subsequent attempts, as necessary, will be made every 2 weeks via various modes of communication. If there is still no response from the provider, a final communication will be sent indicating the case is lost to follow-up. If this communication prompts a response from the HCP or the requested data is later received, the case will be re-opened and assessed for evaluability. If, at any point in the follow-up process, the reporter indicates that the patient is lost to follow-up, no further attempts will be made.

Follow-up Process for Clarification of Information

For critical data points, if there are outstanding questions, discrepancies between forms, or missing data, the appropriate reporter will be contacted for clarification. Three subsequent attempts, as necessary, will be made every 2 weeks. If no further information is obtained on an otherwise evaluable case, the discrepant information in the data fields may be left blank, identified as "unspecified." On a case-by-case basis, qualified registry staff or the principal investigator may make a determination on discrepant information (e.g., determination of partially illegible word or illogical year).

9.4.1 Operational Exposure Definition

At least 1 dose of BEXSERO administered 30 days prior to LMP or at any time during pregnancy (from conception until pregnancy outcome) will constitute exposure. In the event that it cannot be ascertained to which meningococcal B vaccine the woman was exposed, an unknown exposure cohort will be established and analyzed separately. The 30-day window prior to conception corresponds with the time to immunologic response as indicated in the BEXSERO product label (Bexsero® prescribing information, 2015). BEXSERO exposure will be further categorized by earliest trimester of exposure. BEXSERO is not contraindicated in pregnancy, but should be used during pregnancy only if clearly needed (Bexsero® prescribing information, 2015). Inadvertent exposure within 30 days prior to LMP or early in the first trimester (before pregnancy status is

known) may also be expected to occur because the age group targeted for the vaccine includes young women of reproductive potential. For this registry, gestational weeks will be estimated from the most reliable EDD as reported by the HCP. If a CEDD is provided by the HCP, it will be used instead. The date of conception will be calculated as the most reliable EDD minus 38 weeks. If the EDD is not available or never estimated, the first day of the LMP may be used to estimate gestational age. The second trimester will be considered to begin at week 14 after the date of conception or LMP, and the third trimester, at week 28. If there is a discrepancy between gestational age calculated from LMP and reported gestational age, the HCP will be asked to verify the data.

When a pregnant woman enrolls in the registry, she will be asked when and where she was immunized with the BEXSERO vaccine, or any meningococcal B vaccine if the brand is unknown. She will then be asked to provide a medical release that allows the registry to confirm with the appropriate source the exposure to a meningococcal B vaccine occurred. The registry will contact the vaccine provider to confirm the vaccination date, brand, and lot number. If HCPs provide de-identified data to the registry, they must be able to verify the vaccination with BEXSERO and date of vaccination. In the event that it cannot be ascertained to which meningococcal B vaccine the woman was exposed, an unknown exposure cohort will be established and analyzed separately.

9.4.2 Operational Outcome Definition and Identification Process

All outcome variables will be provided by the obstetric HCP and/or pediatrician attending the birth. The HCP will be asked to describe any MCMs observed in the infant or fetus and will also be asked to report the gestational age and birth weight. These 2 variables will be used to calculate preterm birth (gestational age <37 weeks at birth) and LBW (birth weight <2500 g). A teratologist/geneticist will review all reported congenital anomalies and classify them using the CDC's MACDP system as specified in Section 9.3.2. Additionally, the teratologist/geneticist will provide an opinion regarding the possible temporal association of the BEXSERO exposure to the development of observed defects. If additional information is needed to aid in classification or temporality assessment, the teratologist will request additional information using the targeted follow-up process outlined in Section 9.4.

The SAC will meet periodically to review the data, discuss the MCM cases and their classification and temporality with the teratologist, and reach consensus on the coding and classification of MCMs and other primary endpoints.

9.4.3 Operational Variable(s) Definition

As is indicated in Section 9.4, for women who self-enroll in the registry, maternal characteristics will be provided by the pregnant woman at registry enrollment. After the

woman provides consent and medical release for her HCP(s) to provide data, the obstetric HCP will provide prenatal data (LMP, EDD, and CEDD), prenatal test data (test, date of test, and result), obstetrical history (previous pregnancies, live births, stillbirths, SABs, IABs, births with congenital malformations, and family history of congenital malformations), concurrent medical conditions, concomitant medications and vaccines, and alcohol, tobacco, and illicit drug use. At pregnancy outcome, the obstetric HCP will provide pregnancy outcomes data (live birth, stillbirth, SAB, IAB, or ectopic or molar pregnancy) and infant outcome (gestational age, birth weight, and sex).

If HCPs provide de-identified data to the registry, they will provide required data on maternal characteristics, prenatal data, obstetrical data, and pregnancy outcome data.

9.4.4 Advisory Committee(s)

An SAC will be established to oversee the scientific affairs of the registry, including its ongoing monitoring. The SAC will comprise recognized experts in the fields of teratology, epidemiology, maternal and fetal medicine, and therapeutic areas from government, academia, private practice, and GSK. The SAC will meet prior to each registry report to review the accumulated body of data from the registry, including review and classification of reported MCMs, and to carry out any actions required, including review and interpretation of interim data analyses and reports and publications of registry data. The SAC may meet on ad hoc occasions if indicated. In addition to the above activities, the SAC will design and implement strategies to heighten awareness of the registry.

9.4.5 MCM Monitoring and Signal Generation

On an ongoing basis, the registry teratologist and SAC will review all reports of MCM individually and cumulatively for potential signals that are generated in the collection of this information. The registry will adopt a plan developed by the Antiretroviral Pregnancy Registry to determine what constitutes a signal for a MCM, how it is reviewed, and what action might be taken should such a signal be seen (Covington, 2004). For example, the "Rule of Three" convention specifies that once 3 similar MCMs have accumulated with any specific exposure, these cases are flagged for immediate review. The likelihood of finding 3 of any specific MCM in a cohort of <600 by chance alone is less than 5% for all but the most common MCM classes (i.e., those occurring with the rate of <1/700). To enhance the insurance of prompt, responsible, and appropriate action in the event of a potential signal, the registry will employ the strategy of "threshold" based on the Council of International Organizations for the Medical Sciences (CIOMS, 1999). The threshold for action will be determined by the extent of certainty about the cases and tempered by the specifics of the cases.

9.5 Study Size

The pregnancy registry is a PMC agreed upon with the CBER to commence enrolment on 31 January 2016 and to continue for a period of 3 years or pending CBER review and discussion of results with GSK. will submit a full study report to CBER by 31 May 2020.

The registry will prospectively enroll women with confirmed or possible (i.e. if the brand is unknown) exposure to BEXSERO 30 days prior to LMP or at any time during pregnancy. BEXSERO is not contraindicated during pregnancy, but should be used during pregnancy only if clearly needed. Under the current ACIP recommendations, the CDC estimates 350,000 individuals will be advised to receive a meningococcal B vaccine (MacNeil, 2015), of whom it is likely that a small proportion will be exposed during pregnancy. There are uncertainties regarding the degree of market penetration and vaccine uptake that will be achieved in at-risk groups. A recent US study of the safety of Cervarix® in pregnancy was terminated due to low accrual of subjects attributed to low uptake of the vaccine in the US (GSK, 2015). To account for this, and that the proportion of clinically recognized pregnancies that can be expected to result in a live birth is approximately 62% (Martin, 2015), a range of sample size estimates was considered, from a minimum of 5 to 150 live births.

It is likely that the majority of exposures (99%) will be the result of inadvertent exposure within 30 days prior to LMP or early in the first trimester before pregnancy status is known. If exposures occur later in pregnancy, results will be stratified by trimester of exposure, acknowledging that the power of stratified analyses to detect statistically significant differences will be limited by the sample size of each subgroup.

The expected low frequency of BEXSERO exposure in pregnancy will limit the statistical power of this study. As the sample size of the study increases, there will be a corresponding increase in the power of the study to detect increases in the prevalence of outcomes. The study will have greater power to detect prevalence increases for relatively common outcomes (with higher prevalence) but will have less power to for more uncommon outcomes, such as MCM.

According to the CDC MACDP, the prevalence of MCMs for mothers <25 years of age in the US is 2.54% (Correa, 2007). According to the CDC National Vital Statistics System (NVSS), the prevalence of preterm birth and LBW for mothers <25 years of age are 11.71% and 8.50%, respectively (Martin, 2015).

The table below depicts sample sizes of 5, 20, 50, 100, and 150 live births and the associated effect sizes (i.e., the ratio of the registry-derived prevalence versus the reference prevalence) that would be detectable using a binomial distribution, a power of 80%, and a 1-sided Type I (false positive) error rate of 5% (Altman, 1991). For example, with a sample size of 100 live births, the study will have 80% power to detect a 1.79-fold

increase in the prevalence of preterm birth compared with the reference of 11.71% (population prevalence). In other words, if the registry-derived prevalence estimate is at least 1.79 times higher than the reference prevalence of preterm birth, the 1-sided 95% confidence interval for the estimate will exclude 11.71% (i.e., will lie above 11.71%), with a probability of 80%.

Table 9.5-1 Detectable effect size assuming 80% power

Sample size (N of live births)	Effect size (ratio of the registry-derived prevalence versus the reference prevalence for mothers <25 years of age)		
	MCM [reference = 2.54%]	PTB [reference = 11.71%]	LBW [reference = 8.50%]
5	19.30	5.75	7.92
20	7.95	3.13	3.69
50	4.23	2.24	2.59
100	3.07	1.79	1.96
150	2.66	1.63	1.82

Abbreviations: LBW = low birth weight; MCM = major congenital malformations; PTB = preterm birth.

9.6 Data Management

9.6.1 Data Processing

Data for this prospective registry will be managed with an electronic data capture (EDC) platform, which is 21 Code of Federal Regulations (CFR) Part 11 compliant. Participants and their HCPs will provide data over the phone or by completing a paper case report form (CRF), which can be submitted to the registry via mail or fax. The data will be reviewed by a registry clinical research associate for correctness and completeness and entered into the database.

9.6.2 Software and Hardware

Power calculations presented in this protocol were conducted using SAS statistical software and a 1-sample binomial distribution with a 1-sided Type I error rate of 5%. Data analyses will be performed similarly using SAS (version 9.2 or higher; SAS Institute, Cary, NC).

9.7 Data Analysis

Registry Case Management and Disposition

Prospective Registry Reports

The registry will encourage prospective registration, which is defined as registration of a pregnancy exposure prior to knowledge or perceived knowledge of the pregnancy outcome (e.g., structural defect or genetic abnormality noted on a prenatal test). Those with no abnormalities identified on a prenatal test prior to enrollment will be considered prospective and included in the analysis. The rationale, potential bias, and analytic techniques to address any bias that may be introduced by this practice are addressed in Section 9.7.4.

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

Retrospective Registry Reports

Retrospective reports will also include subjects for whom the pregnancy outcome has already occurred or an abnormality has been identified on a diagnostic or screening prenatal test prior to enrollment. Retrospective reports can be biased toward the reporting of more unusual and severe cases and are less likely to be representative of the general population experience than reports reported prior to knowledge of outcome. Therefore, retrospective reports will not be included in the primary analysis and statistical calculations. Retrospective reports with reported MCMs and/or spontaneous fetal losses will be reviewed to aid in detection of early signals and listed in registry reports. Retrospective reports will not be actively solicited by the registry and will not be captured in the registry database unless a congenital anomaly is reported.

Loss to Follow-up

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

Duplicate Registry Reports

With registry reports coming from multiple HCPs, HCP networks, and HMOs, it is important to ensure that each case is counted only once (NBDPN, 2004). Identification of duplicate reports may be problematic for the anonymously reported de-identified cases where there is no specific identifying information. Reports received by the registry will be reviewed for possible duplicate reporting. On receipt of a registration form, the report will

be compared with other reports made by the same reporter or compared with other data (such as age, LMP, EDD, and exposure information) to determine if the same report was received previously. If no duplication is identified, the report will be entered into the database. If a duplicate report is later identified through recall or the systematic check for duplicates, the case reported earliest or the one with the most complete data will be maintained as the valid case and updated with any data from the other report not already captured. The duplicate report will be flagged and designated as "Invalid," with the reason being noted as "duplicate report."

Evaluable Registry Reports

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

Invalid Registry Reports

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

Analysis Population

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

Exclusions for Analysis Purposes

Invalid registry reports and pregnancies deemed lost to follow-up will be excluded from the primary analysis. Retrospective reports will not be included, although retrospective

cases with MCMs will be reviewed and reported separately for signal detection purposes. In the event that it cannot be ascertained to which meningococcal B vaccine the woman was exposed, an unknown exposure cohort will be established and analyzed separately.

Sequential Pregnancies

The number and outcome of sequential pregnancies will be noted and presented. Sequential pregnancies will be included in the analytic dataset.

Multiple Gestation Pregnancies

The number, type (e.g., twin, triplet), and outcome of multiple gestation pregnancies will be noted and presented. Multiple gestation pregnancies will be included in the analytic dataset.

General Considerations for Data Analyses

This study is observational, and epidemiological methods will be employed for data collection and analyses.

Descriptive analysis will be performed for all prospective, evaluable data. The summary statistics for continuous and categorical variables to be used will be specified in the statistical analysis plan (SAP) but may include means, standard deviations, medians, minimums, maximums, percentiles, frequencies, and percentages. For analyses of associations between pregnancy outcomes and BEXSERO exposure, confounding and effect modification will be evaluated descriptively.

The registry will identify the number of cases for the primary outcomes of MCM, preterm birth, LBW, and in addition for second trimester SABs; prevalence estimates will be calculated as proportions of these outcomes from the total number of pregnant women or live births, or in the case of second trimester SABs, the subset of women exposed prior to the 20th week of gestation. For each prevalence estimate, both 1-sided and 2-sided 95% confidence intervals will be calculated and reported. One-sided confidence intervals are appropriate as we are specifically interested in detecting outcome prevalence estimates greater than their respective reference prevalence, and 2-sided confidence intervals will provide further description of the accuracy of the estimates.

9.7.1 Statistical Hypotheses

This registry is primarily descriptive and designed to detect potential safety signals, rather than test hypotheses. We are specifically interested in detecting whether the prevalence estimates of MCM, preterm birth, and LBW among the live births of pregnant women

exposed to BEXSERO are greater than the prevalence of these outcomes among the general population.

9.7.2 Analysis of Demographics and Baseline Characteristics

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

9.7.3 Statistical Methods

Overall and stratum-specific point estimates and 95% confidence intervals will be calculated using the binomial distribution for prevalence estimates of MCMs, preterm birth, and LBW among pregnant women exposed to BEXSEROand their live births. For each prevalence estimate, both 1-sided and 2-sided 95% confidence intervals will be calculated and reported. One-sided confidence intervals are appropriate as we are specifically interested in detecting outcome prevalence estimates greater than their respective reference prevalence, and 2-sided confidence intervals will provide further description of the accuracy of the estimates.

Because most structural defects have their origins in the first trimester of pregnancy during the period of organogenesis, analyses of MCM will be stratified by trimester of exposure, if applicable. It is expected that the vast majority (99%) of prenatal exposures will occur during the first trimester before the pregnancy is recognized. The prevalence of combined MCMs reported to the registry will be calculated as a proportion with the number of MCMs as the numerator and the number of live births as the denominator. Pregnancy losses with reported MCMs occurring at or after 20 weeks' gestation will be included in the numerator of the estimate of risk for MCMs to increase sensitivity and to allow comparison of outcomes with the CDC MACDP, which calculates prevalence by this convention. A secondary analysis will be conducted including pregnancy losses with reported MCMs occurring at less than 20 weeks' gestation. The prevalence of combined MCMs in exposed cases will be compared with that of the CDC MACDP (Correa, 2007).

Only cases meeting the CDC MACDP criteria for a defect or with 2 or more conditional defects will be included in the primary analysis. Single minor defects do not constitute a MCM according to the CDC MACDP classification; therefore, they will be listed in the report, but not included in the primary analysis.

The prevalence of preterm births and LBW will be calculated as proportions, with the number of live births as the denominator. These prevalence estimates in exposed cases will be compared with those of the CDC NVSS (Martin, 2015). Because MCMs are often associated with preterm birth and LBW, sensitivity analyses will be performed excluding infants with MCMs from the numerator and denominator when prevalence estimates are determined for these outcomes.

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

$$\text{MCM prevalence} = \frac{\text{Number of live births and fetal losses occurring at } \geq 20 \text{ weeks gestation with MCM}}{\text{Number of live births (all fetal losses excluded from denominator per MACDP convention)}}$$

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

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

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

If it is feasible, descriptive comparisons between the registry and an appropriate internal and/or external comparison group will be examined (see Section 9.2.3 for a description of potential reference groups).

Methods to Control for Confounding and Effect Modification

For analyses of associations between pregnancy outcomes and BEXSERO exposure, confounding and effect modification will be evaluated descriptively. A detailed description of these analyses will be available in the SAP. Potential confounders/effect modifiers may include the following:

- Maternal characteristics (e.g., age, ethnicity, race)

- Previous pregnancy outcomes (e.g., MCMs, stillbirth)
- Pregnancy complications (e.g., preterm labor, eclampsia, placental abruption)
- Comorbidities (e.g., diabetes, hypertension)
- Concomitant exposures (e.g., medications, alcohol, tobacco)
- Infant/fetus sex

Subgroup Analyses

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

9.7.4 Statistical Considerations

Because early prenatal testing is so frequent, it may be difficult to achieve adequate numbers of prospectively identified pregnant women if all pregnancies with prior prenatal testing are excluded from the analysis. Therefore, the primary analysis will include pregnancies enrolled prior to outcome but after prenatal test as long as the test does not indicate an abnormality. However, this practice could potentially bias the results by lowering the overall risk of MCMs (Honein, 1999). The analysis will attempt to determine bias introduced by this practice by examining the data with and without these cases.

While the registry analysis will be limited primarily to prospective reports, some pregnancy exposures will be reported only following pregnancy outcome (retrospective cases). Each retrospective report will be carefully reviewed. In general, retrospective reports of exposures to vaccines or medication following notification of outcome are biased toward reporting of the severe and unusual cases and are not reflective of the general experience with the vaccine or medication. Moreover, information about the total number of exposed persons is not known. Therefore, prevalence estimates of outcomes cannot be calculated from these data. However, a series of reported MCMs can be analyzed to detect patterns of specific MCMs and can identify early signals of vaccine or medication risks.

Those pregnancies that have reached EDD, but for which outcome information was unobtainable after 4 attempts, will be considered lost to follow-up. It is possible that outcomes among pregnancies lost to follow-up could differ from those with documented outcomes. Because of differences in individual reporting patterns, it is currently not possible to assess with any certainty what impact the potential biases the losses to follow-up may have on the analysis. However, efforts at comparing some of the characteristics of

each group may be conducted in an attempt to assess this potential source of bias (details to follow in the SAP).

When an analysis includes data from an external comparator, it is important to thoroughly understand the methodology of the external comparator and to take this into consideration when designing the analysis plan (Kennedy, 2004). As such, MACDP convention will be followed for the calculation of MCM prevalence: only live births of 20 weeks of gestation or greater will be included in the denominator. Fetal losses (SABs, IABs, stillbirths, etc.) with or without detected MCMs will be excluded from the denominator. The MACDP excludes fetal losses from the denominator to maintain consistency over time, as fetal death records were unavailable prior to 1994. In addition, the inclusion of fetal losses in the denominator may introduce classification bias. The percentage of these pregnancies consisting of potentially normal outcomes or MCMs is unknown. The data collection form attempts to obtain information on MCMs detected at the time of the outcome. However, the reporting physician may not know the condition of the aborted fetus. It is acknowledged that including only live births in the denominator is likely to overestimate the defect prevalence; however, there is only a small difference between prevalence estimates calculated using only live births versus live births plus fetal losses in the denominator given that the number of fetal deaths that are reported are a small proportion of the pregnancies 20 weeks or greater (Correa, 2007).

9.8 Quality Control

9.8.1 Validation

Ensuring that the data obtained and delivered to GSK are of high quality will be an ongoing, multi-step process involving programming of edit checks for critical data variables in the EDC system and visual review for completeness, logic, consistency, and accuracy. As recommended in regulatory guidance documents, CRFs are carefully designed to ensure data quality and integrity. All subject-reported data will be verified by the appropriate HCP.

9.8.2 Record Retention

Investigators must retain all study records required by GSK and by the applicable regulations in a secure and safe facility. The investigator must consult a GSK representative before disposal of any study records, and must notify the sponsor of any change in the location, disposition, or custody of the study files. Documents that individually and collectively permit evaluation of the conduct of a study and the quality of the data produced will be retained for a period of 5 years in accordance with Good Pharmacoepidemiological Practice (GPP) guidelines (GPP, 2009). These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor

to inform the investigator/institution as to when these documents no longer need to be retained.

These principles of record retention will also be applied to the storage of laboratory samples, if applicable and provided that the integrity of the stored sample permits testing.

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

9.9 Limitations of the Research Methods

Since participation in the registry will be accomplished in 3 ways (through voluntary self-enrollment by the pregnant women, through HCP enrollment on behalf of the woman with her consent, or finally, through the collection of de-identified data from HCPs within a network/HMO), the included subjects may not be representative of the overall population of US pregnant women. If possible, a sensitivity analysis will be conducted according to pregnant women's method of enrollment: the data collected from pregnant women who provide consent and either self-enroll or authorize their HCPs to enroll them in the registry will be examined separately from the de-identified data collected from HCPs on pregnancy exposures and outcomes within a network/HMO.

Additionally, it is possible that even in prospectively reported cases, potential bias could exist. For example, high-risk pregnancies or low-risk pregnancies may be more likely to be reported. It is also possible, and entirely likely, that differences in the prevalence estimates of pregnancy outcomes will be observed due to random variability (NBDPN, 2004). With the prevalence of the outcomes of interest being relatively low, cases of a particular outcome can be expected to be quite rare, and the coincidence of 2 or more cases in time may be just that: a coincidence. Confidence intervals will be carefully examined in order to assess the potential role of random variability.

Furthermore, it will be important to rule out other explanations for changing prevalence over time, including changes in medical diagnoses and technologies, changes in reporting and case ascertainment, and changes in the population at risk. In order to minimize the effect of these changes, the most current prevalence estimates available at the time of reporting for the population of interest will be used for analyses.

9.10 Other Aspects

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

GSK respects the subjects' rights to privacy and will ensure the confidentiality of their medical information in accordance with applicable laws and regulations.

Each patient's identity will be known only to the third-party contractor (PPD), the central registry site (principal investigator and RCC), and the enrolling individual (i.e., patient or HCP). The registry will assign patient and infant identification numbers, which will be used to identify registry participants and their infant offspring. The dataset used in each analysis of data from the registry will contain coded registry subject identifiers only for both the pregnant mothers and infants.

Each full-time and temporary employee in the RCC is fully trained in the protection of human subjects and data privacy and follows established standard operating procedures (SOPs) that outline specifically how to maintain confidentially and data protection of all registry participants. These SOPs also establish procedures to take should privacy be compromised in any way. The RCC staff must train and test on these privacy SOPs annually.

Exemption of Health Insurance Portability and Accountability Act Authorization

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

The US CFR, 45 CFR 164.512, states:

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

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

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

> "…the HIPAA Privacy Rule specifically permits the disclosure of protected health information by covered entities such as physicians or hospitals for public health purposes related to the quality, effectiveness and safety of FDA-regulated products to both the manufacturers and directly to the FDA. This includes collecting or reporting adverse events, tracking FDA-regulated products and conducting post-marketing surveillance to comply with requirements or at the direction of the FDA." (Kennedy, 2004).

10.1 Regulatory and Ethical Compliance

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

10.2 Informed Consent

Informed consent will be obtained for each registry participant who self-enrolls or is enrolled by her HCP. As is noted below, this registry qualifies for a waiver of documentation of informed consent. Adult participants will be given the option to provide verbal consent under the waiver of documentation of informed consent or signed informed consent if they prefer where consent is obtained in person. If the participant chooses the verbal consent option, the RCC completes and signs and dates a form documenting that the RCC read the registry participant information sheet to the participant via telephone, answered all of the participant's questions regarding the registry, and verbally consented to participate. A copy of this form is then mailed to the participant and the original is filed in the registry file.

Minors are defined as individuals who have not attained the legal age for consenting to treatments, procedures, or clinical investigations under applicable law in various states within the US. The definition of a minor and an emancipated minor varies by state within the US. Given the patient population for BEXSERO vaccine, many of the potential registry participants may be minors. This registry will follow applicable laws for the state in which the participant resides. If a minor requests participation in the registry and all eligibility criteria are met, the registry will obtain assent from the minor and signed written consent from a parent or guardian. Written consent from both parent(s) or both guardian(s) will be obtained in the US states in which this is required by local laws and regulations.

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

Waiver of Documentation of Informed Consent

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

As stated in the US 21 CFR 56.109 (and additionally in 45 CFR 46.117[c][2]):

- "(c) An IRB shall require documentation of informed consent in accordance with
- 50.27 of this chapter, except as follows:
- The IRB may, for some or all subjects, waive the requirement that the subject, or the subjects legally authorized representative, sign a written consent form if it finds that the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside the research context.
- (d) In cases where the documentation requirement is waived under paragraph
- (c)(1) of this section, the IRB may require the investigator to provide subjects with a written statement regarding the research."

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

- An adequate plan is provided to protect the identifiers from improper use and disclosure (see Section 10).
- An adequate plan is provided to remove the identifiers at the earliest opportunity.
- Adequate assurances are provided that the protected health information will not be reused or disclosed to any other person or entity.

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

For HCPs who report de-identified pregnancy exposure and outcome data to the registry, a waiver of informed consent is applicable as specified under CFR 46.116 (d) waiver of informed consent requirement and CFR 45, part 164.512 waiver criteria for post-marketing surveillance for the initial enrollment and follow-up through outcome of pregnancy.

The research will involve no more than minimal risk to the subjects. This will be an observational registry that is a PMC with CBER. It involves no experimental intervention and poses no possibility of physical harm. The pregnant patient's HCP, who is strictly obligated to maintain confidentiality, will submit routinely collected data to the registry. Patient confidentiality will be protected, as no identifying information will be sent to the registry. Only the HCP will know the identity of the patient. As described above, extensive safeguards will be in place to assure that patients' privacy is protected.

The waiver will not adversely affect the rights and welfare of the subjects. The privacy risks to individuals whose protected health information will be used or disclosed are reasonable in relation to the anticipated benefits to future patients, and the importance of the knowledge that may reasonably be expected to result from the research.

The research could not practicably be conducted without the waiver. A critical component of a registry such as this is the need to enroll a substantial number of subjects to have the statistical power necessary to assess risk. In order to enroll as many patients as possible, this registry seeks to accept self-enrollments from patients as well as de-identified data from HCPs under this waiver of informed consent.

10.3 Responsibilities of the Investigator and IRB

The protocol, waiver of documentation of informed consent, and waiver of informed consent will be reviewed and approved by an IRB before study implementation. A signed and dated statement that the protocol and waivers have been approved by the IRB will be given to GSK before study initiation. Prior to study start, the investigator will sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol. If an inspection of the site is requested by a regulatory authority, the investigator must inform GSK immediately that this request has been made.

The principal investigator is responsible for providing oversight of the registry and all submissions (protocol, amendments) to the IRB. The principal investigator will be available to GSK and the SAC for ongoing consultations regarding the review, analysis, and conduct of the registry.

The RCC is responsible for assisting the principal investigator in all aspects of patient recruitment, informed consent, data collection, and management. As is noted in Section 10, the RCC staff is fully trained and compliant in SOPs on the protection of human subjects and data privacy.

10.4 Protocol Adherence

The registry investigator will apply due diligence to protocol adherence. If a protocol amendment is necessary to improve the conduct of the study, such an amendment will be agreed upon by GSK and approved by the IRB before it can be implemented.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ ADVERSE REACTIONS

The registry will follow industry guidance (FDA, 2002) for regulatory reporting of adverse events (AEs), as stated below:

"The Agency considers pregnancy exposure registry reports (both prospective and retrospective) as derived from active solicitation of patient information. Accordingly, a sponsor holding marketing authorization for an approved drug or licensed biological product must submit to the Agency, within 15 calendar days, reports of adverse events from the registry that are both *serious* and *unexpected* by regulatory definition and where a reasonable possibility exists that the drug or biological product caused the adverse event [see 21 CFR 310.305(c)(1), 314.80(c)(2)(iii) and (e), and 600.80(c)(1), (c)(2)(iii) and (e)]. Current reporting requirements in the regulations consider any congenital anomaly within the definition of a serious adverse event [21 CFR 314.80(a) and 600.80(a)]." (FDA, 2002)

In addition to the above, because the registry is a study specifically to follow-up in pregnant women, exposure in pregnancy to the vaccine of interest itself will not be reported individually but will be reported by PPD to the sponsor's Safety Department on a monthly basis as line listings. The registry final report will summarize the data on these exposures in pregnancy reported to the registry. Additionally, annual CBER PMC updates, periodic safety update reports (PSURs), and development safety update reports (DSURs) will provide data on exposure in pregnancy reported to the registry. For subjects enrolled in the registry, exposure in pregnancy to any other product (as well as the vaccine of interest) for which the sponsor is the market authorisation holder (MAH) will be collected and reported on the monthly line listing. For subjects not enrolled in the registry, exposure to any product for which the sponsor is the MAH will be reported within 1 business day to the sponsor's safety department as an individual report.

The registry will limit active solicitation of AEs to specific pregnancy outcomes and they will be classified as serious adverse events (SAEs). These actively solicited SAEs include MCM, LBW, preterm birth, SAB, still birth, IAB, molar pregnancy, and ectopic pregnancy. In addition to actively solicited SAEs, any maternal death will be reported as individual case safety reports (ICSRs) to the sponsor's safety department.

For any product for which the sponsor is the MAH, all AEs and special scenarios, whether actively sought or not actively sought, which are reported to the study staff will be collected during the course of the registry and will be reported to the sponsor's Safety Department within 1 business day of awareness by PPD. The sponsor's Safety Department will be responsible for assessing the seriousness of these events.

The following reports are considered as special scenarios, irrespective if a clinical event has also occurred.

- Drug-drug or drug-food interaction
- Drug use during lactation or breast-feeding
- Lack of effectiveness
- Overdose
- Drug abuse and misuse
- Drug maladministration or accidental exposure
- Dispensing errors / medication errors
- Withdrawal or rebound symptoms

All AEs reported for the vaccine of interest that were not actively sought will be summarized in the interim and final study reports as line listings in the appendix.

Reports of AEs for all products for which the sponsor is the MAH from subjects who are not enrolled in the registry will also be reported to the sponsor's Safety Department but will not be listed in the study report.

All AE reports will use the sponsor's report forms.

The sponsor's Safety Department will forward all applicable valid ICSRs of actively sought AEs and vaccine exposure in pregnancy data to the appropriate regulatory authorities within the required timeframe, as required by regulations.

12. PLANS FOR DISSEMINATING AND COMMUNICATING RESULTS

12.1 Registration in Public Database(s)

Key design elements of this registry will be posted in publicly accessible databases including, but not limited to, the FDA pregnancy registry website and clinicaltrials.gov. Furthermore, key results of this registry will be posted in publicly accessible databases within the required time-frame from completion of the data collection where applicable and in compliance with current regulations.

12.2 Publications

Annual interim reports will be provided to CBER per the PMC.

Upon closure of the registry, a final report will be generated which will be submitted to the relevant regulatory authorities. The final report will also be available to HCPs.

The data may also be considered for reporting at scientific conferences or for publication in scientific journals. Preparation of such manuscripts will be prepared independently by the SAC and in accordance with the current guidelines for STrengthening the Reporting of OBservational studies in Epidemiology (STROBE, 2009). GSK will be entitled to view the results and interpretations included in the manuscript and provide comments prior to submission of the manuscript for publication.

13. CRITERIA FOR STUDY TERMINATION

In accordance with FDA guidance (FDA, 2002), it is proposed that enrollment in the pregnancy registry will be reviewed by CBER on receipt of each annual report. In discussion with GSK, criteria for discontinuing the registry will include the following:

- The sample size recruited is insufficient to detect a minimum 2-fold increase in the prevalence of at least one of the major outcomes.
- The feasibility of collecting sufficient information diminishes to unacceptable levels because of low exposure rates, poor enrollment, or loss to follow-up. The vaccine is currently recommended for those in the US who are at high risk of meningitis and are ≥10 years of age. Given the limited size of the population for whom the vaccine is recommended and the young age of the population targeted, low levels of exposure are likely even in the event of high vaccine uptake in the target group.
- More appropriate methods of gathering information for exposure during pregnancy are preferable or become available (e.g., if the vaccine is used in a sufficient quantity in the target population in another jurisdiction that is deemed acceptable to CBER).

The registry acknowledges the challenges of enrolling exposed pregnancies and will carefully monitor enrollment trends and outcomes. This is an open registry with initiation of patient recruitment from the time of launch.

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APPENDIX 1: LIST OF STAND-ALONE DOCUMENTS

Not applicable.

APPENDIX 2: ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Doc.Ref. EMA/540136/2009

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 3)

Adopted by the ENCePP Steering Group on 01/07/2016

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:

BEXSERO® pregnancy registry: an observational study of the safety of BEXSERO exposure in pregnant women and their offspring.

Study reference number:

V72_82OB

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

Comments:

This is an FDA PMC. EMA has accepted this study in replacement of another study which was agreed with EMA and GSK. For this reason it was registered in EUPAS Register but this is not a milestone in the protocol

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

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

[2] Date from which the analytical dataset is completely available.

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
generalised)	☒	☐	☐	9.2.3
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	9.7.1

Comments:

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

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, new or alternative design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1
3.3 Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk)	☒	☐	☐	11
3.4 Does the protocol specify measure(s) of association? (e.g. relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	7
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	9
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	9.2.1
4.2.2 Age and sex?	☒	☐	☐	9.2.2
4.2.3 Country of origin?	☒	☐	☐	9.2.2
4.2.4 Disease/indication?	☒	☐	☐	9.2.2
4.2.5 Duration of follow-up?	☒	☐	☐	9.2.1
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2.3

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.2.3
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	9.2.3
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	9.2.2
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of				

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
the drug?	☐	☐	☒	

Comments:

Exposure must occur within 30 days prior to last menstrual period or at any time during pregnancy

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.3.2
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.2
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	9.3.2
6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol describe how confounding will be addressed in the study?	☒	☐	☐	9.7.3, 9.7.4
7.1.1. Does the protocol address confounding by indication if applicable?	☒	☐	☐	9.7.3
7.2 Does the protocol address:				
7.2.1. Selection biases (e.g. healthy user bias)	☒	☐	☐	9.7.3
7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias)	☒	☐	☐	9.3, 9.4, 9.7, 9,9
7.3 Does the protocol address the validity of the study covariates?	☒	☐	☐	9.3.3

Comments:

Section 8: Effect modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	9.7.3

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	9.4.1
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	9.4.2
9.1.3 Covariates?	☒	☐	☐	4.9.3
9.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.4.1
8.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.4.2
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	9.4.3
9.3 Is a coding system described for:				
9.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☒	☐	☐	9.3
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.3
9.3.3 Covariates?	☒	☐	☐	9.3
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

The exposure (the vaccine) will be described by lot number where available.

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Is the choice of statistical techniques described?	☒	☐	☐	9.7.3
10.2 Are descriptive analyses included?	☒	☐	☐	4.7.3
10.3 Are stratified analyses included?	☒	☐	☐	9.7.3
10.4 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	9.7.3
10.5 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7
10.6 Is sample size and/or statistical power estimated?	☒	☐	☐	9.5

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.8.2
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	3.4

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.9
12.1.2 Information bias?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding?	☒	☐	☐	9.9
(e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)				
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	9.5

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10.2 10.3
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	10.3
13.3 Have data protection requirements been described?	☒	☐	☐	10

Comments:

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

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12-12.2
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12-12.2

Comments:

Name of the main author of the protocol: _____

Date: / /

Signature: _____

APPENDIX 3: ADDITIONAL INFORMATION

Not applicable.

Novartis

Document Approval Certificate /
Freigabenachweis Dokument /
Certificazione per l'approvazione di un documento

The individuals listed have approved this document for implementation using an electronic signature in the Atlas EDMS. / Die aufgeführten Personen haben durch ihre elektronische Unterschrift, dieses Dokument im Atlas EDMS genehmigt. / Le persone sotto riportate hanno approvato questo documento per consentirne l'utilizzo (l'approvazione avviene mediante firma elettronica su sistema Atlas EDMS).

UserName: [redacted]
Title: Cluster Head
Date: Monday, 05 September 2016, 07:49 GMT
Meaning: As an approver, I agree with the content and format of this document.
==========

Doc Number: 81194458

OBSERVATIONAL STUDY PROTOCOL V72_82OB

Amendment Number 1

Amendment Date: 12AUG16

BEXSERO® pregnancy registry: an observational study of the safety of BEXSERO® exposure in pregnant women and their offspring.

The present amendment introduces changes to the study protocol since the version 1 of the protocol. These changes are reflected into the revised protocol associated to this amendment.

RATIONALE AND DESCRIPTION OF CHANGE(S)

Rationale for major changes:

As of March 2, 2015 GlaxoSmithKline Biologicals has acquired the non-influenza vaccines business from Novartis Vaccines and Diagnostics.

The Marketing Authorization Holder (MAH) for BEXSERO® in the US market was Novartis Vaccines and Diagnostics Inc. until June 15th when CBER has officially approved the transfer of MAH to GlaxoSmithKline Biologicals S.A.

This Protocol Amendment v.1. reflects the change of the Study Sponsor from Novartis Vaccines and Diagnostics Inc. to GlaxoSmithKline Biologicals S.A.

As a consequence of the acquisition also MAH contacts have been updated (both address and e-mail contacts).

Rationale for minor Change:

The EU PAS Register Number has been added to the coversheet of Study Protocol v. 2.

The name of the vaccine has been capitalized.

The ENCePP Checklist has been produced for this protocol and attached as a separate document

LIST OF CHANGE(S)

CHANGE 1 (throughout the text of the Protocol)

Previously read:

Novartis Vaccines and Diagnostics (or NVD)

Now reads:

GlaxoSmithKline Biologicals S.A. (or GSK)

Rationale for change:

To reflect the change of Sponsor from Novartis Vaccines and Diagnostics to GlaxoSmithKline Biologicals.

CHANGE 2 (Coversheet of the Protocol)

Previously read:

EU PAS register number was not indicated

Now reads:

EU PAS Register number: EUPAS 12183

Rationale for change:

EMA has accepted to replace commitment for study V72_39OB with study V72_82OB and it has been included in the RMP as a Post Authorization Safety Study (PASS) cat. 3. Therefore it has been registered in EU PAS Register and a registration number has been attributed.

CHANGE 3 (throughout the text of the Protocol)

Previously read:

Bexsero

Now reads:

BEXSERO

Rationale for change:

The name of the vaccine "BEXSERO" has been capitalized according to GSK indications.

CHANGE 4 (APPENDIX 2 ENCEPP CHECKLIST FOR STUDY PROTOCOLS)

Previously read:

Not applicable

Now reads:

"See attached appendix 2"

Rationale for change:

When the version 1 of the protocol was finalized, it was not supposed to be registered to ENCePP and a ENCePP checklist was not applicable. After the approval from EMA to accept V72_82OB in place of another commitment with EMA (V72_39OB), this Study Protocol was posted in ENCePP (EU PAS Register)

and a ENCePP Checklist is now produced and attached to the Revised Study Protocol .

Novartis

Document Approval Certificate /
Freigabenachweis Dokument /
Certificazione per l'approvazione di un documento

The individuals listed have approved this document for implementation using an electronic signature in the Atlas EDMS. / Die aufgeführten Personen haben durch ihre elektronische Unterschrift, dieses Dokument im Atlas EDMS genehmigt. / Le persone sotto riportate hanno approvato questo documento per consentirne l'utilizzo (l'approvazione avviene mediante firma elettronica su sistema Atlas EDMS).

UserName: [redacted]
Title: Cluster Head
Date: Monday, 05 September 2016, 07:48 GMT
Meaning: As an approver, I agree with the content and format of this document.
==========

Doc Number: 81195352