STATISTICAL ANALYSIS PLAN

Study Title: Statistical Analysis Plan for the MENVEO® pregnancy registry: an observational study on the safety of MENVEO exposure in pregnant women and their offspring

Study Number: V59_72OB

Protocol Version and Date: V3.0, 11 AUG 16

Phase of Development: Observational

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Version and Date: Version 2.0: Date: 22JUN17

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LIST OF ABBREVIATIONS

ACIP	Advisory Committee on Immunization Practices
CBER	Center for Biologics Evaluation, Research 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
FDA	Food and Drug Administration
GSK	GlaxoSmithKline Biologicals S.A.
HCP	Health care provider
HMO	Health maintenance organization
IAB	Induced abortion
IRB	Institutional review board
LMP	Last menstrual period
LBW	Low birth weight
MACDP	Metropolitan Atlanta Congenital Defects Program
MCM	Major congenital malformation
MSL	Medical science liaison
NVSS	National Vital Statistics System
Ob	Obstetrician
PMC	Post marketing commitment
PSUR	Periodic Safety Update Report
RCC	Registry Coordination Center
SAB	Spontaneous abortion
SAC	Scientific Advisory Committee
SAP	Statistical analysis plan

STROBE	STrengthening the Reporting of OBservational studies in Epidemiology
US	United States

1. BACKGROUND AND RATIONALE

The MENVEO® Pregnancy Registry is established to meet a Center for Biologics Evaluation, Research and Review (CBER) Post marketing commitment (PMC) and is designed to collect prospective data on pregnancy outcomes among pregnant women vaccinated with MENVEO within 28 days prior to conception or at any time during pregnancy. The 28-day window prior to conception corresponds with the time to immunologic response as indicated in the MENVEO product label (MENVEO package insert, 2012). The Advisory Committee on Immunization Practices (ACIP) recommends routine administration of a MenACWY vaccine for all persons aged 11 through 18 years. Thus, the registry population will primarily consist of adolescents. MENVEO is not indicated in pregnancy. However, inadvertent pregnancy exposures are anticipated because the targeted age group for the vaccine includes young women of reproductive potential. The registry will add to the current clinical experience with MENVEO by 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. GlaxoSmithKline Biologicals S.A. (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.

For further details please refer to Section 7.0 of the protocol.

2. OBJECTIVES

The objective of the MENVEO Pregnancy Registry is to evaluate pregnancy outcomes among women immunized with the MENVEO vaccine within 28 days prior to conception or at any time during pregnancy. The primary outcomes of interest include major congenital malformations (MCM), 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 rate 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.

3. STUDY DESIGN

The MENVEO Pregnancy Registry is a prospective, observational study of pregnant women immunized with the MENVEO vaccine within 28 days prior to conception 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 Food and Drug Administration (FDA) guidance for designing and implementing pregnancy exposure registries (FDA, 2002).

3.1 Setting

3.1.1 Study Period

The pregnancy registry will be implemented after approval by applicable regulatory authority and central institutional review board (IRB). The target enrollment goal of the registry is 100 prospectively enrolled pregnant women. The data collection process for each participant will begin at enrollment (during 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).

Table 3.1.1-1: Summary table of registry milestones

Milestone	Planned date
Start of data collection	The registry will be implemented after approval by applicable regulatory authority and central IRB. Data collection will commence after a start-up period of approximately 4 months.
End of data collection	The registry seeks to enroll 100 participants, and enrollment is expected to take approximately 3 years. After all available follow-up data are collected on participants, the data will be cleaned. This follow-up and cleaning process may take approximately 10 months.

Milestone	Planned date
Annual updates	Annual updates will be provided in the Annual CBER PMC updates and in the Periodic Safety Update Reports (PSURs) and Development Safety Update Report (DSUR).
Final report of study results	A final report will be produced approximately 6 months after all data have been collected and cleaned.

3.1.2 Study Subjects

The study population will include pregnant women within the US who were immunized with the MENVEO vaccine within 28 days prior to conception or at any time during pregnancy. Because the vaccine is not indicated in pregnancy, the majority of exposures will likely be inadvertently administered in the first trimester of pregnancy. Enrollment and data collection will be coordinated through a registry coordination center (RCC). Eligible pregnant women may self-enroll in this pregnancy registry, and HCPs may also report de-identified data on pregnancy exposures and outcomes.

3.1.3 Study Population Selection

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

- Sufficient evidence to confirm that MENVEO exposure occurred within 28 days prior to conception 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.)

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 MENVEOvaccine. These providers will be identified through GSKMENVEO distribution data and medical science liaisons (MSLs), as well as HCP provider networks and health maintenance organizations (HMOs).

3.1.3.1 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 rates from external surveillance sources and rates from published literature will be the primary comparators. To the extent possible, comparator rates will be age-adjusted to reflect the age distribution of the MENVEO Pregnancy Registry population.

Background rates on pregnancy outcomes

Background rates in the general population on pregnancy outcomes, such as premature birth and LBW, are readily available from national vital statistics or publications in the scientific literature (Martin, 2012).

Background rates on congenital anomalies

Published rates of MCMs are available from the Centers for Disease Control and Prevention (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 rates from the general population, this is not an unrealistic comparison (Honein, 1999), and background rates 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). 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).

Background rates 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 rates.

3.2 Variables

The sections below describe the theoretical aspects of relevant variables. Data sources and operational definitions are discussed in Section 3.3.

3.2.1 Exposure of Interest

This pregnancy registry is strictly observational, and prior MENVEO vaccination is a condition of enrollment. MENVEO vaccination is not indicated in pregnancy. Therefore, MENVEO vaccination exposure in pregnancy is expected to be inadvertent and to occur within 28 days of conception or in early pregnancy. 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.

3.2.2 Outcomes of Interest

MCM

The registry defines and codes MCMs with criteria specified by CDC MACDP (CDC, 2007). 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 these defects are not likely to contribute to a risk for a vaccine exposure, 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
LBW	An infant whose birth weight is <2500 g

3.2.3 Other Variables

Maternal characteristics	Age, ethnicity, race
Prenatal data	Last menstrual period (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

Concomitant 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
- SAB: fetal death or expulsion of products of conception prior to 20 weeks' gestation. Terminology may include missed abortion, incomplete abortion, and inevitable 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

3.3 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. 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.

Registry enrollment may be initiated by pregnant women or by their HCPs, who will act as data reporters to the registry. After applicable subject informed consent is obtained from eligible women, the reporter will 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.

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.

Table 3.3-1: 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 Provided by relevant HCP
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 & timing)	X	X [a]	X [a]	
Obstetrical history (number and outcome of previous pregnancies)	X	X [a]		X [b]
Family history of MCMs	X	X [a]		X [b]
MENVEO exposure information (dose, timing, lot number)	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, IAB, ectopic pregnancy, molar pregnancy, gestational age, birth weight, infant/fetus sex)			X	
MCM noted & description			X	
Contributing factors			X	X[b]

[a] Obtain updated information since the previous contact.
[b] Collect information not previously obtained, to facilitate characterization of the fetal loss and or MCMs.

3.3.1 Operational Exposure Definition

MENVEO administered 28 days prior to conception or at any time during pregnancy (from conception until pregnancy outcome) will constitute exposure. The 28-day window prior to conception corresponds with the time to immunologic response as indicated in the MENVEO product label (MENVEO package insert, 2012). MENVEO exposure will be further categorized by earliest trimester of exposure. MENVEO is not indicated in pregnancy and is typically given to adolescents and young adults. Thus, the vast majority of pregnancy exposures will be inadvertent first trimester exposures, most likely prior to recognition of the pregnancy. 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 MENVEO vaccine. She will then be asked to provide a medical release that allows the registry to confirm MENVEO vaccination with the appropriate source. The registry will contact the MENVEO vaccination 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 MENVEO vaccination and date of vaccination.

3.3.2 Operational Outcomes Definitions 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 3.2.2. Additionally, the teratologist/geneticist will provide an opinion regarding the possible temporal association of the MENVEO 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 of the protocol.

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.

3.3.3 Operational Variable(s) Definition

As is indicated in Section 9.4 of the protocol, 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), concomitant 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.

For further details please refer to Section 9.0 of the protocol.

4. SAMPLE SIZE AND POWER CONSIDERATIONS

The registry is expected to prospectively enroll approximately 100 women with exposure to MENVEO 28 days prior to conception or during pregnancy over a 3-year period. Research indicates that approximately 58% of these pregnancies can be expected to result in a live birth (Ventura, 2012). Given the patient population will be mainly adolescents, a high percentage of these pregnancies can be expected to be unintended, unwanted, and likely to result in IAB. Therefore, it is anticipated that the registry will yield approximately 58 live births. It is expected that the vast majority (99%) of pregnancy exposures will occur within 28 days prior to conception 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 MENVEO exposure in pregnancy will limit the statistical power of this study. As noted below, there should be sufficient power to identify risks for relatively common outcomes such as preterm birth and LBW. However, there is less power to identify risks of rarer outcomes such as MCM.

According to the CDC MACDP, the prevalence rate of MCMs for mothers <25 years of age in the US is 2.54% (Correa, 2007). With a sample size of 58 first trimester exposed pregnancies, the study will have 80% power to detect a 4.46-fold increase in the prevalence rate of MCMs as compared with the CDC MACDP rate.

According to the CDC National Vital Statistics System (NVSS), the prevalence rate of preterm birth for mothers <25 years of age is 12.37% (Martin, 2012). With a sample size of approximately 58 exposed live births, the study will provide 80% power to detect a statistically significant 1.99-fold increase in the prevalence rate of preterm birth as compared with the CDC NVSS rate.

According to the CDC NVSS, the prevalence rate of LBW for mothers <25 years of age is 8.70% (Martin, 2012). With a sample size of 58 exposed live births, the study will provide 80% power to detect a statistically significant 2.40-fold increase in the prevalence rate of LBW as compared with the CDC NVSS rate.

Power calculations were conducted using a 1-sample binomial distribution with a 1-sided Type I error rate of 5%. For details please refer to section 9.5 of the protocol.

5. DATA MANAGEMENT

5.1 Data Processing

Data for this prospective registry will be managed by PPD, utilizing an electronic data capture (EDC) platform, which is 21 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. Database will be maintained in PPD, and will be accessed by GSK for data analysis as needed.

5.2 Analysis Software

All analyses will be performed using SAS Software version 9.2 or higher (SAS Institute, Cary, NC).

6. STUDY POPULATION

6.1 Enrolled Population

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 of the protocol.

Data from HCP provider 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

While the analysis population will be limited to prospective reports, some pregnancy exposures will be reported only following pregnancy outcome (retrospective cases). 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. Moreover, information about the total number of exposed persons is not known. Therefore, rates of outcomes cannot be calculated from these data.

Retrospective reports will not be included in the analysis population for the statistical calculation of risk. 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 as part of the enrolled population but will not be included in the analysis population.

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 address this potential source of bias.

Duplicate Registry Reports

With registry reports coming from multiple health care providers, health care provider 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 “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 analysis population. Evaluable retrospective reports and 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 analysis population, but will be summarized separately in the report.

6.2 Analysis Population

The analysis population will include prospective, evaluable subjects exposed to MENVEO. Invalid registry reports and pregnancies deemed lost to follow-up will be excluded from the analysis population. Retrospective reports will not be included, although retrospective cases with MCMs will be reviewed and reported separately for signal detection purposes. Sequential and multiple gestation pregnancies will be included in the analysis population.

Because early prenatal testing is so prevalent, 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 population. Therefore, the analysis population will include pregnancies enrolled prior to outcome but after prenatal test as long as the test does not indicate an abnormality. This practice could potentially bias the results by lowering the overall risk of MCMs (Honein, 1999), which will be examined descriptively by comparing those in the analysis population with those excluded due to prior prenatal testing.

7. CONSIDERATIONS FOR STATISTICAL ANALYSES

This study is observational, and epidemiological methods will be employed for data collection and analyses. Statistical analyses will likely be limited to descriptive analyses given the small sample size.

Descriptive analysis will be performed for all prospective, evaluable data. Continuous variables will be summarized by frequency, mean, standard deviation, median, minimum, and maximum unless otherwise stated. Categorical variables will be summarized by frequency and percentage in each category. The denominator for percentages will be the number of pregnancies or live births in the analysis population unless otherwise stated. All data will be listed as appropriate.

7.1 Adjustment for covariates

Using the analysis population, confounding and effect modification will be evaluated descriptively and, if appropriate, using logistic regression analysis. Logistic regression analysis may be used to analyze the effect of potential confounders and effect modifiers on the association between MENVEO exposure and each of the outcomes of interest (MCM, preterm birth and LBW). Backward stepwise regression method may be used for the elimination of the non-significant variables. 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

Confounders/effects with p-value < 0.05 will be considered statistically significant. The analysis for the confounders/effect will be presented along with the outcomes of interest.

7.2 Handling Missing Data

There may be occurrences of partial missing dates for exposures or medical conditions of interest. When reporting these dates in listing format the date will be presented unaltered with the missing information displayed as reported. No date imputation is planned for calculating summary estimate outcomes other than birth defects. It is of interest in this study to evaluate birth defect rates (i.e. MCM, preterm birth, LBW) in relation to timing of MENVEO exposure. As a conservative estimate of birth defect rate, for subjects where only the day of birth is missing, 15^{th} of the month will be used. A missing date will be

imputed to correspond to the 1st trimester of exposure when assessing MENVEO exposure.

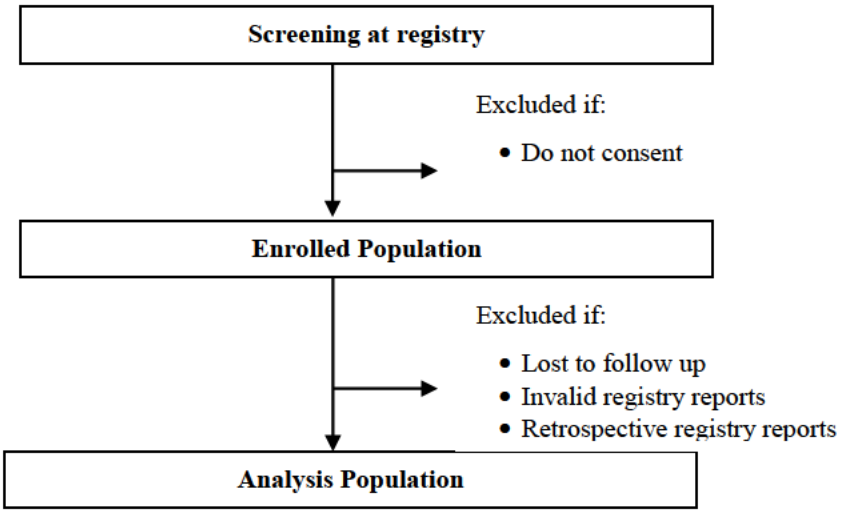
7.3 Subgroup Analyses

Analysis of the outcomes of interest (MCM, preterm birth, and LBW) will be stratified by trimester of exposure and potentially by other subgroups of interest, including gestational age at enrollment and maternal age. Comparisons may be made to external cohorts (from other pregnancy registries), if appropriate.

8. STUDY SUBJECTS

8.1 Disposition of Registry Reports

The numbers of subjects who consent, fulfill the criteria for the analysis population, and complete the study, as well as prospective, retrospective, lost to follow-up, invalid, and evaluable registry reports will be summarized. In addition the reasons why subjects not included in the analysis population will be presented as will the reasons for early withdrawal.



9. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics will be summarized using descriptive statistics and data listings for the enrolled population. Results will be stratified by population subset (e.g., analysis population, lost to follow-up, etc.) assess potential differences. If appropriate, a two-sided t –test will be used for analysis of differences and a p-value < 0.05 will be considered significant. These data will also be reviewed for potential confounding factors that could affect the interpretation of comparisons of registry outcome rates with that of comparators.

Continuous variables, including maternal age, will be summarized by reporting the mean, standard deviation, median, minimum, and maximum. Categorical variables, including ethnicity and race, will be summarized as frequencies and percentages. Frequencies and percentages of subjects with reported obstetrical histories, family history of congenital anomalies, and concurrent medical conditions at baseline will also be presented.

10. EXPOSURES

10.1 MENVEO

A descriptive table summarizing the analysis population's exposure to MENVEO will be reported. In addition, the proportion of subjects exposed to MENVEO during each of the following time periods will be summarized:

- Prior to conception
- 1st trimester
- 2nd trimester
- 3rd trimester

10.2 Concomitant Medications and Vaccines

The frequencies and percentages of subjects in the analysis population with reported concomitant medications and vaccines will be reported in a table. Results will be summarized for the entire time period of interest and by trimester of exposure.

10.3 Recreational Drugs

Details of exposure to alcohol, tobacco, and other recreational drugs are collected for the time period throughout the pregnancy duration as well as prior to conception. Frequencies and percentages of each product will be reported in a table for all subjects in the analysis population. Results will be summarized for the entire time period of interest and by trimester of exposure.

11. OUTCOMES

11.1 Outcomes of interest

For the outcomes of interest (MCM, preterm birth, and LBW), prevalence rates will be calculated by dividing the number of cases of each primary outcome by the total number of pregnant women or live births in the analysis population as appropriate. In addition, point estimates and 1-sided 95% Clopper-Pearson confidence intervals will be calculated using the exact binomial distribution.

Most structural defects have their origins in the first trimester of pregnancy, the period of organogenesis. In addition to overall prevalence of MCM, the analysis of MCMs will be stratified by trimester of exposure to MENVEO. The prevalence rate 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, among women with first trimester exposure.

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 rates by this convention. An exploratory analysis will be conducted including pregnancy losses with reported MCMs occurring at less than 20 weeks' gestation in the calculation of risk. The 95% Clopper-Pearson confidence interval will be presented for the prevalence rate of combined MCMs in exposed cases and will be compared with that of the CDC MACDP (Correa, 2007).

Following the MACDP convention, calculation of MCM risk will exclude fetal losses (SABs, IABs, stillbirths, etc.) for which no MCMs have been detected as they may introduce a classification bias. The percentage of these pregnancies consisting of potentially normal outcomes or MCMs is unknown. The data collection form attempts to obtain information on MCMs detected at the time of the outcome. However, the reporting physician may not know the condition of the aborted fetus.

Only cases confirmed by the birth defect evaluator as 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.

$$\text{Prevalence rate of combined MCMs} = \frac{\text{Number of MCMs among women with 1st trimester MENVEO exposure*}}{\text{Number of live births among women with 1st trimester MENVEO exposure**}}$$

*Numerator: Primary analysis will include pregnancy losses with reported MCMs occurring at or after 20 weeks' gestation in the numerator; Exploratory analysis will also include pregnancy losses with reported MCMs occurring at less than 20 weeks' gestation in the numerator; Fetal losses with no reported MCMs will be excluded from all analyses.

**Denominator: Only live births (not fetal deaths) are included in the denominator to allow comparison with the MACDP prevalence rate, which calculates prevalence in this manner.

The prevalence rate of preterm births and LBW will be calculated as proportions, with the number of live births as the denominator. These prevalence rates in exposed cases will be compared with those of the CDC NVSS (Martin, 2012). Because MCMs are often associated with preterm birth and LBW, infants with MCMs will be excluded from analyses of these outcomes and will not be counted in the numerator or denominator when prevalence rates are determined.

$$\text{Prevalence rate of preterm birth*} = \frac{\text{Number of preterm births}}{\text{Number of live births}}$$

*Infants with MCMs will not be included in the numerator or denominator

$$\text{Prevalence rate of LBW*} = \frac{\text{Number of LBW infants}}{\text{Number of live births}}$$

*Infants with MCMs will not be included in the numerator or denominator

The outcome data will be stratified by the earliest trimester of exposure to MENVEO. 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 LMP and reported gestational age, the HCP will be asked to verify the data.

If it is feasible, 95% Clopper-Pearson confidence intervals will be presented for the registry and comparisons between the registry and an appropriate internal and/or external

comparison group will be examined (see Section 3.1.3.1 for a description of potential comparators).

11.2 Other Outcomes

For first trimester SABs, the data will be stratified by gestation age at registry enrollment and examined descriptively. For second trimester SABs, prevalence rates and 1-sided 95% Clopper-Pearson confidence intervals will be presented. Prevalence rates will be calculated by dividing the number of second trimester SABs by the total number of pregnant women exposed prior to the 20^{th} week of gestation.

13. SCIENTIFIC ADVISORY COMMITTEE

The SAC will 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, andGSK. 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.

14. PLANS FOR DISSEMINATING AND COMMUNICATING RESULTS

14.1 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.

14.2 Publications

Annual updates will be provided in the Annual FDA PMC updates and in the Periodic Safety Update Reports (PSURs) and Development Safety Update Reports (DSUR).

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 of STrengthening the Reporting of OBservational studies in Epidemiology (STROBE). 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.

15. LIST OF FINAL REPORT TABLES, LISTINGS AND FIGURES

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Table 2	Summary of Study Disposition (Prospectively Enrolled Pregnancies)
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Listing 1	Subject Disposition
Listing 2.1	Demographic and Baseline Characteristics
Listing 2.2	Obstetrical History
Listing 2.3	Family History of Congenital Anomalies
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Listing 5.4	Preterm Births
Listing 5.5	Low Birth Weight
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16. LAYOUT SPECIFICATIONS FOR TABLES, LISTINGS AND FIGURES

All TFL is to include the following header:

GlaxoSmithKline Biologicals S.A.	Vaccine: MENVEO
Final Report: Study V59 _72OB	Page X of Y

General

1. All TLFs will be produced in landscape format.
2. All TLFs will be produced using Courier New, size 9.
3. Margins will be set according to the PPD template for tables, figures, and listings. All SAS outputs will be fitted into the PPD Word template.
4. Headers and footers for figures will be in Courier New, size 9.
5. All spelling should adhere to American English.
6. TLFs will be in black and white (no color).
7. Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TLFs. On some occasions, superscripts ‘a’, ‘b’, ‘c’, etc. may be used (see below).
8. Only standard keyboard characters will be used in the TLFs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (e.g. u will be used in place of μ). Certain superscripts (e.g., cm^2) will be employed on a case-by-case basis.
9. Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats.
10. Each TLF will be identified by a numeral, and the designation (i.e., Table 1) will be centered. A decimal system (x.y and x.y.z) will be used to identify TLFs with related contents. The title is centered in initial capital characters. The analysis cohort will be identified on the following line as the title. A solid line spanning the margins will separate the display titles from the column headers. There will be one blank line between the last title and the solid line.

    Table x.y.z

    First Line of Title

11. All computed percentages will be presented using one decimal place. Percentages will be rounded according to the following rule.

    0.005 - <0.01 => rounded up to 0.01

    0.00 - <0.049 => rounded down to 0.00

12. The precision of continuous data will depend upon the precision of raw data. Means and medians will be displayed to one more decimal place than the raw data, SDs to two more decimal places, and minimum and maximums to the same level of precision as the raw data. For example, if numerical results are to be presented using two decimal places, then they will be rounded according to the following rule.

    0.005 - <0.01 => rounded up to 0.01

    0.000 - <0.0049 => rounded down to 0.00

13. All abbreviations used in a table/listing must be defined in a footnote on each page, where the abbreviation occurs.

17. REFERENCES

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