PASS information

Title	BEXSERO Pregnancy Registry: an observational study of the safety of BEXSERO exposure in pregnant women and their offspring.
Version identifier of the final study report	205533 [MENB REC 2ND GEN-047 EPI VS US PR (V72_82OB)]
Date of last version of the final study report	Final: 20 February 2020
NCT Number **EU PAS Register Number**	NCT02640677 ENCEPP/SDPP/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	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 (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.
Country of study	United States
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1. LIST OF ABBREVIATIONS

AAP	American Academy of Pediatrics
AAFP	American Academy of Family Physicians
ACIP	Advisory Committee on Immunization Practices
CBER	Center for Biologics Evaluation and Review
CDC	Centers for Disease Control and Prevention
EMA	European Medicines Agency
FAQ	Frequently asked questions
FDA	Food and Drug Administration
GPP	Good Pharmacoepidemiological Practice
GSK	GlaxoSmithKline
HCP	Health care provider
HIPAA	Health Insurance Portability and Accountability Act
HMO	Health maintenance organization
HPA	Health Protection Agency (now Public Health England)
IDSA	Infectious Disease Society of America
IEC	Independent Ethics Committee
IRB	Institutional Review Board
LBW	Low birth weight
LMP	Last menstrual period
LSFV	Last subject first visit
MAH	Marketing authorization holder
MCM	Major congenital malformation
MSL	Medical science liaison
PASS	Post-authorization safety study
PHE	Public Health England

PI	Principal investigator
PMC	Post marketing committment
PV	Pharmacovigilance
RCC	Registry Coordination Center
SAB	Spontaneous abortion
UK	United Kingdom
US	United States
WIRB	Western Institutional Review Board

Trademark Information

Trademarks of the GlaxoSmithKline group of companies	Generic description
BEXSERO	Meningococcal Group B vaccine
Cervarix	Human Papilloma Virus Vaccine.

Trademarks not owned by the GlaxoSmithKline group of companies	Generic description
Not applicable	Not applicable

2. NAMES AND AFFILIATIONS OF PRINCIPAL INVESTIGATORS

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3. MILESTONES

Milestone	Planned date	Actual date	Comments
Start of data collection	31 January 2016	31 January 2016	No comment
End of data collection	30 November 2019	30 November 2019	The pregnancy registry was open for enrolment for a period of 3 years (final enrollment: 30 January 2019). The study completion date included the subsequent maximum 10 months' follow-up period post enrollment (until 30 November 2019).
Registration in the EU PAS register	25 January 2016	25 January 2016	No comment
Study progress report 1 submission	Q1 2017	02 March 2017 To EMA: 23 March 2017 To CBER: 23 March 2017	No registrations were reported
Study progress report 2 submission	Q1 2018	16 March 2018 To EMA: 25 March 2018 To CBER: 23 March 2018	No registrations were reported
Study progress report 3 submission	Q1 2019	12 March 2019 To EMA: 28 March 2019 To CBER: 22 March 2019	Two registrations were reported in this period. One of the women withdrew consent; therefore, no pregnancy outcome data are available. One of the women was lost to follow up and no pregnancy outcome data are available.
Final report of study submission	By 31 May 2020	20 February 2020 By 31 May 2020	This final report is prepared after the study completion date was reached. No pregnancy outcome data are available.

Abbreviations: CBER = Center for Biologics Evaluation and Review; EU = European Union; GSK = GlaxoSmithKline; PAS = post-authorisation study; Q = quarter.

4. ETHICS

4.1. Independent Ethics Committee (IEC) or Institutional Review Board (IRB) and ethical conduct of the study

The amended study protocol, informed consent and assent forms, the brochure, and other information that required approval were reviewed and approved by the Western Institutional Review Board (WIRB).

This study was conducted in accordance with Good Pharmacoepidemiological Practice [GPP, 2015], with applicable local regulations and with the ethical principles laid down in the Declaration of Helsinki. No ethical issues were raised during the study. At the end of the data collection period, and on receipt of CBER approval to close the registry, WIRB were duly informed. On 26 September 2019, WIRB formally acknowledged the closure and the conclusion of IRB oversight of the study.

4.2. Subject information and consent

As a post-marketing safety reporting activity, this registry qualified for exemption from the US Health Insurance Portability and Accountability Act (HIPAA) authorization. It also qualified for a waiver of documentation of informed consent (verbal consent) for adult women who self-enroll, and it qualified for a waiver of informed consent for de-identified data reported to the registry. If a minor would request participation in the registry and all eligibility criteria were met, the registry would obtain assent from the minor and signed written consent from the parent or guardian. The protocol and informed consent waivers were submitted to the WIRB for approval prior to registry implementation.

5. INTRODUCTION

BEXSERO is a vaccine indicated for active immunization to prevent invasive meningococcal disease caused by *Neisseria meningitidis* serogroup B. BEXSERO was approved by the European Medicines Agency in January 2013 for individuals two months of age and older and by the Food and Drug Administration (FDA) in the USA in January 2015 for use in individuals 10 through 25 years of age [FDA, 2015].

A condition of licensure for both EMA and FDA was that the safety of BEXSERO during pregnancy would be evaluated post authorization. The post-authorization safety study (PASS) originally proposed to EMA by GSK, to monitor safety in pregnancy in the UK (V72_39OB), was not feasible due to insufficient vaccination in the UK of the target population. With EMA's approval in November 2015, the Company replaced the commitment for study V72_39OB, with a post marketing commitment (PMC) agreed with FDA. The PMC was to establish a pregnancy registry in the United States (US) to prospectively collect data on spontaneously reported exposures to BEXSERO occurring within 30 days prior to the last menstrual period (LMP) or at any time during pregnancy (V72_82OB).

The BEXSERO Pregnancy Registry opened as planned on 31 January 2016. Per agreement with the FDA, the pregnancy registry would continue enrolling exposed pregnancies for a period of 3 years or pending review by the FDA's Center for Biologics Evaluation and Review (CBER) and subsequent discussion of results with GSK. Final enrollment (last subject first visit – LSFV) was to take place on 30 January 2019 (to allow for a maximum follow-up of 10 months post- enrollment), in order to achieve the agreed study completion date of 30 November 2019.

As LSFV approached without any registered exposures during pregnancy, GSK formally contacted CBER on 5 December 2018 to request a review of the PMC and possible discontinuation of the registry. This was on the basis that the lack of registrations was reflective of a low probability of exposure during pregnancy in the US during the study period. The 3rd annual and 3-year summary report were submitted in parallel to EMA and CBER in March 2019, as per commitment. Following the assessment of the reports, CBER concluded on 28 August 2019, that GSK could be released from the PMC because "the feasibility of collecting sufficient information had diminished to unacceptable levels". CBER agreed to the proposal to continue to collect pregnancy exposure and outcome data through routine Pharmacovigilance activities in the US and worldwide.

In this final study report, we provide a description of the study and the activities undertaken to boost recruitment to the registry. The epidemiology of pregnancy in adolescents and young adults in the US is discussed along with consideration of vaccine uptake in the target group. Finally, the rationale to close the registry is articulated and a status update to the 'study completion' date of 30 November 2019, is provided.

6. RATIONALE AND BACKGROUND

BEXSERO was licensed in the US on 23 January 2015. Meningococcal group B (MenB) vaccines were subsequently recommended by the Advisory Committee on Immunization Practices (ACIP) in February 2015 for use among certain groups of persons aged ≥10 years who are at increased risk for serogroup B meningococcal disease (Category A recommendation) [Folaranmi, 2015]. ACIP further recommended, in June 2015, that adolescents and young adults aged 16 to 23 years may be vaccinated with MenB vaccines to provide short-term protection against most strains of serogroup B meningococcal disease (Category B recommendation) [MacNeil, 2015a].

Pregnant women were excluded from enrollment in clinical studies pre-licensure. Despite this exclusion, pregnancy was reported in 29 subjects who had each received at least 1 dose of BEXSERO in clinical or third-party studies (V72P10, V72_29, V72_68TP, V72_70TP, V72P4, V72P5, V102_03), and independent review of pregnancy outcomes found no adverse outcome associated with BEXSERO vaccination [Rastogi, 2015]. In addition, 8 pregnancies exposed to BEXSERO were reported in studies sponsored by Centers for Disease Control and Prevention (CDC) at Princeton University and the University of California, Santa Barbara. For all 8 women, therapeutic abortion (unrelated to any adverse pre-natal outcome) was reportedly planned [Duffy, 2017].

Well-controlled studies in pregnant women were not available and levels of real-world vaccine use and exposure during pregnancy remained low. It was intended that the

registry would add to the current clinical experience with BEXSERO, supplementing data from animal toxicology studies and other human exposure data as reported. FDA's Guidance for Industry [FDA, 2002] on how to establish pregnancy exposure registries to monitor the outcomes of pregnancies exposed to specific medical products was followed.

7. RESEARCH QUESTION AND OBJECTIVES

The objective of the BEXSERO Pregnancy Registry was 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 included major congenital malformation (MCM), preterm birth, and low birth weight (LBW). Secondary outcomes included spontaneous abortions (SABs) and stillbirths

8. RESEARCH METHODS

8.1. Study design

The BEXSERO Pregnancy Registry was a prospective observational study. A woman could self-enroll in the registry by calling the pregnancy registry telephone number directly, or the health care provider (HCP) could, with the woman's consent, enroll her on her behalf. Alternatively, HCPs had the option to report anonymous data on pregnancy exposures and outcomes occurring within their practices or health maintenance organizations (HMOs).

8.2. Setting

The study occurred in the context of routine clinical care of pregnant women vaccinated with MenB vaccine in the US. The study was conducted by a third-party contractor (PPD), overseen by a central principal investigator (PI) and facilitated by a central registry coordination center (RCC). Data collection for each participant began at enrollment (during pregnancy), and follow-up occurred at the end of the second trimester (approximately 24 weeks of gestation) and at pregnancy outcome (delivery or early termination). The registry was proposed to run for a 3-year period or pending review by CBER.

8.3. Subjects and study size, including dropouts

The study population included pregnant women within the US who received at least 1 dose of BEXSERO vaccine within 30 days prior to the LMP or at any time during pregnancy. There were uncertainties regarding the degree of vaccine uptake that might be expected among the targeted study population. To account for the likelihood that the population exposed during pregnancy was small, 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. Detectable effect sizes for this range of sample sizes were calculated and ranged from 1.63 to 19.30 for the primary outcomes, MCM, preterm birth, and LBW.

8.4. Outcomes and Variables Collected

The primary outcome variables included MCM, preterm birth, and LBW as defined below. Other pregnancy outcomes also to be collected, included SABs and stillbirths.

- **MCM:** The registry defined 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 of gestation or weighing <500g).
- **Preterm birth:** An infant born at gestational age <37 weeks.
- **LBW:** An infant whose birth weight is <2500 g.

Additional variables collected were those related to the exposure of interest (at least 1 dose of BEXSERO, date of vaccination, facility where vaccinated, dose and lot number if available) and others considered potential confounders or effect modifiers, including maternal characteristics (age, ethnicity, race), previous pregnancy outcomes (e.g., MCMs, stillbirth), pregnancy complications (e.g., preterm labor, eclampsia, placental abruption), comorbidities (e.g., diabetes, hypertension), and concomitant exposures (e.g., medications, alcohol, tobacco).

8.5. Data sources

The pregnant woman and appropriate members of her health care team could serve as data reporters to the registry. The registry was strictly observational, and only data noted as part of routine care would be collected.

9. RECRUITMENT INITIATIVES

To maximize the possibility of identifying BEXSERO exposures during pregnancy, active awareness and recruitment activities were undertaken throughout the study period. To facilitate contact with the registry, a pregnant woman (or her HCP on her behalf) could contact the registry directly. The toll-free contact telephone number PPD was provided on the package insert. Women or their HCPs who were interested in the registry could also find the registry contact telephone number and/or other registry information at the following online locations:

- GSK, dedicated BEXSERO pregnancy registry web page: [http://pregnancyregistry.gsk.com/bexsero.html]
- FDA listing of the registry: [http://www.fda.gov/ScienceResearch/SpecialTopics/WomensHealthResearch/ucm134848.htm]
- PPD website (registry now closed): [http://www.ppdi.com/Services/Post-Approval/Patient-Registries-and-Observational-Studies/Pregnancy-Registries/Registry-Descriptions]

- Clinicaltrials.gov: [https://clinicaltrials.gov/ct2/show/NCT02640677?term=BEXSERO+Pregnancy+Registry&rank=1]

To raise awareness among women and their HCPs, we drew on the experience of other pregnancy registries within GSK. The recruitment strategy for the BEXSERO Pregnancy Registry targeted HCPs who were already vaccinating or are likely to vaccinate patients with the BEXSERO vaccine. These providers were identified by GSK BEXSERO medical science liaisons (MSLs) throughout the course of the study, as well as HCP networks and HMOs, and GSK distribution data. MSLs generally interact with HCPs and academic institutions by providing them with knowledge of a particular product and/or therapeutic area at their request. Thus, they have an established relationship with providers who attend the eligible patient population for the registry and could educate these providers on the importance of enrollment of the patients they vaccinate. Education sessions were provided by the registry team to the MSLs on a regular basis to inform and update them about the registry. These sessions continued regularly throughout the course of the registry. Each session consisted of a short briefing about the BEXSERO vaccine, FDA licensing of MenB vaccines, and updates on ACIP recommendations, and details of the registry design, recruitment methods, and operational aspects. Awareness materials (i.e., brochure, frequently asked questions [FAQs], participant consent forms, and registrations forms) were provided to the MSLs, who in turn can inform interested HCPs and HMOs and distribute the available material as appropriate. The brochure was also made available at medical booths at relevant conferences during the course of the study (e.g. in 2018 at conferences of the American Academy of Pediatrics [AAP], the American Academy of Family Physicians [AAFP], and the Infectious Disease Society of America [IDSA] among others). In addition, during numerous promotional BEXSERO speaker programs hosted by GSK US at regular intervals nationwide, speakers made attendees aware of the registry. This program was hosted by GSK medical staff and is tailored for HCPs. It included meningococcal disease information, guidelines for vaccine usage, and information from the BEXSERO Prescribing Information [FDA, 2018]. The BEXSERO pregnancy registry was routinely referred to during the presentation and during routine speaker training. Speakers were instructed to verbally draw the attention of the attendees to the existence of the pregnancy registry and the associated phone number. Over the course of the 3-year study period (31 January 2016 until 30 January 2019), GSK US hosted 1536 live programs, with a total of 24,168 attendees at those programs. Additionally, there were 213 webinars (web-based lectures with the same content as the live program) broadcast at 1091 sites, with a total of 6024 attendees. In conclusion, a range of efforts were undertaken to maximize awareness of the registry among HCPs and the pregnant women they serve.

10. RESULTS

The registry opened on 31 January 2016. To achieve the study completion date as defined by CBER (30 November 2019), the planned last subject first visit (LSFV) was on 30 January 2019 to allow for a maximum 10-month up follow up period to date of delivery. During the study period, two participants were enrolled in the registry. One participant self-enrolled in the registry on 26 June 2018. She provided informed consent and registration data on 25 July 2018. This 20-year-old white woman of Hispanic ethnicity

reported no previous pregnancies and no family history of birth defects. She was vaccinated with BEXSERO in the first trimester of pregnancy. Her expected date of delivery was 8 February 2019. She withdrew consent to participate further in the registry on 15 August 2018.

An HCP reported de-identified data on another pregnancy in a 16-year-old of Hispanic ethnicity. She was vaccinated with BEXSERO in the second trimester of pregnancy and received a booster later in the second trimester. She reported no previous pregnancies and no family history of birth defects. She had a screening ultrasound on 17 October 2018 with no abnormal results reported. She reported no other medical conditions during pregnancy and no exposures to concomitant medications, alcohol, tobacco, or illicit drugs. Her expected date of delivery was on 21 February 2019. After repeated efforts to determine the outcome (per-protocol), this subject was deemed lost to follow up.

LSFV passed on 30 January 2019 without any exposures during pregnancy in the registry and subsequently zero outcomes to report on 30 November 2019.

11. DISCUSSION

In 2015, the CDC estimated that about 350,000 individuals were at high risk of meningococcal B disease in the US and were advised to receive MenB vaccine [MacNeil, 2015b]. Since the initial recommendation in high-risk individuals, adolescents and young adults aged 16 to 23 years have also been advised that they may receive the vaccine (preferentially from 16 to 18 years of age). This is not a universal recommendation (Category A), but the vaccine can be recommended at the discretion of the prescribing physician (Category B recommendation [CDC, 2016]).

Birth rates for individuals in the targeted age group for the vaccine have decreased significantly in recent years, from 34.2 per 1000 females aged 15 to 19 years in 2010 to 17.4 in 2018. In fact, the birth rate for this age group has fallen to a new low each year, with an overall decrease of 58% since 2007 and 72% since the 1991 [Martin, 2019]. Additionally, abortion ratios (number of abortions per 1000 live births) between 2007 and 2016 were higher among adolescents and young adults <24 years, than among any other age groups [Jatlaoui, 2019].

At the time of this report, the proportion of the target population vaccinated with BEXSERO is low on a population level, and, according to a recent report in the CDC's *Morbidity and Mortality Weekly Report*, MenB vaccination rates are low (17.2%) among adolescents [Walker, 2019]. Therefore, it is expected that the level of BEXSERO vaccine exposure in adolescents and young adults during pregnancy in the US is also low. This situation is not unprecedented for a newly licensed vaccine. CERVARIX, a vaccine indicated for prevention of cervical cancer and related conditions caused by oncogenic human papillomavirus infection, was licensed in the US in 2009 and approved for girls aged 9 to 25 years (i.e., spanning a similar age group as is currently indicated for MenB vaccination). One of the post-marketing commitments was a cohort study of the risk of spontaneous abortion post-administration of CERVARIX in pregnancy. In 2015, the study was terminated with the agreement of FDA because of low accrual of subjects, which in turn was attributed to low uptake of the vaccine in the US [GlaxoSmithKline,

2018]. GSK also established a Pregnancy Exposure Registry for CERVARIX in the US, in collaboration with Public Health England (PHE), formerly the Health Protection Agency (HPA) in the United Kingdom. As with the BEXSERO pregnancy registry, registration was on a voluntary basis, and the registry could be accessed by telephone in the same way as the BEXSERO registry. Over an 8-year period (September 2007 to November 2015, when the registry was formally closed), the CERVARIX pregnancy registry recorded only 16 exposures in the US [López-Fauqued, 2017].

In a recent systematic review and meta-analysis, the correlation between product utilization among pregnant women and pregnancy registry enrollment was examined among 34 pregnancy registries. The study found that product utilization among pregnant women was the strongest predictor of enrollment in pregnancy registries. Products with very low utilization during pregnancy had correspondingly low enrollment rates in the pregnancy registry. Among 9 registries for which drug utilization during pregnancy was categorized as <0.5 per 100,000 live birth pregnancies, median enrollment was 3 women, with a range of 0 to 4. In the US, 15.8 pregnancies are enrolled in a registry for every 100 total spontaneous reports [Bird, 2018].

With this in mind, and to further investigate exposure to BEXSERO vaccination during pregnancy in women of reproductive age, we conducted a feasibility study using Truven Health MarketScan Commercial Claims and Encounters (CCAE) and Medicaid databases in February 2018 (ODA-BEXSERO-004 Marketscan US). The objective was to estimate the proportion of women aged 10 to 50 years who were vaccinated with BEXSERO according to their pregnancy status in each database. Of the 62,166,096 women aged 10 to 50 years in the CCAE database on 1 February 2018, 32,415 (0.0521%) were vaccinated with BEXSERO, and 29 (0.005%) were potentially vaccinated during pregnancy. In the Medicaid database, results were similar; of the 8,847,508 women aged 10 to 50 years in the database on 1 February 2018, 423 (0.048%) were vaccinated with BEXSERO, and 2 (0.0009%) were potentially vaccinated during pregnancy.

Real-world reporting of exposures in pregnancy has also been very limited in regions where BEXSERO has been used extensively in the target age group. In the Saguenay-Lac-Saint-Jean region in Quebec, Canada in 2014, where approximately 15,000 adolescents and young adults were vaccinated, no notifications of exposure during pregnancy were reported. More recently, approximately 59,000 doses were administered to adolescents aged 15 to 18 years, vaccinated in the context of a large randomized controlled trial conducted in 2017 and 2018 in South Australia. Exposure during pregnancy was reported by four study participants, of whom three consented to follow up. From a search in the Company Safety Database (confirmed by the study team [S. Lee 2018, personal communication, 18 December]), all three pregnancies resulted in a live birth with no abnormalities reported.

12. CONCLUSION

Despite numerous awareness activities by the BEXSERO Pregnancy Registry, only 2 women were enrolled in the registry in a 3-year period, 1 of whom subsequently withdrew consent, and the second of whom was lost to follow up. This low enrollment rate is reflective of the rarity of BEXSERO exposure during pregnancy, which is due to

multiple factors including low uptake of the vaccine and low pregnancy and live birth rates in the target population.

The challenges of enrolling exposed pregnancies were anticipated and acknowledged in the protocol (Section 13). In accordance with FDA guidance [FDA, 2002], it was proposed that enrollment in the pregnancy registry would be reviewed annually by CBER and criteria for discontinuing the registry were defined as follows:

- 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.
- 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).

As LSFV approached on 30 January 2019, it was GSK's contention that two of the three criteria specified above had been met. As was noted in the protocol, approximately 100 live births would be required in the registry to have 80% power to detect a 2-fold increase in the prevalence of preterm birth compared with the reference of 11.71% (major outcome with the highest population prevalence). Given the limited enrollment exhibited over the 3-year study period, the likelihood that the registry would achieve a sample size that would produce any meaningful results or conclusions was extremely low.

Consideration has been given to alternative study settings elsewhere in the world. In February 2019, the first state-wide meningococcal group B vaccination programme targeting adolescents launched in South Australia, a state in Australia with a total population of 1.7 million and a cohort of 102,974 persons aged 15-19 years in 2018 [Australian Bureau of Statistics, 2018]. The programme targets school-going adolescents aged 15 years with a catch up programme for those aged 16-20 years. The birth rate in this cohort is lower than in the US (7.9/1000 in adolescent girls in South Australia aged 15-19) and with attendant difficulties recruiting and retaining young pregnant women in a study, we do not consider this a viable alternative study setting at this time. There are no other national or state-wide programmes planned at the time of writing.

On these bases, GSK submitted a proposal to CBER on 5 December 2018, requesting that CBER consider the discontinuation of the BEXSERO Pregnancy Registry. As an alternative, GSK proposed to continue to collect pregnancy exposure and outcome data through routine PV activities in US and worldwide. CBER reviewed the register in the context of the 3rd annual report and 3-year summary report, which were submitted in parallel to EMA and CBER as per commitment, in March 2019.

In the period after LSFV and before study end (30 November 2019), the pregnancy registry telephone line remained open. On 28 of August 2019, CBER notified GSK that they concurred with GSK's position, and that "the feasibility of collecting sufficient information had diminished to unacceptable levels". CBER agreed to the proposal to continue to collect pregnancy exposure and outcome data through routine

Pharmacovigilance activities in the US and worldwide. Since the date of BEXSERO registration in the EU (14 January 2013) until 30 November 2019, 20 exposures during pregnancy or within 28 days prior to conception were recorded in the GSK worldwide clinical safety database from spontaneous reports. Sixteen of the 20 spontaneously reported pregnancies were ongoing or lost to follow up or had an unknown outcome. For 4 of the 20 reports, the outcomes are known: 3 live infants with no apparent congenital anomaly (2 prospective; 1 retrospective) and 1 spontaneous abortion with no apparent congenital anomaly (<22 weeks of gestation) (retrospective).

Prospective and retrospective data on exposure to BEXSERO during pregnancy will continue to be collected routinely and recorded in the GSK safety database (Table 1). For prospective pregnancy cases, appropriate follow up information requests will be sent, as per routine practice, after the estimated delivery date with specific questionnaire for HCP requesting information on pregnancy outcome. For retrospective pregnancy cases, information on pregnancy outcome will be requested. Aggregate data analyses will continue to be provided in the periodic safety report.

Table 1 Attributes of BEXSERO pregnancy registry compared to routine pharmacovigilance (PV) activities

Attribute	Bexsero pregnancy registry	Routine PV activities
Dedicated Protocol	Yes	No
Annual report	Yes	No
Intermittent summary reports	Yes	Yes*
Prospective pregnancy registration	Yes	Yes
Retrospective pregnancy registration	Yes	Yes
Active follow up of pregnancy outcome	Yes	Yes
Comprehensive data collection	Yes	Yes
Demographic maternal characteristics	Yes	Yes
Maternal Prenatal data	Yes	Yes
Obstetrical history	Yes	Yes
Concurrent medical conditions	Yes	Yes
Maternal Alcohol, tobacco, and illicit drug use	Yes	Yes
Worldwide data collected	No	Yes

* Aggregate data analyses are provided in the periodic safety report (PBRER).

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Signature of Principal or Coordinating Investigator

GlaxoSmithKline Biologicals
Vaccines R&D
Investigator Approval Page

STUDY TITLE: BEXSERO Pregnancy Registry: an observational study of the safety of BEXSERO exposure in pregnant women and their offspring

Study: 205533 [MENB REC 2ND GEN-047 EPI VS US PR (V72_82OB)]

Development Phase: Observational Study

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Name of Investigator:	Deborah Covington,
Affiliation /investigational centre:	Evidera Evidence, Value & Access by PPD
Signature of Investigator:	_____
Date:	_____

GlaxoSmithKline Biologicals
Vaccines R&D
Sponsor Signatory Approval Page

Please note that by signing this page, you take responsibility for the content of the Abridged Study Report

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Name of Sponsor Signatory:	Daniela Toneatto
Title of Sponsor Signatory:	Clinical and Epidemiology Project Lead
Signature:	_____
Date:	_____