Title	Post-licensure observational effectiveness study of meningococcal B vaccine 4CMenB (Bexsero®) vaccination.
Protocol version identifier	3
Date of last version of protocol	03 September 2015
EU PAS registry number	Not Available
Active substance	NA
Medicinal product	4CMenB (Bexsero)
Product reference	NA
Procedure number	NA.
Marketing authorisation holder(s)	GSK Vaccines S.r.l.
Joint PASS study	No
Research question and objectives	The objective of this post-marketing observational study is to assess the impact on invasive meningococcal disease (all capsular groups) and effectiveness of 4CMenB vaccination against MenB and vaccine-type disease, after introduction of 4CMenB in the UK.
Country(ies) of study	United Kingdom
Author	[redacted], MD MPH EPIET; Global Epidemiology, GSK Vaccines
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2. LIST OF ABBREVIATIONS

4CMenB (Bexsero)	Meningococcal Serogroup B vaccine containing 4 main antigens: fHbp, NadA, NHBA and PorA P1.4 (OMV)
CSF	Cerebrospinal fluid
ECDC	European Centre for Disease Prevention and Control
EMA	European Medicines Agency
EMGM	The European Meningococcal disease Society
fHbp	Factor H binding protein (fHbp), derived from MenB strain MC58 (company code 741; GNA1870), is included in 4CMenB as a fusion with accessory protein 936 (GNA2091), which was derived from strain 2996. The fHbp recombinant fusion protein has been previously referred to as 936-741 or GNA2091-1870
GSK	GlaxoSmithKline Vaccines S.r.l.
HPA	Health Protection Agency
IEC	Independent Ethics Committee
IMD	Invasive Meningococcal Disease
IRB	Institutional Review Board
MATS	Meningococcal Antigen Typing System
MenB	Meningococcal capsular group B
MenC	Meningococcal capsular group C
MRU	Meningococcal Reference Unit in Manchester (UK)
NadA	Neisserial adhesin A (NadA, company code 961c) is included in 4CMenB as a single recombinant protein derived from MenB strain 2996
N. meningitidis	*Neisseria meningitidis*

NHBA	Neisseria Heparin Binding Antigen (NHBA) fusion protein (company code 287;GNA2132), derived from MenB strain NZ98/254, is included in 4CMenB as a fusion with accessory protein 953 (GNA1030), derived from MenB strain 2996. The NHBA recombinant fusion protein has been previously referred to as 287-953 or GNA2132-1030
NIGB	National Information Governance Board for Health and Social Care
NIP	National Immunisation Programme
OMV	Outer membrane vesicle
OR	Odds Ratio
PBT	Positive Bactericidal Threshold
PCR	Polymerase Chain Reaction
PCV	Proportion of cases that are vaccinated
PHE	Public Health England
PMS	Post-marketing surveillance
PorA	PorA P1.4 is the immunodominant protein antigen contained in the OMV derived from MenB strain NZ98/254
PPV	Proportion population vaccinated (coverage)
REB	Research Ethics Board
UK	United Kingdom
VE	Vaccine effectiveness

3. RESPONSIBLE PARTIES

See above/below

3.1 Main Author(s) of the Protocol

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The Netherlands

3.2 Principal Investigator

Not applicable (NA). This study will be run by Public Health England (PHE). Study throughout this protocol refers to the provision of customised post-marketing surveillance reports of independently generated data to assist GSK Vaccines S.r.l. in meeting its regulatory commitment.

3.3 Coordinating Investigator(s)

This study will be run by Public Health England (PHE).

3.4 Advisory Committee

GSK Vaccines S.r.l. does not foresee the need for a Study Steering Group given PHE's expertise in vaccine effectiveness studies.

4. ABSTRACT

Name of MAH: GSKVaccines S.r.l.	**Protocol number:** V72_38OB	**Date of Protocol Abstract:** 26 Oct 11, amended on 03 July 2015 (version 2.0)
Title of Study: Post-licensure observational effectiveness study of meningococcal B vaccine 4CMenB (Bexsero®) vaccination.		
Study Period: 3 years	**Study Type:** Required observational post-marketing study.	

Rationale and Background: Invasive meningococcal disease (IMD) is an important cause of meningitis and septicemia. There are 12 diverse polysaccharide capsules but only A, B, C, W, and Y capsular groups commonly cause IMD. According to the European Centre for Disease Prevention and Control (ECDC) surveillance report for 2007, 74% of IMD was caused by meningococcal capsular group B (MenB), with more than 3,406 cases and a case fatality ratio of almost 7.5% [ECDC, 2007]. The incidence of MenB disease is highest in infants and toddlers, followed by another peak in adolescents 15 to 19 years of age.

4CMenB vaccine (Bexsero®) has been registered with EMA in January 2013 for use in children from 2 months of age and over. Up to 2011, the safety of the 4CMenB vaccine was evaluated in 8 studies including 7 randomised controlled clinical trials with 6,427 subjects (from 2 months of age) who received at least one dose of 4CMenB. Among 4CMenB recipients, 4,843 were infants and toddlers, and 1,584 were adolescents and adults. Of the subjects who received primary infant series of 4CMenB, 1,630 received a booster dose in the second year of life.

This synopsis is based on assumptions regarding vaccine usage. GSK Vaccines S.r.l. is planning the study in England and proposes to collaborate with Public Health England (PHE) and its Meningococcal Reference Unit (MRU).

The purpose of this study is to investigate the effectiveness of 4CMenB vaccination during routine clinical care in the UK national immunisation programme (NIP).

This study will be conducted in compliance with the protocol, and the applicable regulatory requirement(s).

Name of MAH: GSKVaccines S.r.l.	**Protocol number:** V72_38OB	**Date of Protocol Abstract:** 26 Oct 11, amended on 03 July 2015 (version 2.0)

Research Question and Objectives: The objective of this post-marketing observational study is to assess the impact on MenB and effectiveness of 4CMenB vaccination against MenB disease, after introduction of 4CMenB in the UK.

Study Design: The study is a post-marketing observational effectiveness study of 4CMenB vaccination, given as part of routine clinical care in England.

Study in this protocol refers to the provision of customised post-marketing surveillance reports of independently generated data to assist GSK Vaccines S.r.l. in meeting its regulatory commitment.

The proposed designs of the study are as follows:

1. Descriptive study (no hypothesis testing): summary of the epidemiology of meningococcal disease, by vaccination status, age, etc. This description would focus on the epidemiology not only of MenB, but, if possible, also include other capsular groups in order to evaluate both cross protection against meningococci with other capsular groups and any strain replacement after introduction of the vaccine.
2. Analyses for effectiveness of 4CMenB will be performed prospectively using the screening method. If the screening method is inapplicable then a case control method would be used. All these study designs have successfully been used to assess effectiveness of the meningococcal capsular group C (MenC) conjugate vaccine in England [Bose et al., 2003], [Ramsay ME et al., 2001], [Trotter CL et al., 2004]. Similarly to other retrospective methods, the screening method is based on a comparison of the proportion vaccinated among the cases and the population. However, it differs from other methods in that control is achieved by external standardisation, using an estimate of vaccine coverage which is derived from sources external to the study.

Data sources

Data for this study will be collected through the national surveillance system, as well as an additional source(s) to collect data regarding vaccinations in the population (e.g. COVER and/or the General Practice Research Database). All cases of confirmed MenB disease will routinely be followed up to obtain vaccination history (including batch number) through enhanced surveillance by PHE. Additionally, demographics and medical history will be ascertained.

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GSK Vaccines S.r.l. has developed a strategy to estimate potential strain coverage called Meningococcal Antigen Typing System (MATS) [Donnelly J et al., 2010]. A survey of approximately 1,000 different invasive meningococcal serogroup B isolates collected during 2007-2008 in 5 European countries (incl. England) showed that, depending on the country of origin, between 73% and 87% of meningococcal serogroup B isolates had an appropriate MATS antigen type to be covered by the vaccine. These 5 countries represented 59% of the total notified cases (3,396) in Europe in 2007. Sero(sub)type distributions in the remaining European countries were comparable with this subset. Overall, 78% (95% confidence limits from 66-91%) of the approximately 1,000 strains surveyed using MATS were found to have a potentially susceptible antigen type.

Definitions

A case of *Neisseria meningitidis* is defined by culture of *Neisseria meningitidis* or identification of meningococcal DNA from a normally sterile site. For the purposes of surveillance cases will be further classified as:

A. A case of capsular group B *Neisseria meningitidis* is defined as isolation of capsular group B *Neisseria meningitidis* or positive capsular group B specific PCR from a normally sterile site.

B. **Capsular group B-vaccine-type**

I. **Confirmed case – capsular group B-vaccine-type:**

a. Isolation with ≥ 1 vaccine antigen above positive bactericidal threshold (PBT) by MATS-ELISA or PorA P1.4 from a normally sterile site (**MATS-positive**), or

b. PCR on a normally sterile site + B isolation from throat swab with ≥ 1 vaccine antigen above PBT by MATS-ELISA or PorA P1.4 (**MATS-positive**), or

c. PCR on a normally sterile site + PorA P1.4 identified on genosubtyping

II. **Probable case – capsular group B-vaccine-type:** PCR on a normally sterile site + fHBP sub-variant 1, 4, 37, 232

III. **Unlikely case – capsular group B-vaccine-type:** isolation (Ia or Ib) from a normally sterile site with three vaccine antigens below positive bactericidal threshold (PBT) by MATS-ELISA + PorA P1 ≠ 4 (**MATS-**

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negative)

IV. **Indeterminate case – capsular group B-vaccine-type:** capsular group B, but not in I, II, III

<u>Vaccine (Bexsero) failure against vaccine-type-specific B disease</u>: Reported to authorities

- Case as defined for above subgroup I or II *, and
- Confirmation that patient was age appropriately and fully vaccinated as recommended and with a reasonable delay for full effect of immunization, e.g. effectiveness of primary vaccination:
  a. At least 14 days after the 3rd injection in the routine schedule (standard primary infant and booster), or
  b. If primary vaccination was not given as part of the standard routine infant schedule, then at least 14 days after the 2nd injection

(Subgroups III and IV: fully vaccinated reported to authorities, but not defined as vaccine failure)*

Our analyses will only include individuals in England fully and timely vaccinated according to the routine, standard national immunization schedule as described in 3.5.1. Exploratory analyses could be envisioned such as for other schedules (e.g. catch-up at 3,4,12 months or 4,12 months), capsular non-B, other regions (Wales, Scotland), if data become available.

Population:

<u>United Kingdom</u>

Meningococcal capsular group B disease (MenB) is an important public health concern in England with annually more than 1,000 laboratory confirmed cases, of which up to 60% in children < 5 years of age, and one of the highest incidences globally in that age group (around 20 per 100,000) [HPA, 2008-2009]. In the epidemiological year 2009-2010*, almost half of all cases were reported in children aged 2 years or less (n = 380, 48). Incidences are highest in infants and toddlers, with another small peak in late teens [HPA, 2011].

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General population, depending on how 4CMenB is being used in the UK campaign expected to start Sep 2015:

1. Infants standard routine at age 2, 4 with a booster at 12 months (3 doses in total)
2. Infants for a NIP with small catch-up campaign, e.g. at age 3 and 4 months with a booster at 12 months (3 doses in total), or at 4 months with a booster at 12 months (2 doses in total)

Inclusion Criteria

According to the case definitions as given above. Final criteria for 4CMenB failure will depend on the schedule for use of 4CMenB in the population.

Exclusion Criteria

Excluded will be those who have not been offered the vaccine (e.g. immigrants) and individuals who were not vaccinated according to the NIP (partially vaccinated). From previous vaccine studies, we know that the proportion partially vaccinated will be low (PHE personal communication).

The full list of inclusion and exclusion criteria is included in protocol section 9.2.3.

Variables:

Exposure(s) of interest

GSK Vaccines' 4CMenB vaccine is used in this study as part of routine clinical care, e.g. as recommended in the NIP. The commercial product should be stored and administered in accordance with applicable national or EU guidelines and in accordance with the package insert. Co-administration of other vaccines is permitted as consistent with clinical practice.

Outcome(s)

Effectiveness outcomes

The primary outcome is a capsular group B confirmed case by culture and/or PCR from a normally sterile site (case definition A), regardless of MATS.

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The secondary outcome is a confirmed or probable case of capsular group B 4CMenB-vaccine-type where protection would have been expected based on the vaccine antigens (case definition B).

Other Variables

Vaccination status, age and gender, will be collected for the screening method. Dates of exposure are essential to allow for sensitivity analyses on the index dates.

Data Sources: Data for this study will be collected through the national surveillance system, as well as an additional source(s) to collect data regarding vaccinations. All cases of confirmed MenB disease will routinely be followed up to obtain vaccination history (including batch number) through enhanced surveillance by PHE. Additionally, demographics and medical history will be ascertained.

For the analytical study the screening method will be used. As above, vaccine history of confirmed cases will be collected to assess the proportion of cases that were fully vaccinated (PCV).

The comparator will be national vaccination rates as the proportion population vaccinated (PPV). These data may for instance be taken from the Cover Of Vaccination Evaluated Rapidly (COVER) system which collects data about the coverage of routine infant vaccination from health authorities in England, and/or from a General Practice Research Database [Anon, 1999]. COVER data would have some limitations as it only provides coverage at fixed time points (12, 24 months) and we would not know about partial vaccination. Data will therefore be supplemented by disaggregate data obtained from either general practice or child health database to provide estimates of dose specific coverage at specific ages.

The study will be partnered with Public Health England (PHE) and its Meningococcal Reference Unit (MRU) in England, so that national laboratory surveillance data for meningococcal disease can be used [Gray SJ et al., 2006]. PHE's national surveillance system consists of statutory reporting of confirmed invasive meningococcal disease by laboratories. Statutory notification by physicians to local units of PHE ensures rapid follow up of clinically diagnosed cases and helps to ensure complete laboratory investigation. Clinical specimens and isolates of *Neisseria meningitidis* are also referred for capsular group specific PCR and routine serogrouping and subtyping.

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In addition, all isolates referred to MRU from individuals eligible for vaccination will have qualitative and quantitative assessment of meningococcal antigens (Meningococcal Antigen Typing System or MATS) will be evaluated for each case where the organism is identified by culture.

If it is decided to pursue a case-control study instead of using the screening method, for instance if uptake information is difficult to obtain, three controls per case will be selected from the same population as where the cases arose from. This can for instance be from the same general practitioner's practice or local health economy, as where the case is registered in order to control for residential area. Three controls per case could be matched by age at the date the case occurred (date of month) and gender.

Data Analysis: This study will provide a summary of the epidemiology of all capsular groups of meningococcal disease, e.g. by vaccination status, age, setting and method. The method will be purely descriptive and summarize the observed number of *N. meningitidis* (all capsular groups) cases reported to PHE, stratified by variable of interest.

Vaccine effectiveness (VE) is generally defined as the % reduction in the attack rate in vaccinated compared with unvaccinated children in the same birth cohorts. VE will be assessed by the screening method, or by a case-control method if the screening method cannot be used (for example, if appropriate coverage data cannot be determined):

a. Screening method:

   For this method, the VE can be estimated using the formula below, where PCV is the proportion of cases that are vaccinated and PPV is the proportion population vaccinated (coverage):

$$VE = 1 - \frac{(PCV \times (1-PPV))}{((1-PCV) \times PPV)}$$

   The vaccine effectiveness estimate will be calculated along with the 95% confidence interval using the exact binomial distribution for the proportion of cases vaccinated in each of the study settings.

b. Case-control method:

   In case-control studies, vaccine effectiveness is based on the odds ratio (OR) and is

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defined as: VE = 1 - OR

The vaccine effectiveness estimate will be calculated along with the 95% confidence interval using the standard errors from logistic regression.

Sample size considerations

a. Screening method

If we assume 90% vaccine coverage and observe 60% vaccine effectiveness, then with 175 cases, the lower limit of the 95% confidence interval for vaccine effectiveness will be above 40%.

b. Case-control method

If we assume a vaccine exposure rate in the control population of 90% and observe 60% vaccine effectiveness, then with 284 cases and 852 controls (1:3 matching), the lower limit of the 95% confidence interval for vaccine effectiveness will be above 40%.

Expected numbers and feasibility

From UK data presented at EMGM 2011, it is known that about 40% of IMD cases below the age of one year occur in infants < 5 months of age. Taking into account that these children may not be well protected by the 4CMenB vaccine yet, the calculations use a VE of 0% at < 5 months of age. For children 5 - 12 months of age, the vaccine effectiveness of 4CMenB is estimated to be approximately 50%.

Example: assuming a coverage of 90% (with 10% for unvaccinated) and VE of 60% in fully vaccinated infants between 12 and 24 months of age that currently have an observed number of 119 cases per year: (119*10%)+(119*90%*40%) = 55 expected cases per year.

However, these are rough, very first estimates based on several assumptions as described in the protocol. The study is expected to last 3 years.

Interim analysis

Study progress reports, including (as soon as applicable) interim results, will be provided by the mentioned affiliations every six months for the 3-year study duration.

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Informed Consent and Ethical Approval: In 2001, the HPA (now PHE) received approval from the Department of Health's Patient Information Advisory Group (PAIG) application to continue the collection of personal's identification data for the surveillance, control and prevention of communicable diseases. This ongoing approval covers the routine meningococcal surveillance system.		
Milestones: Important milestones, such as start, duration and reporting of this study, largely depend on whether or not 4CMenB will be registered and introduced into the UK, under which circumstances (NIP or outbreak setting), and which age groups are indicated to receive the vaccine. A large NIP catch-up campaign would reduce the absolute number of reported meningococcal cases and as a result it will take more time before the required sample size has been reached. This would cause an increase of the total study duration and, therefore, a later date for the report(s) and publication(s). We assume the total study (descriptive and analytical) will take 3 years, with another six months for the final report(s) and publication(s).		

5. AMENDMENTS AND UPDATES

Amended on 03 of July 2015 (Protocol Amendment number 1)

Amended on 03 of September 2015 (Protocol Amendment number 2)

6. MILESTONES

Important milestones, such as start, duration and reporting of this study, largely depend on whether or not 4CMenB will be registered and introduced into the UK, under which circumstances (NIP or outbreak setting), and which age groups are indicated to receive the vaccine. A large NIP catch-up campaign would reduce the absolute number of reported meningococcal cases and as a result it will take more time before the required sample size has been reached. This would cause an increase of the total study duration and, therefore, a later date for the report(s) and publication(s).

We assume the total study (descriptive and analytical) will take 3 years, with another six months for the final report(s) and publication(s).

A figure of the estimated timelines was included earlier in this protocol (Figure 4).

Overview of study milestones.

Milestone	**Planned date**
Start of data collection	With launch in the UK NIP, expected 1 Sep 2015
End of data collection	3 years after study start
Study progress reports	Every 6 months for the 3-year study duration
Registration in the EU PAS register ENCePP	At least 4 week before study start
Submission to Ethics Committee/Institutional Review Board	NA, see section 10 (role of NIGB in approving national surveillance activities)
Final report of study results	6 months after end of the 3-year study duration

7. RATIONALE AND BACKGROUND

Invasive meningococcal disease (IMD) is an important cause of meningitis and septicemia. There are 12 diverse polysaccharide capsules but only capsular groups A, B, C, W, and Y commonly cause IMD. According to the European Centre for Disease Prevention and Control (ECDC) surveillance report for 2007, 74% of IMD in Europe was caused by meningococcal capsular group B (MenB), with more than 3,406 cases and a case fatality ratio of almost 7.5% [ECDC, 2007].The incidence of MenB disease is highest in infants and toddlers, followed by another peak in adolescents 15 to 19 years of age.

4CMenB vaccine (Bexsero®) has been registered with EMA in January 2013 for use in children from 2 months of age and over. Up to 2011, the 4CMenB vaccine was evaluated in 8 studies including 7 randomised controlled clinical trials with 6,427 subjects (from 2 months of age) who received at least one dose of 4CMenB. Among 4CMenB recipients, 4,843 were infants and toddlers, and 1,584 were adolescents and adults. Of the subjects who received primary infant series of 4CMenB, 1,630 received a booster dose in the second year of life.

This synopsis is based on assumptions regarding vaccine usage. GSK Vaccines S.r.l. is planning the study in England and proposes to collaborate with Public Health England (PHE) Immunisation Department at Colindale, London, and PHE's Meningococcal Reference Unit (MRU) in Manchester.

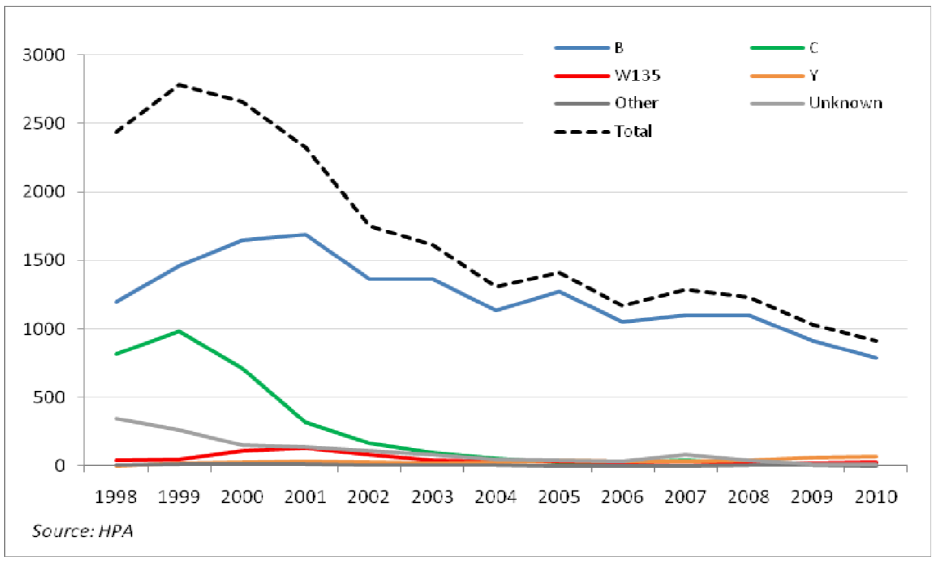
The purpose of this study is to investigate the effectiveness of 4CMenB vaccination during routine clinical care in the UK national immunisation programme (NIP).

This study will be conducted in compliance with the protocol, and the applicable regulatory requirement(s).

Background epidemiology in the United Kingdom

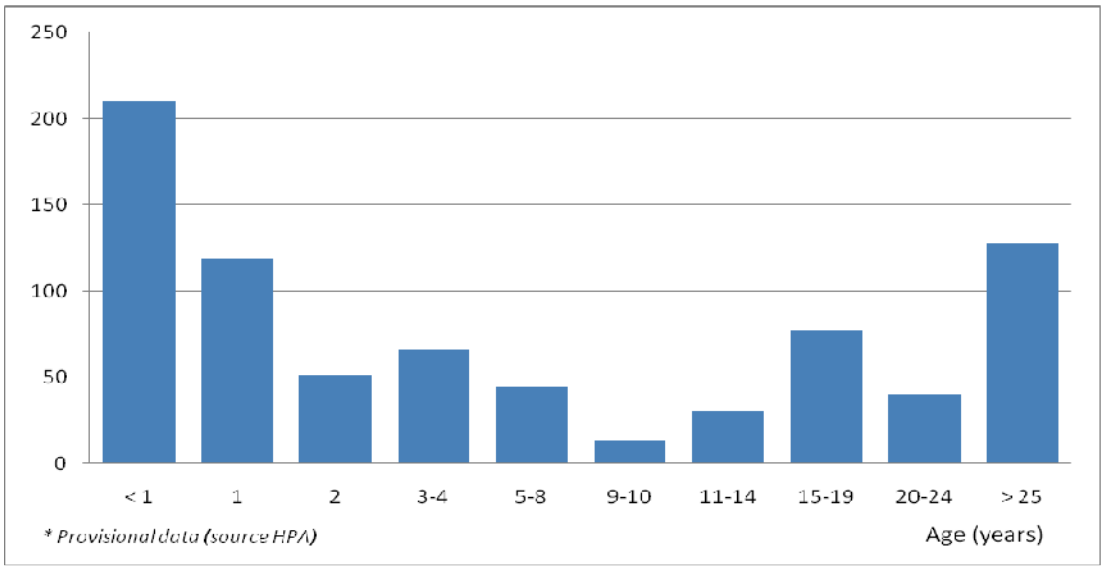
Meningococcal capsular group B disease (MenB) is an important public health concern in England with annually more than 1,000 laboratory confirmed cases, of which up to 60% in children < 5 years of age, and one of the highest incidences globally in that age group (around 20 per 100,000) [HPA, 2008-2009]. Figure 1 shows the absolute number of IMD cases in England and Wales over the past decade [HPA, 2001].

Figure 1 **Absolute number of IMD cases by capsular group, England & Wales, 1998-2010**



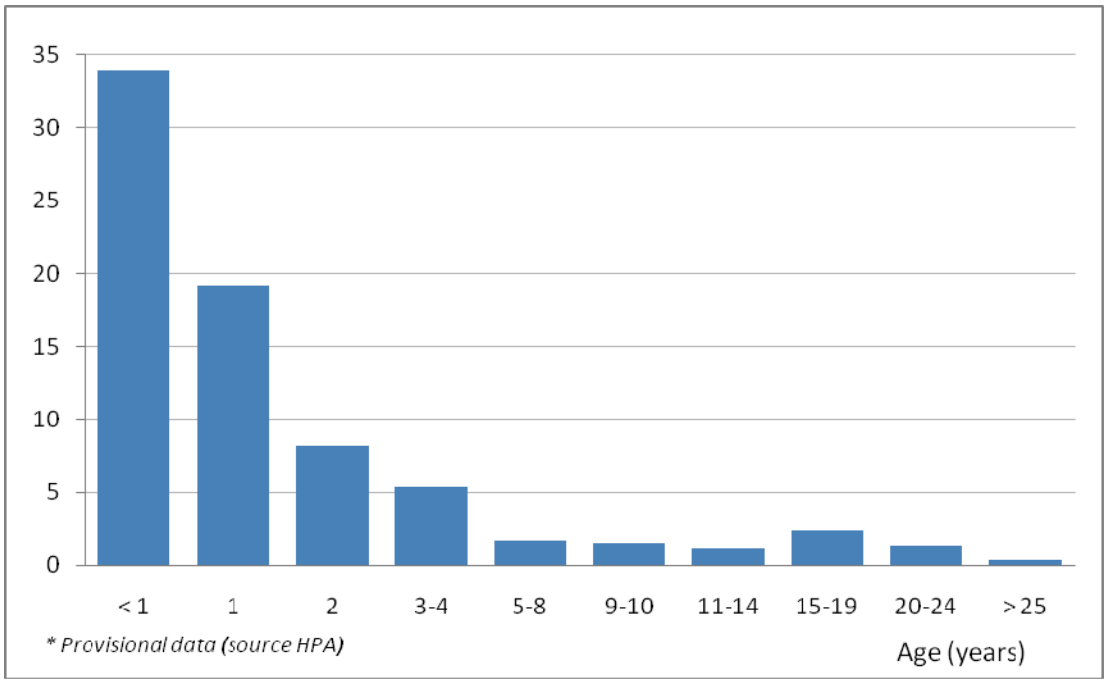
In the epidemiological year 2009-2010***, almost half of all cases were reported in children aged 2 years or less (n = 380, 48%, Figure 2). Incidences are highest in infants and toddlers, with another small peak in late teens (Figure 3).

Figure 2 **Absolute number of laboratory confirmed cases of MenB, by age in years, England & Wales, 2009-2010* (N = 785)**



*** 1 July 2009 – 1 July 2010

Figure 3 **Incidence of laboratory confirmed cases of MenB per 100,000, by age in years, England & Wales, 2009-2010*****



Meningococcal Antigen Typing System [Donnelly J et al., 2010]

GSK Vaccines S.r.l. has developed a strategy to estimate potential strain coverage called Meningococcal Antigen Typing System (MATS). A survey of approximately 1,000 different invasive MenB isolates collected during 2007-2008 in 5 European countries (incl. England) showed that, depending on the country of origin, between 73% and 87% of MenB isolates had an appropriate MATS antigen type to be covered by the vaccine. These 5 countries represented 59% of the total notified cases (3,396) in Europe in 2007. Sero(sub)type distributions in the remaining European countries were comparable with this subset. Overall, 78% (95% confidence limits from 66-91%) of the approximately 1,000 strains surveyed using MATS were found to have a potentially susceptible antigen type.

Post-marketing studies

Epidemiological studies have been done previously e.g. after introduction of the Meningococcal capsular group C (MenC) conjugate vaccine in England in November 1999. The first article describing MenC vaccine's high efficacy was published about one year later by Ramsay, Andrews, Kaczmarski and Miller from HPA [Lancet, January 2001]. Three years after, they published a follow-up article describing the effectiveness in

more detail [Trotter, Andrews, Kaczmarski, Miller and Ramsay, Lancet 2004]. This 4CMenB study proposes to collaborate with the same institutions, including many of the same experts as were involved in the MenC vaccine effectiveness studies, building upon previous studies and methodology that demonstrated the effectiveness of the MenC vaccine programme.

The impact of the MenC vaccine in England can clearly be seen in Figure 1, with a drastic drop in MenC cases after 1999. Although reports of MenB disease have gone down slightly, it does show a similar number of cases in England population as MenC had at the time of vaccine introduction. Therefore, data on 4CMenB vaccine impact and effectiveness may be expected relatively soon after introduction in England.

8. RESEARCH QUESTION AND OBJECTIVES

The objective of this post-marketing observational study is to assess the impact on invasive meningococcal disease (all capsular groups) and effectiveness of 4CMenB vaccination against MenB and vaccine-type disease, after introduction of 4CMenB in the UK.

9. RESEARCH METHODS

The study is a post-marketing observational effectiveness study of 4CMenB vaccination, given as part of routine clinical care in England. Study throughout this protocol refers to the provision of customised post-marketing surveillance reports of independently generated data to assist GSK Vaccines in meeting its regulatory commitment.

Part of the study will be a prospective description of all reported meningococcal cases (all capsular groups) as reported through routine national surveillance to Public Health England (PHE) and its Meningococcal Reference Unit (MRU). Observations will start with introduction of the vaccine into routine clinical care in England and last for the 3-year study duration. Additionally, there will be retrospective reporting of the prospective collection of cases for the 3-year study duration.

The second part of the study will be analytical in nature and assess the effectiveness of the 4CMenB vaccine. The study duration will depend on the number of meningococcal cases required to reach sufficient precision, currently estimated to be 3 years. The screening method is proposed, unless issues with obtaining relevant coverage data call for alternative designs (e.g. the case-control method).

A figure with study timelines is included below (Figure 4).

9.1 Study Design

The proposed designs of the study are as follows:

1. Descriptive study (no hypothesis testing): summary of the epidemiology of meningococcal disease, by vaccination status, age, etc. This description would focus on the epidemiology not only of MenB, but, if possible, also include other capsular groups in order to evaluate both cross protection against meningococci with other capsular groups and any replacement that may occur after introduction of the vaccine.
2. Analyses for effectiveness of 4CMenB will be performed prospectively using the screening method (see a brief outline below). If the screening method is inapplicable then a case control method would be used. All these study designs have successfully been used to assess effectiveness of the MenC conjugate vaccine in England [Bose A et al., 2003], [Ramsay ME et al., 2001], [Trotter CL et al., 2004].
3. Similarly to other retrospective methods, the screening method is based on a comparison of the proportion vaccinated among the cases and the population. However, it differs from other methods in that control is achieved by external standardisation, using an estimate of vaccine coverage which is derived from sources external to the study [Farrington CP, 1993].

9.2 Setting

9.2.1 Study Period

Overall study period

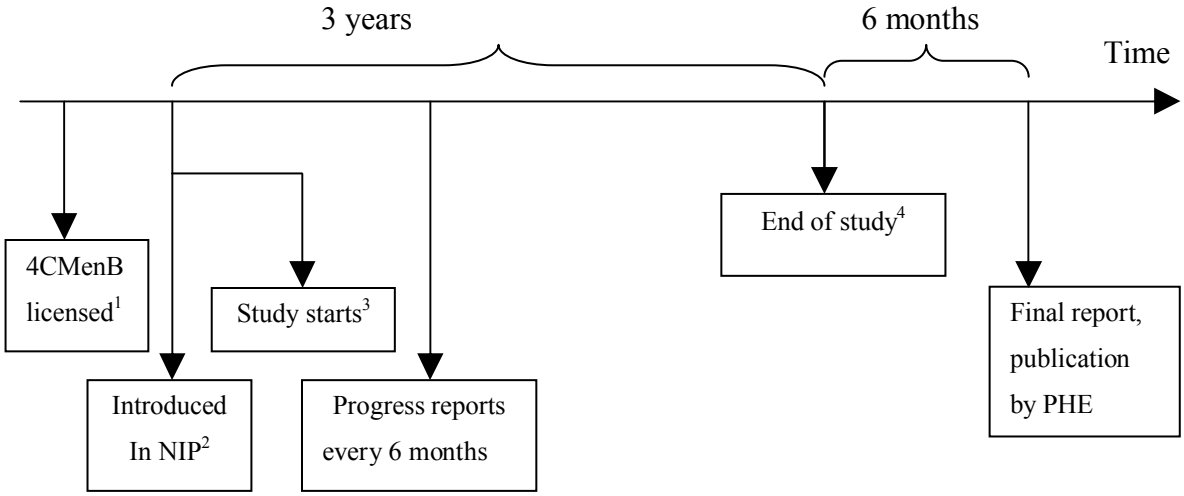
The overall study period will consist of the 3-year study duration, and time needed for analysis of data, production of the final report and writing of publication(s). The latter is estimated to take approximately 6 months. A figure depicting the study timelines is given below (Figure 4).

Observation period

The observation period will be 3 years, during which the descriptive and analytical study will take place.

Study timelines

Figure 4 Study Timelines



[1] EMA registration Jan 2013
[2] UK introduction expected Sep 2015
[3] Start of study expected Sep 2015 (with introduction into NIP)
[4] Total study duration 3 years

9.2.2 Study Subjects

All meningococcal cases reported during the above mentioned timeframe(s) will be included in both parts of the study (descriptive and analytical). Data from the national surveillance on meningococcal disease, as well as vaccination status of the cases, will be collected through PHE in England.

9.2.3 Study Population Selection

The study population for the descriptive part of the study is the general population in England. Individuals will be included in the cohorts targeted for vaccination in England. Exploratory analyses could be envisioned for other regions (Northern Ireland, Wales, Scotland), if data become available.

Inclusion Criteria

Case definitions are given in section 9.4.2. Final criteria for 4CMenB failure will depend on the schedule for use of 4CMenB in the population. The design of the study will also affect inclusion criteria, e.g. for case-control study controls will be included as defined in section 9.5.

Exclusion Criteria

Excluded will be those who have not been offered the vaccine (e.g. immigrants) and individuals who were not vaccinated according to the NIP (partially vaccinated). From previous vaccine studies, we know that the proportion partially vaccinated will be low (PHE personal communication).

9.3 Variables

9.3.1 Exposure of Interest

GSK Vaccines' 4CMenB vaccine is used in this study as part of routine clinical care, e.g. as recommended in the NIP. Information on how the commercial product should be stored and administered is in accordance with applicable national or EU guidelines and is described in the package insert. Co-administration of other vaccines may occur as consistent with clinical practice.

Indication and schedule

The 4CMenB was registered in Europe in January 2013. The indication of the 4CMenB vaccine is for active immunisation against invasive disease caused by MenB strains in individuals from 2 months of age and older (3+1 schedule).

The anticipated schedule for 4CMenB in the UK is:

1. Infants standard routine at age 2, 4 with a booster at 12 months (2+1 schedule, 3 doses in total)
2. Infants for a NIP with small catch-up campaign, e.g. at age 3 and 4 months with a booster at 12 months (3 doses in total), or at 4 months with a booster at 12 months (2 doses in total)

9.3.2 Outcome(s)

The primary outcome is a capsular group B confirmed case by culture and/or PCR from a normally sterile site (case definition A), regardless of MATS.

The secondary outcome is a confirmed or probable case of capsular group B 4CMenB-vaccine-type where protection would have been expected based on the vaccine antigens (case definition B).

Additional calculations can be envisioned to investigate the dose-response relationships for each antigen in the vaccine (versus having at least one antigen, as described in the secondary objective). Exploratory analyses on the effectiveness of 4CMenB against other meningococcal capsular groups could take place at a later stage.

9.3.3 Other Variables

Vaccination status, age and gender, will be collected for the screening method. Dates of exposure are essential to allow for sensitivity analyses on the index dates.

9.4 Data Sources

Exposure of interest

Data for this study will be collected through the national surveillance system, as well as an additional source(s) to collect data regarding vaccinations. All cases of confirmed MenB disease will routinely be followed up to obtain vaccination history (including batch number) through enhanced surveillance by PHE. Additionally, demographics and medical history will be ascertained.

For the analytical study the screening method will be used. As above, vaccine history of confirmed cases will be collected to assess the proportion of cases that were fully vaccinated (PCV).

The comparator will be national vaccination rates as the proportion population vaccinated (PPV). These data may for instance be taken from the Cover Of Vaccination Evaluated Rapidly (COVER) system which collects data about the coverage of routine infant vaccination from health authorities in England, and/or from a general practice database [Anon, 1999]. COVER data would have some limitations as it only provides coverage at fixed time points (12, 24 months) and we would not know about partial vaccination. Data will therefore be supplemented by disaggregate data obtained from either general practice or child health database to provide estimates of dose specific coverage at specific ages.

Outcomes of interest

The study will be partnered with Public Health England (PHE) and its Meningococcal Reference Unit (MRU) in England, so that national laboratory surveillance data for meningococcal disease can be used [Gray SJ et al., 2006]. PHE's national surveillance system consists of statutory reporting of confirmed invasive meningococcal disease by laboratories. Statutory notification by physicians to local units of PHE ensures rapid follow up of clinically diagnosed cases and helps to ensure complete laboratory investigation. Clinical specimens and isolates of *Neisseria meningitidis* are also referred for capsular group specific PCR and routine serogrouping and subtyping.

In addition, all isolates referred to MRU from individuals eligible for vaccination will have qualitative and quantitative assessment of meningococcal antigens (Meningococcal antigen typing system or MATS) will be evaluated for each case where the organism is identified by culture. For cases with PCR-only confirmation of capsular group B (no

isolate available from sterile site), but where a capsular group B isolate from a throat swab is available, MATS will be performed on the throat isolate instead.

GSK Vaccines will provide MATS kits to MRU.

If it is decided to pursue a case-control study instead of using the screening method, for instance if uptake information is difficult to obtain, three controls per case will be selected from the same population as where the cases arose from. This can for instance be from the same general practitioner's practice or local health economy, as where the case is registered in order to control for residential area. Three controls per case could be matched by age at the date the case occurred (date of month) and gender.

9.4.1 Operational Exposure Definition

Vaccination status by individual, including the type of vaccine, batch number and date of vaccination, is included in the enhanced surveillance system.

9.4.2 Operational Outcome Definition and Identification Process

A case of *Neisseria meningitidis* is defined by culture of *Neisseria meningitidis* or identification of meningococcal DNA from a normally sterile site. For the purposes of surveillance cases will be further classified as:

A. A case of capsular group B *Neisseria meningitidis* is defined as isolation of capsular group B *Neisseria meningitidis* or positive capsular group B specific PCR from a normally sterile site.

B. **Capsular group B-vaccine-type**

I. **Confirmed case – capsular group B-vaccine-type:**

a. Isolation with ≥ 1 vaccine antigen above positive bactericidal threshold (PBT) by MATS-ELISA or PorA P1.4 from a normally sterile site (**MATS-positive**), or

b. PCR on a normally sterile site + B isolation from throat swab with ≥ 1 vaccine antigen above PBT by MATS-ELISA or PorA P1.4 (**MATS-positive**), or

c. PCR on a normally sterile site + PorA P1.4 identified on genosubtyping

II. **Probable case – capsular group B-vaccine-type:** PCR on a normally sterile site + fHBP sub-variant 1, 4, 37, 232

III. **Unlikely case – capsular group B-**vaccine**-type:** isolation (Ia or Ib) from a normally sterile site with three vaccine antigens below positive

bactericidal threshold (PBT) by MATS-ELISA + PorA P1 ≠ 4 (**MATS-negative**)

IV. **Indeterminate case – capsular group B-vaccine-type:** capsular group B, but not in I, II, III

Vaccine (Bexsero) failure against vaccine-type-specific B disease: Reported to authorities

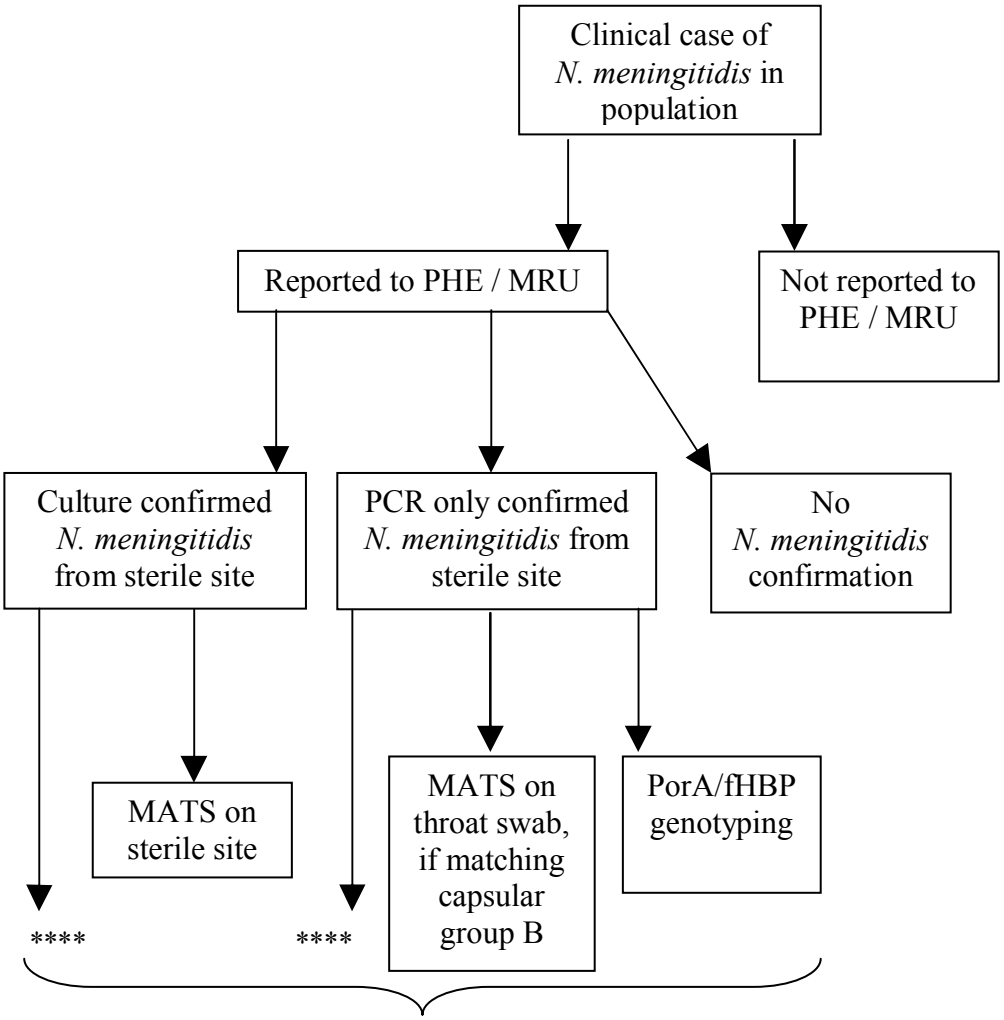
- Case as defined for above subgroup I or II *, and
- Confirmation that patient was age appropriately and fully vaccinated as recommended and with a reasonable delay for full effect of immunization, e.g. effectiveness of primary vaccination:
  a. At least 14 days after the 3rd injection in the routine schedule (standard primary infant and booster), or
  b. If primary vaccination was not given as part of the standard routine infant schedule, then at least 14 days after the 2nd injection

  (Subgroups III and IV: fully vaccinated reported to authorities, but not defined as vaccine failure)*

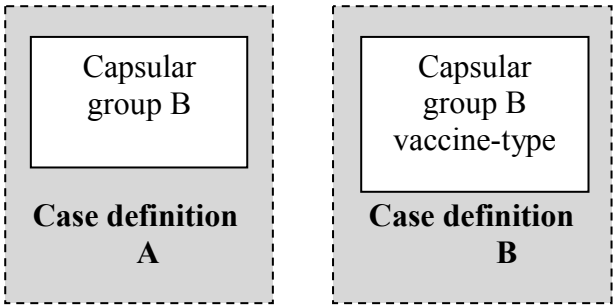
Our analyses will only include individuals in England fully and timely vaccinated according to the routine, standard national immunization schedule as described in section 9.3.1. Exploratory analyses could be envisioned such as for other schedules (e.g. catch-up at 3,4,12 months or 4,12 months), capsular non-B, other regions (Wales, Scotland), if data become available.

Following these definitions, please find a flowchart with the meningococcal case identification process and case definitions below (Figure 5).

Figure 5 Flowchart - Case identification process in England



Depending on results, fulfilling case definition A or B (or none of these)



**** Only capsular group B (case definitions A or B) or none of these
NB: vaccine failure: A or B, and appropriately vaccinated at least 14 days before

9.4.3 Operational Variable(s) Definition

See above under 9.3.3 and 9.4.2.

9.4.4 Advisory Committee(s)

GSK Vaccines does not foresee the need for a Study Steering Group given PHE's expertise in vaccine effectiveness studies.

9.5 Study Size

a. Screening method

The number of cases required to estimate vaccine effectiveness with various levels of precision (based on the difference between the point estimate of VE and lower limit of the 95%CI) is shown in Table 1 below [Farrington CP, 1993]. Calculations assume 90% vaccine coverage in the populations and consider observed VE for 50% to 80%.

Table 1 Screening Method (Sample Size Calculation)

Vaccine Coverage	Lower 95% CI limit below VE	Vaccine Effectiveness 50%	Vaccine Effectiveness 60%	Vaccine Effectiveness 70%	Vaccine Effectiveness 80%
90%	5%	3022	1742	882	361
	10%	874	516	271	117
	15%	445	269	145	65
	20%	284	**175**	97	45

If we assume 90% vaccine coverage and observe 60% vaccine effectiveness, then with 175 cases, the lower limit of the 95% confidence interval (CI) for vaccine effectiveness will be above 40%.

b. Case-control method

The number of cases and controls required (1:3 ratio) to estimate vaccine effectiveness with various levels of precision (based on the difference between the point estimate of VE and lower limit of the 95%CI) is shown in Table 2 below. The calculations assume 90%

of controls are exposed to vaccine and consider observed VE for 50% to 80% [Schesselman JJ, 1982a], [Schesselman JJ, 1982b].

Table 2 Case-control Method (Sample Size Calculation for 1:3 matching)

Probability of vaccination in controls	Lower 95% CI limit below VE	Vaccine Effectiveness 50%	Vaccine Effectiveness 60%	Vaccine Effectiveness 70%	Vaccine Effectiveness 80%
90%	5%	4900	2820	1428	585
	10%	1400	835	440	190
	15%	720	435	235	105
	20%	460	**284**	157	73

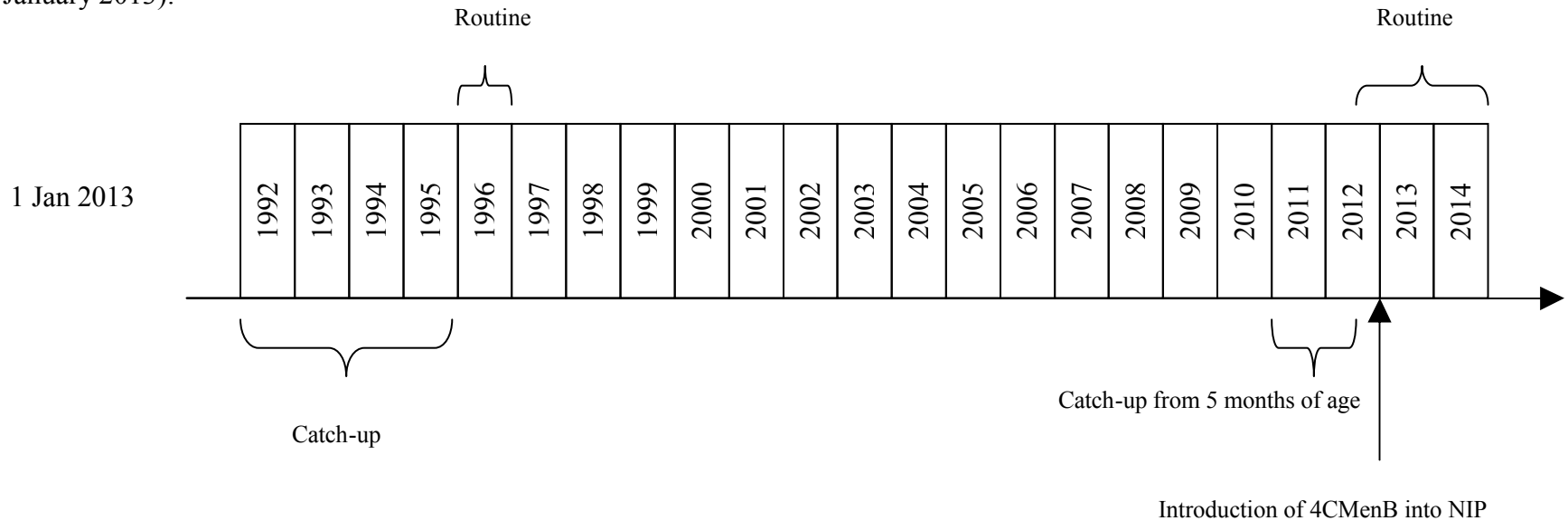
If we assume a vaccine exposure rate in the control population of 90% and observe 60% vaccine effectiveness, then with 284 cases and 852 controls (1:3 matching), the lower limit of the 95% confidence interval for vaccine effectiveness will be above 40%.

Expected numbers and feasibility

In order to calculate the expected number of cases after introduction of the 4CMenB vaccine in the UK, we need to take the currently observed number of cases and the vaccination status by age group into account. Figure 6 shows an assumed vaccination schedule by birth cohort for the years 2013, 2014 and 2015.

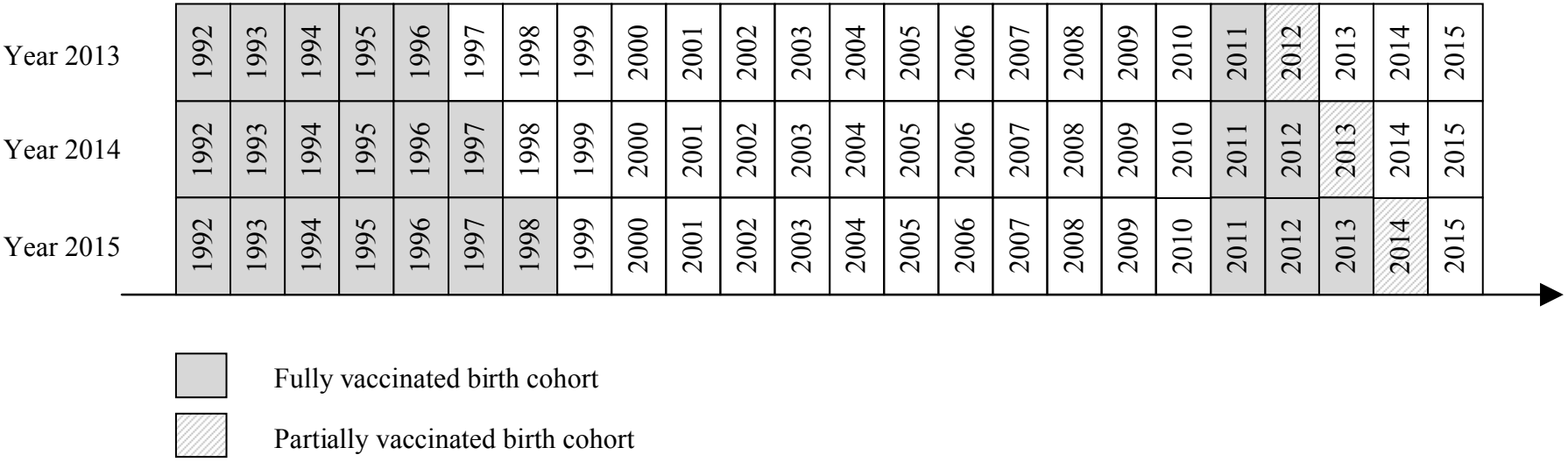
Figure 6 Vaccination Status by Birth Cohort Over Time, UK

Potential situation at baseline: eligibility for vaccination in the first year of introduction of 4CMenB vaccine into the UK (e.g. from 1 January 2013):



From UK data presented at EMGM 2011, it is known that about 40% (5/12) of IMD cases below the age of one year occur in infants under 5 months of age. Taking into account that these children may not be well protected by the 4CMenB vaccine yet, the calculations use a VE of 0% at < 5 months of age. Similarly, for the ages 5 until 12 months of age, we assumed a slightly lower VE of 50%, while for all other ages the VE is assumed to be 60%.

Potential situation after three years (e.g. at 31 December 2015): fully and partially (< 1 year of age) vaccinated birth cohorts:



From this schedule, using observed numbers of cases in the epidemiological year 1 July 2009 until 30 June 2010, the expected number of MenB cases for three years (2013, 2014 and 2015) has been calculated. Table 3 shows the expected numbers of meningococcal B cases after 4CMenB vaccination among infants and children in the United Kingdom assuming vaccine effectiveness of 60% and vaccine coverage of 90%.

Example: assuming a coverage of 90% (with 10% for unvaccinated) and VE of 60% in fully vaccinated infants between 12 and 24 months of age that currently have an observed number of 119 cases per year: (119*10%)+(119*90%*40%) = 55 expected cases per year. This age group is shaded in grey as an example in Table 3.

Table 3 **Observed and Expected Laboratory Confirmed Meningococcal Capsular Group B Cases by Age and Epidemiological Year, England & Wales, 2009-2010*****

Observed # of cases	2009-2010*
< 1 year	210
1 year	119
2 years	51
3-4 years	66
5-8 years	45
9-10 years	13
11-14 years	31
15-19 years	77
20-24 years	40
25+	128
NK	5
Total	785

*** 1 July 2009 - 30 June 2010

Birth cohort	Assumed age in 2013	2013	2014	2015
2014				155
2013			155	55
2012	< 1 year	155	55	51
2011	1	55	51	33
2010	2	51	33	33
2009	3	33	33	11
2008	4	33	11	11
2007	5	11	11	11
2006	6	11	11	11
2005	7	11	11	7
2004	8	11	7	7
2003	9	7	7	8
2002	10	7	8	8
2001	11	8	8	8
2000	12	8	8	8
1999	13	8	8	15
1998	14	8	15	7
1997	15	15	7	7
1996	16	7	7	7
1995	17	7	7	7
1994	18	7	7	4
1993	19	7	4	8
1992	20	4	8	8
1991	21	8	8	8
1990	22	8	8	8
1989	23	8	8	
1988	24	8		

Expected # of cases	2013-2015
< 1 year**	465
1 year	164
2 years	153
3-4 years	198
5-8 years	135
9-10 years	39
11-14 years	93
15 years	46
16-20 years	96
20-24 years	107
25+	384
NK	15
Total	1895

**** 5-12 months 202

For the screening method, if we assumed 90% vaccine coverage and observe 60% vaccine effectiveness, then with 175 cases, the lower limit of the 95% confidence interval for vaccine effectiveness will be above 40%.

In conclusion, the study period may well take 3 years before we can draw final conclusions for the vaccine effectiveness of 4CMenB vaccination against meningococcal capsular group B-vaccine-type disease, in each specific age group.

9.6 Data Management

9.6.1 Data Processing

GSK Vaccines S.r.l. will receive at least twice a year progress reports of meningococcal capsular group B cases from PHE, specified as mentioned above.

Blinding

GSK Vaccines S.r.l. will receive pseudo-anonymised or aggregated data only from PHE.

Data linkage

Data linkage, e.g. between MenB cases and their vaccination status, will be taken care of by PHE.

9.6.2 Software and Hardware

Analyses will be done by PHE.

9.7 Data Analysis

If additional or different analyses are needed, they will be defined before first subject is enrolled.

9.7.1 Statistical Hypotheses

No hypothesis is tested. This study determines the impact on meningococcal disease and effectiveness of 4CMenB vaccination against MenB disease, after introduction of 4CMenB in the UK.

9.7.2 Analysis of Demographics and Baseline Characteristics

Descriptive statistics will be performed as appropriate using standard statistical methods. For continuous variables mean, standard deviation, median, Q1, Q3, minimum and maximum will be calculated overall. Frequency distributions (n, %) of categorical

variables will be summarized overall. To analyze baseline differences in patients characteristics the chi-square test (binary variables), Mantel-Haenszel test for trend (categorical variables) or linear regression models (continuous variables), will be used where appropriate statistical significance will be defined as a P-value less than 0.05, and 95% CI will be therefore calculated.

9.7.3 Statistical Methods

For each of the proposed study designs, the statistical methods are as follows:

1. Descriptive (no hypothesis testing):

This study will provide a summary of the epidemiology of all capsular groups of meningococcal disease, e.g. by vaccination status, age, setting and method. The method will be purely descriptive and summarise the observed number of *N. meningitidis* cases reported to PHE, stratified by variable of interest. More details are described above.

2. Analytical study:

Vaccine effectiveness (VE) is generally defined as the % reduction in the attack rate in vaccinated compared with unvaccinated children in the same birth cohorts. VE will be assessed by the screening method, or by a case-control method if the screening method cannot be used (for example, if appropriate coverage data cannot be determined).

a. Screening method:

For this method, the VE can be estimated using the formula below, where PCV is the proportion of cases that are vaccinated and PPV is the proportion population vaccinated (coverage):

$$VE = 1 - \frac{(PCV \times (1-PPV))}{((1-PCV) \times PPV)}$$

The vaccine effectiveness estimate will be calculated along with the 95% confidence interval using the exact binomial distribution for the proportion of cases vaccinated in each of the study settings.

b. Case-control method:

In case-control studies, vaccine effectiveness is based on the odds ratio (OR) and is defined as: VE = 1 - OR

The vaccine effectiveness estimate will be calculated along with the 95% confidence interval using the standard errors from logistic regression.

If it is decided to pursue a case-control method, for instance if uptake information is difficult to obtain, the three controls for each case would as a minimum be matched on age (same month of birth if that is sufficient to define vaccine eligibility for infants) and sex.

As mentioned earlier, additional calculations can be considered to investigate the dose-response relationships for each antigen in the vaccine (versus having at least one antigen, as described in the secondary objective).

As the number of cases due to other capsular groups is expected to be too small for analysis within the study period, at a later stage, outside the scope of this study protocol, it could be envisioned to evaluate both cross protection against other capsular groups and any capsule replacement after introduction of the vaccine.

Subgroup analyses

If sample size allows, stratified analyses may be performed.

Methods to control for confounding

For this study the screening method will be used, which is a relatively quick and easy way to assess vaccine effectiveness. The 'cost' of the simplicity is that no control for confounding is possible.

For the case-control method, odds ratios and 95% confidence intervals will be calculated by using a multivariate conditional logistic regression after matching by age, gender and calendar time (c-c ratio 1:3). Covariates will be included into the multivariate model if they are significantly ($p<0.05$) associated with meningitis and change the point estimate between 4CMenB vaccination and MenB disease at least 10%.

Stratified analyses will be conducted to estimate the effect by age, gender and in specific subgroups e.g. immunocompromised subjects, method of data collection (databases versus networks) and outcome (meningitis serotypes). For all analyses we will accept statistical significance at a p-value<0.05. Analyses will be performed by using the statistical software package SAS.

Methods to control for effect modification

In case of case-control method, Breslow-Day test for homogeneity of the odds ratios and inclusion of interaction term in the conditional logistic regression model will be used in order to investigate effect modification.

9.7.4 Statistical Considerations

Statistical assumptions

The above are rough, very first estimates based on several assumptions. Interim analyses will take place in order to verify that these assumptions (e.g. in Table 1) were accurate and consider the need for potential adjustments.

Sensitivity analyses

Variations in the PPV will be explored in order to allow for potential errors in the estimates and assumptions used.

9.8 Quality Control

9.8.1 Validation

Validation of vaccination history will be done by PHE.

Due to the severity of meningococcal disease we assume that most cases of *Neisseria meningitidis* are being captured by the national surveillance system. Capsular group confirmation is estimated to be available for more than 90% of confirmed cases, of which 50-60% are confirmed by PCR only (PHE, personal communication). Subsequent evaluation of 4CMenB specific antigens using MATS on culture-positive isolates will be done for part of all notified cases.

9.8.2 Record Retention

NA. The study in this protocol refers to the provision of customised post-marketing surveillance reports of independently generated data to assist GSK Vaccines S.r.l. in meeting its regulatory commitment.. Records retention falls within PHE routine practices for surveillance data.

9.9 Limitations of the Research Methods

Reporting of meningococcal cases is based on passive surveillance which may be an underestimate of true disease. Additionally, the national surveillance system may not capture data from meningococcal patients that died from the disease. However, as meningococcal disease is a serious illness, we expect that not many cases will be missed and that even from deaths samples will be available for diagnostic confirmation of IMD. The main benefit of using national surveillance data is that the results may be generalisable to the whole UK population and potentially even beyond its borders.

For the screening method, aggregated data will be used. The 'cost' of the simplicity is that no control for confounding is possible. However, in a NIP this should not be an issue. Also, the screening method provides a quick and proven design to perform this study.

The study may run into feasibility issues due to lack of precision of estimates, especially with high coverage and/or low vaccine effectiveness. Additionally, meningococcal disease has declined during the past decade in England and Wales.

9.10 Other Aspects

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

Under the Data Protection Act covered by SI 2002/1438, no patient identifiable data will be transferred to a third party.

Details of the person reporting the case to PHE will not routinely be made available to the market authorisation holder (MAH).

10.1 Regulatory and Ethical Compliance

In 2001, PHE (formerly the Public Health Laboratory Service and Health Protection Agency) received approval from the Department of Health's Patient Information Advisory Group (now from the National Information Governance Board, NIGB) to continue the collection of personal's identification data for the surveillance, control and prevention of communicable diseases. This ongoing approval covers the routine meningococcal surveillance system. As such, any addition of vaccines will be notified to NIGB.

10.2 Informed Consent

The descriptive part of this observational study uses data routinely collected for national meningococcal surveillance by PHE. These data will be sent to GSK Vaccines S.r.l. in a pseudo-anonymised format containing no personal information; therefore, no informed consent will be required.

In additional to these data, the analytical part of the study collects history of vaccination data in order to link any occurring outcome of meningococcal disease to their potential exposure to the vaccine. For the screening method, pseudo-anonymised datasets containing no personal information will be used, for which no additional informed consent is required.

Simple demographics and vaccine history are both covered by NIGB's approval.

However, if we need to defer to the case-control design, eligible subjects will only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC/REB-approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the subject. In cases where consent is given by the subject's representative, the subject should be informed about the study to the extent possible given his/her understanding. If the subject is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be

documented in the subject source documents. The consent form must be agreed to by GSK Vaccines S.r.l. and PHE before submission to the IRB/IEC/REB, and a copy of the approved version must be provided to all affiliations after IRB/IEC/REB approval.

10.3 Responsibilities of the Investigator and IRB/IEC/REB

NA, as this is a collaboration for provision of customised post-marketing surveillance reports of independently generated data to assist GSK Vaccines S.r.l. in meeting its regulatory commitment.

10.4 Protocol Adherence

The study in this protocol refers to the provision of customised post-marketing surveillance reports of independently generated data to assist GSK Vaccines S.r.l. in meeting its regulatory commitment. This collaboration makes use of routinely and independently generated national surveillance data, as approved by NIGB. There is no single protocol governing surveillance activities as the nature of vaccination schedule and surveillance requires a level of flexibility, though patient confidentiality is assured at all times.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS

GSK Vaccines S.r.l. will undertake enhanced pharmacovigilance and a post-marketing observational safety study for the 4CMenB vaccine (see protocol V72_36OB), including the establishment of a pregnancy registry in the US (V72_82OB).

Individual cases of vaccine failure of 4CMenB vaccination during this study (V72_38OB) will not be reported as it is a vaccine effectiveness study. Data will be aggregated as per study design and reported to EMA as they become available every six months for the 3-year study duration as well as a final report 6 months after end of the study.

12. PLANS FOR DISSEMINATING AND COMMUNICATING RESULTS

12.1 Registration in Public Database(s)

GSK Vaccines S.r.l. assures that the key design elements of this protocol will be posted in a publicly accessible database where applicable and in compliance with current regulations. GSK Vaccines S.r.l. also assures that key results of this study will be posted in a publicly accessible database within the required time-frame from completion of the data collection where applicable and in compliance with current regulations. For this study, this is not applicable.

12.2 Publications

The final report will be provided by the above mentioned affiliations, and will be available within six months after the end of data collection for the analytical study. The actual date of the final report depends on a variety of factors, such as introduction of 4CMenB into the UK national immunisation schedule (expected Sep 2015), number of meningococcal cases reported and the subsequent power (precision of estimates) related to the analytical study. Based on sample size calculations, the expected total duration of the effectiveness study is 3 years, which would suggest a publication of the final report around early 2019.

Preparation of manuscripts based on PHE surveillance data will be by PHE.

A figure of the estimated timelines was included earlier in this protocol (Figure 4).

13. REFERENCES

Anon. COVER programme: October to December 1999. Vaccination coverage statistics for children up to 5 years of age in the UK. Commun Dis Rep CDR Weekly 2001;11:12.

Bose A, Coen P, Tully J, Viner R, Booy R. Effectiveness of meningococcal C conjugate vaccine in teenagers in England. Lancet 22 Feb 2003;361:675-676.

Donnelly J, Medini D, Bonnadifuoco G, Biolchi A, Ward J, Frasch C, Moxon ER, Stella M, Comanducci M, Bambini S, Muzzi A, Andrews W, Chen J, Santos G, Santini L, Boucher P, Serruto D, Pizza M, Rappuoli R, Giuliani MM. Qualitative and quantitative assessment of meningococcal antigens to evaluate the potential strain coverage of protein-based vaccines. Proc Natl Acad Sci Nov. 2010;107(45):19490-5.

ECDC surveillance report 2007:
http://ecdc.europa.eu/en/publications/Publications/101011_SUR_Surveillance_of_invasive_bacterial_diseases_in_Europe_2007.pdf

Farrington CP. Estimation of vaccine effectiveness using the screening method. Int J of Epi 1993;22(4):742-746

Gray SJ, Trotter CL, Ramsay ME, Guiver M, Fox AJ, Borrow R, Mallard RH, Kaczmarski EB. Epidemiology of meningococcal disease in England and Wales 1993/94 to 2003/4: contribution and experiences of the Meningococcal Reference Unit. J Med Microb 2006;55(7):887-896

HPA Epidemiological data, 2008-2009:
http://www.hpa.org.uk/web/HPAweb&HPAwebStandard/HPAweb_C/1234510036546

HPA Epidemiological data, update 2 August 2011:
http://www.hpa.org.uk/web/HPAweb&HPAwebStandard/HPAweb_C/1234510036546

Ramsay ME, Andrews N, Kaczmarski EB, Miller E. Efficacy of meningococcal serogroup C conjugate vaccine in teenagers and toddlers in England. Lancet 2001;357:195-196.

Schlesselman JJ. Case-control studies, Oxford University Press, 1982;6.11:153.

Schlesselman JJ. Case-control studies, Oxford University Press, 1982;6.6:150.Trotter CL, Andrews NJ, Kaczmarksi EB, Miller E, Ramsay ME. Effectiveness of meningococcal serogroup C conjugate vaccine 4 years after introduction. Lancet 2004;364:365-367.

Trotter CL, Andrews NJ, Kaczmarksi EB, Miller E, Ramsay ME. Effectiveness of meningococcal serogroup C conjugate vaccine 4 years after introduction. Lancet 2004;364:365-367.

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 2, amended)

Adopted by the ENCePP Steering Group on 14/01/2013

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 page number(s) 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). Note, 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:

Study reference number:

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	20,27,28
1.1.2 End of data collection[2]	☒	☐	☐	
1.1.3 Study progress report(s)	☒	☐	☐	
1.1.4 Interim progress report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS register	☒	☐	☐	
1.1.6 Final report of study results.	☒	☐	☐	

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
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)	☒	☐	☐	
2.1.2 The objective(s) of the study?				

[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**	**Page Number(s)**
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☒	☐	☐	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	
	☒	☐	☐	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	

Comments:

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

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☒	☐	☐	
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☒	☐	☐	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☒	☐	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☒	☐	☐	

Comments:

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☐	☒	☐	

Comments:

Section 7: Confounders and effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☒	☐	☐	

Section 7: Confounders and effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☒	☐	☐	

Comments:

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	
8.1.3 Covariates?	☒	☐	☐	
8.2 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)	☒	☐	☐	
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.3 Is a coding system described for: 8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10) 8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events) 8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☒ ☐ ☐	☐ ☐ ☒	☐ ☒ ☐	
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	

Comments:

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☐	☐	☒	
10.2 Is the choice of statistical techniques	☒	☐	☐	

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
described?				
10.3 Are descriptive analyses included?	☒	☐	☐	
10.4 Are stratified analyses included?	☒	☐	☐	
10.5 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	
10.6 Does the plan describe methods addressing effect modification?	☒	☐	☐	

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.1 Is information provided on the management of missing data?	☒	☐	☐	
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☐	☐	☒	
11.3 Are methods of quality assurance described?	☒	☐	☐	
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	
11.5 Is there a system in place for independent review of study results?	☐	☒	☐	43

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss: 12.1.1 Selection biases? 12.1.2 Information biases? (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. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	
12.3 Does the protocol address other limitations?	☒	☐	☐	

Comments:

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

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Page Number(s)**

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

Comments:

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

Comments:

Name of the main author of the protocol: _____

Date: / /

Signature: _____

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