Amsterdam, 23 January 2020
EMA/71871/2020
Committee for Medicinal Products for Human Use (CHMP)

Type II variation assessment report

Procedure No. EMEA/H/C/001095/II/0093

Invented name: Menveo

International non-proprietary name: Meningococcal group A, C, W135 and Y conjugate vaccine

Marketing authorisation holder (MAH): GSK Vaccines S.r.l

This application is in the area of: (Non-)Clinical

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Table of contents

1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, GSK Vaccines S.r.l submitted to the European Medicines Agency on 5 November 2019 an application for a variation.

The following changes were proposed:

Variation requested		**Type**	**Annexes affected**
C.I.3.b	C.I.3.b - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Change(s) with new additional data submitted by the MAH	Type II	I, II, IIIA and IIIB

Update of section 4.8 of the SmPC in order to include lymphadenopathy as a new expected adverse reaction after vaccination in Post-marketing experience based on final results from study V59_77 and substantiated by supportive clinical data only to establish frequency, following CHMP assessment of procedure P46/039. Section 4 of the Package Leaflet is updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to bring the PI in line with the latest QRD template version 10.1.

The requested variation proposed amendments to the Summary of Product Characteristics, Annex II, Labelling and Package Leaflet.

2. Overall conclusion and impact on the benefit/risk balance

A review of lymphadenopathy was carried out. The MAH's clinical trial database (including the case report from clinical study V59_77 reporting 'lymphadenopathy'), the MAH's safety database, the Eudravigilance database and literature were considered.

Study V59_77 was previously assessed by CHMP in procedure P46/039 (AR included as Appendix).

In most of the case reports of 'lymphadenopathy', including those published in literature (35 out of 48), lymphadenopathy events occurred in close temporal association with the vaccine administration. The causality between product administration and the occurrence of lymphadenopathy is considered very likely due to these plausible time to onset (TTO).

Section 4.8 of the SmPC has been amended to in order to include 'lymphadenopathy', and section 4 of the Package Leaflet was updated accordingly.

The proposed frequency categorisation as 'rare' is acceptable, as the reported frequency in clinical trials was <1%.

The benefit-risk balance of Menveo remains positive.

3. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation accepted		Type	Annexes affected
C.I.3.b	C.I.3.b - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Change(s) with new additional data submitted by the MAH	Type II	I, II, IIIA and IIIB

Update of section 4.8 of the SmPC in order to include lymphadenopathy as a new expected adverse reaction after vaccination in Post-marketing experience based on final results from study V59_77 and substantiated by supportive clinical data (mainly to establish frequency), following CHMP assessment of procedure P46/039.
Section 4 of the Package Leaflet is updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to bring the PI in line with the latest QRD template version 10.1.

is recommended for approval.

4. EPAR changes

The table in Module 8b of the EPAR will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Menveo-H/C/001095-II-93'

Annex: Rapporteur’s assessment comments on the type II variation

5. Introduction

Menveo has a marketing authorisation valid throughout the European Union since 15 March 2010. It is indicated for active immunization of children (from 2 years of age), adolescents and adults at risk of exposure to Neisseria meningitidis groups A, C, W-135 and Y, to prevent invasive disease.

With this application, the MAH proposed an update of section 4.8 of the SmPC in order to include 'lymphadenopathy' as a post-marketing experience adverse drug reaction after vaccination, based on final results from study V59_77 and substantiated by supportive clinical data only to establish frequency, following CHMP assessment of procedure P46/039 (AR included as Appendix).

6. Clinical Safety aspects

6.1. Methods – analysis of data submitted

Following assessment of Menveo study V59_77 Clinical Study Report (CSR) to the European Medicines Agency (EMA), submitted in the framework of Article 46 of the EU paediatric regulation (EC) No 1901/2006, the final CHMP assessment report (EMA/H/C/01095/P46), requested the MAH to add lymphadenopathy in section 4.8 of the summary of product characteristics (SmPC).

Study V59_77 was a phase 3b, controlled, open-label, multi-center clinical trial conducted to evaluate safety and immunogenicity of Menveo after a single vaccination in healthy individuals, 15 through 55 years of age, who were vaccinated with Menveo or Menactra 4 to 6 years before and in vaccine-naive individuals. In this study, a single case of an ipsilateral lymphadenopathy (swollen lymph node under left arm after vaccination in left deltoid) 3 days after receiving Menveo was reported for one subject aged 16 years, among the 701 exposed to Menveo during the study. The event was medically attended and identified by the investigator as possibly related with vaccination. This case report triggered a CHMP request for SmPC modification to include lymphadenopathy as an adverse reaction following Menveo administration.

The current safety signal analysis of lymphadenopathy has been made on cases reported in clinical trials, in the GSK worldwide safety database, in the Eudravigilance database and in the literature. During the signal evaluation, cases of lymphadenopathy possibly related to Menveo administration were reported from the safety database, Eudravigilance search and literature sources.

6.2. Results

Clinical trial database
Among the 127 events reported after Menveo administration, 36 of the 127 events occurred within 7 days from the vaccination. Among the events where both site of vaccination and site of adverse event were mentioned, 14 reports of the event occurred homolaterally to the site of vaccination with Menveo, of which 12 were reporting the PT 'Lymphadenopathy', and 2 the PT 'Lymph node pain'. Eleven of these 14 events were assessed as possibly related to Menveo by the investigator. Lymphadenopathy was reported in less than 1% of subjects exposed to at least one dose of Menveo.

Spontaneous reports (MAH's safety database)
A total of 89 cases were retrieved following a search in the MAH's safety database until 10 April 2019, using the following MedDRA preferred terms (PTs): Lymphadenopathy, Injection site lymphadenopathy, Lymphadenitis, Vaccination site lymphadenopathy, Lymph node pain, Administration site lymphadenopathy, Lymphoid hyperplasia, Lymphatic gland hypertrophy, Lymph node swelling.

Of the retrieved 89 cases in the dataset, 27 cases were excluded due to insufficient information present for assessment and 14 cases were excluded because these cases reported with other more likely causes of the adverse event (e.g. concurrent medical conditions or other treatments). The remaining 48 cases where the potential association of lymphadenopathy with Menveo could not be excluded were further reviewed.

Characteristics of the 48 cases:

Characteristic	Statistics or subcategories	Value	Unit
Subject Age N=46 (95.8%)[1]	Range	10-72	years
	Median	28.5	years
Patient Gender N=46 (95.8%)[1]	Male	21 (45.6%)	n (%)[2]
	Female	25 (54.3%)	n (%)[2]
Report Type	Spontaneous Reports	47 (97.9%)	n (%)
	Post Marketing Surveillance Reports	1 (2.1%)	n (%)
Report Source	Health Care Professional	45 (93.7%)	n (%)
	Consumer	3 (6.2%)	n (%)
Time to Onset of Event N=47 (97.9%)[1]	Range	From <1d to 17 days	days
	Median	1	day
Outcome 37 (77.1%)[1]	Resolved	18 (48.6)%	n (%)[2]
	Recovering/Resolving	9 (24.3%)	n (%)[2]
	Unchanged	5 (13.5%)	n (%)[2]
	Not Recovered/Not Resolved	4 (17.6%)	n (%)[2]
	Recovered with sequelae	1 (2.7%)	n (%)[2]
	Fatal (due to event)	0 (0%)	n (%)[2]
Seriousness	Yes	9 (18.7%)	n (%)
	No	39 (81.2%)	n (%)

[1] Number and percentage of reports with available data
[2] Number of reports with available data was used as the denominator
Source: Vaccine Clinical Safety and Pharmacovigilance Safety Evaluation and Risk Management document for *Menveo*: Lymphadenopathy

The lymphadenopathy events occurred in close temporal association with vaccine administration: 35 cases out of 48 had onset within 24 hours from the vaccination (reported as on the same day of the vaccination or within one day from vaccination).

In 25 of these cases, the lymphadenopathy events were reported to be occurring homolaterally to the site of vaccination with Menveo. In the remaining cases, the information on the injection site or on the site in which the event occurred was not reported.

The reported lymphadenopathy events were generally mild to moderate in intensity and were self-limiting. Of the 9 serious cases, 3 cases were reported as requiring intervention. 1 case was reported as medically significant, 1 case as hospitalized and 1 case as disabled without any further details on the disability of the patient; 3 cases were reported as serious by the reporter without providing the reason.

There were no trends or patterns observed in analysis including subject age or gender or number of doses of Menveo administered. There were no reports of Menveo re-administration, or of recurrence of lymphadenopathy following another dose of Menveo in the same subject.

Among the 48 cases the outcome was recovered or recovering in 32/48 cases, unknown in 9/48 cases, and not recovered in 7/48 cases at the time of the report.

Eudravigilance (EV) database / Eudravigilance Data Analysis System (EVDAS)
The EVDAS electronic reaction monitoring report (eRMR) for meningococcal group A, C, W135 and Y conjugate vaccine with DLP 27 March 2019 using the similar PTs retrieved 96 cases. Of the 96 cases retrieved from the line listing requested from EVDAS, 11 cases, reported for Menveo or for an unspecified quadrivalent meningococcal vaccine, were inserted into the MAH's Safety database and were considered as new cases. These cases have been included in the evaluation described in section - Spontaneous reports (MAH's safety database) - above.

Literature
One article reported the occurrence of lymphadenopathy, or lymphadenitis after the administration of Menveo. Holmes et al. described a case report of a 17 years old female patient who was diagnosed with Systemic Lupus Erythematosus with palpable right posterior cervical chain lymphadenopathy at the physical examination, occurred at her admission to the emergency room (15 days after vaccine administration). A causal association with the vaccine could not be determined due to insufficient information.

In addition, a different article [Mayeta et al] presented the outcome of a surveillance study of vaccine adverse events reported from 2011 to 2012 in the French armed forces with Menveo being one of the vaccines administered. Among local reactions reported after Menveo administration, 5 cases with lymphadenopathy (1 case) or lymphadenitis (4 cases) with TTO between 1 and 4 days after vaccination with Menveo alone (3 cases) or in co-administration with other vaccines (2 cases) were reported to the MAH (data not reported in the article). All the cases received from the literature search have been included in the evaluation described in section - Spontaneous reports (MAH's safety database) - above.

6.3. MAH's discussion

Whether a possibility exists for a causal association between lymphadenopathy and administration of Menveo vaccination was analysed according to the WHO assessment causality, as follows:

- Temporality: From both the clinical trial and the safety databases, some events reported to occur with close temporal association with vaccination were retrieved.
- Biological Plausibility: The occurrence of lymph node enlargement as an immune-mediated process after vaccination is biologically plausible and is well explained in the literature.
- Strength of association: Regardless of TTO, age categories or ethnicities, the data across the clinical trials after a pooled analysis had shown similar frequencies of occurrence of Lymphadenopathy (<1%) in Menveo and placebo group with a relative risk (Menveo versus placebo) of 1.84 (95% CI; 0.49-6.93).
- Specificity: Lymphadenopathy is not linked specifically and uniquely with Menveo. The patho-physiology of a lymph node enlargement and lymphocyte activation due to an immune mediated antigen-antibody response is well understood, however the same can be caused by other aetiologies such as systemic infection (which may be viral, bacterial, fungal, or protozoan), autoimmune diseases, storage diseases, drug reactions, histiocytic disorders, and disseminated neoplastic diseases.
- Consistency: In clinical trials, lymphadenopathy was shown to be reported with a low frequency in all groups following the administration with Menveo or placebo (<1%). Similar data were obtained from the spontaneous reporting were, considering the vast number of doses distributed for Menveo (i.e., more

than 49 million doses since January 2011), 48 cases represent a reporting rate of 0.1 cases per 100,000 doses distributed.

'Local lymphadenopathy' was proposed by the MAH for addition to the Post Marketing sections of the PI, considering that:

- spontaneous reports of cases with at least possible causal association with Menveo vaccination which are progressively accumulating as more doses are being administered and with the occurrence of lymphadenopathy being a biologically plausible adverse reaction after vaccination.
- The clinical trial database analysis is considered inconclusive.

Assessment comment

Following the CHMP assessment of the results of the clinical study V59_77 (EMA/H/C/01095/P46), the MAH was requested to include 'lymphadenopathy' in section 4.8 of the SmPC. In this variation application a review of lymphadenopathy in the MAH's clinical trial database (including the case report from clinical study V59_77 reporting 'lymphadenopathy'), MAH's safety database, Eudravigilance database and literature was submitted. In most of the case reports 'lymphadenopathy' including those published in literature (35 out of 48), lymphadenopathy events occurred in close temporal association with the vaccine administration. The causality between product administration and the occurrence of lymphadenopathy is very likely due to these plausible TTOs.

Slightly deviating from the CHMP recommendation, the MAH proposed to include 'local lymphadenopathy' as adverse event in section 4.8 of the SmPC instead of 'lymphadenopathy' as requested by the CHMP. Of the 48 cases presented with the current variation, there were no reports of 'local lymphadenopathy'; all were reporting 'lymphadenopathy'. Besides, the term 'lymphadenopathy' is conforming to the Medical Dictionary for Diagnosis Registration and Analysis (MedDRA) a preferred term (PT) where the term 'local lymphadenopathy' is not. Furthermore, in another SmPC of a meningococcal vaccine (Menjugate) 'lymphadenopathy' is listed. Therefore, the MAH's proposal to include 'local lymphadenopathy' instead of 'lymphadenopathy' was not acceptable.

The MAH therefore agreed to include the initially requested by CHMP term 'lymphadenopathy' in section 4.8 of the SmPC with the frequency 'rare', as the reported frequency in clinical trials was <1%. Section 4 of the Package Leaflet was also updated accordingly (see attachment 1)

7. PRAC advice

N/A

8. Changes to the Product Information

Slightly deviating from the CHMP recommendation, the MAH initially proposed to include 'local lymphadenopathy' as adverse event in section 4.8 of the SmPC instead of 'lymphadenopathy' as requested by the CHMP. For the reasons detailed in Section 6 of this Report, this initial MAH's proposal was not acceptable.

The MAH therefore agreed to include the term recommended by CHMP ('lymphadenopathy') in section 4.8 of the SmPC, with the frequency 'rare', as the reported frequency in clinical trials was <1%. A SmPC amended accordingly was provided, together with correspondingly amended Package Leaflet (Section 4, see attachment 1).

In addition, the Marketing authorisation holder (MAH) took the opportunity to bring the PI in line with the latest QRD template version 10.1

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

9. Appendix 1

CHMP Assessment Report for Menveo P46 039 (EMEA/H/C/001095/P46/039), dated 28 February 2019

28 February 2019
EMA/71871/2020
Human Medicines Evaluation Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Menveo

meningococcal group a, c, w135 and y conjugate vaccine

Procedure no: EMEA/H/C/001095/P46/039

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

1. Introduction

On 8 August 2018, the MAH submitted a completed paediatric study for Menveo, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

Menveo is indicated for active immunization of children (from 2 years of age), adolescents and adults at risk of exposure to Neisseria meningitidis groups A, C, W135 and Y, to prevent invasive disease.

The use of this vaccine should be in accordance with official recommendations.

Menveo should be administered as a single dose (0.5 ml). To ensure optimal antibody levels against all vaccine serogroups, the primary vaccination schedule with Menveo should be completed one month prior to risk of exposure to Neisseria meningitides groups A, C, W135 and Y.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that "*A Phase 3b, Controlled, Open-Label, Multi-Center Study to Evaluate Safety and Immunogenicity of a Single Dose of GlaxoSmithKline's Meningococcal ACWY Conjugate Vaccine (Menveo), Administered to Healthy Individuals 15 through 55 years of age, approximately 4-6 years after primary ACWY vaccination.*" is a stand alone study.

2.2. Information on the pharmaceutical formulation used in the study

The study vaccine specific to this study was the MenACWY-CRM vaccine (Menveo, GSK Biologicals). There is no specific paediatric formulation. The meningococcal ACWY conjugate vaccine was to be reconstituted just before injection of the lyophilized MenA-CRM component with the MenCWY-CRM full liquid vaccine. The pharmaceutical form was a powder and solution for injection. Menveo was provided as vial/vial presentation. MenA lyophilised conjugate component (glass vial) and MenCWY liquid conjugate component (glass vial). One 0.5 mL single dose of Menveo was to be administered by intramuscular injection in the deltoid area of non-dominant arm (preferably) in Menveo-Menveo, Menactra-Menveo treatment groups and to treatment Naive group on day 1.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

Clinical study V59_77: "A Phase 3b, Controlled, Open-Label, Multi-Center Study to Evaluate Safety and Immunogenicity of a Single Dose of GlaxoSmithKline's Meningococcal ACWY Conjugate Vaccine (Menveo), Administered to Healthy Individuals 15 through 55 years of age, approximately 4-6 years after primary ACWY vaccination."

2.3.2. Clinical study

Description

Methods

Objectives

Primary objectives:

• To demonstrate a sufficient immune response following a booster dose of MenACWY-CRM (Menveo) vaccine, given to subjects who previously received Menveo, as measured by the percentage of subjects with human serum bactericidal assay (hSBA) seroresponse against *N meningitidis* serogroups A, C, W and Y at day 29 after vaccination.

• To demonstrate a sufficient immune response following a booster dose of MenACWY-CRM (Menveo) vaccine, given to subjects who previously received Menactra, as measured by the percentage of subjects with hSBA seroresponse against *N meningitidis* serogroups A, C, W and Y at day 29 after vaccination

Assessor's comments

A sufficient immune response was defined as the hSBA seroresponse >75%; please see section on endpoints.

Secondary objectives aimed at comparing the immune response to the booster dose between subjects who previously received Menveo, subjects who previously received Menactra, and subjects who previously received Menveo or Menactra (pooled vaccine group) and following a single dose in vaccine-naive individuals, as measured by the percentages of subjects with hSBA seroresponse, hSBA $\geq$ 8 and $\geq$ 16, and hSBA GMTs against *N meningitidis* serogroups A, C, W and Y at day 1, day 4, day 6, and day 29 after vaccination, and to assess the persistence of bactericidal antibodies approximately 4 to 6 years after primary vaccination with Menveo and Menactra, as compared to naturally acquired levels (vaccine naïve individuals) as measured as the % with hSBA ≥1:8 at day 1.

In addition the reactogenicity and safety of MenACWY-CRM vaccine when administered to subjects who previously received Menveo or Menactra (vaccine-primed) and vaccine-Naïve individuals was assessed.

Study design

This was a phase 3b, controlled, open-label, multi-center study to evaluate safety and immunogenicity of Menveo after a single vaccination in healthy individuals who were vaccinated with Menveo or Menactra 4 to 6 years before and in vaccine- Naïve individuals.

Study population /Sample size

Approximately 700 healthy subjects 15 through 55 years of age were to be enrolled in the study. The sample size was based on data from study V59P13E1 which was used to estimate the statistical power. Overall statistical power to show sufficiency of immune response to a booster dose of Menveo for each serotype in both the Menveo-Menveo and the Menactra-Menveo group was to be at least 92%.

In order to participate in this study, all individuals had to meet all of the following criteria at study entry:

1. Individuals (male/female) of 15 through 55 years of age on the day of informed consent or assent.

2. Individuals who received Menveo 4 to 6 years prior to enrollment at an age of 11 years or older (Menveo-Menveo group)

Or

Individuals who received Menactra 4 to 6 years prior to enrollment at an age of 11 years or older (Menactra-Menveo group)

Or

Individuals who had not received any previous meningococcal vaccine (Naive group).

3. Individuals who gave written informed consent and who were able to comply with study procedures including follow-up

4. Males or females of non-childbearing potential or using an effective birth control method until at least 30 days after study vaccination.

Exclusion criteria common for vaccine studies were applied here (e.g. current or previous, confirmed or suspected disease caused by N meningitidis, meningococcal vaccination other than the investigational vaccine, progressive unstable or uncontrolled clinical conditions, hypersensitivity to any component of the vaccines, abnormal function of the immune system, recent treatment with systemic antibiotics, immunoglobulins or blood products, recent or planned vaccination with a vaccine other than the investigational vaccine, fever or any other clinical condition that, in the opinion of the investigator, might pose additional risk to the subject due to participation in the study, etc).

Assessor's comments

The inclusion of a naïve control group is appropriate as it is relevant to evaluate the persistence, as natural boosting can be expected for certain serogroups, and similarly important to evaluate the booster response.

Treatments

All subjects were to receive a single dose of Menveo at day 1.

Study groups:

• Group Menveo-Menveo: approximately 300 subjects, who were vaccinated with a single dose of Menveo 4 to 6 years before, were to receive 1 dose of Menveo.

• Group Menactra-Menveo: approximately 300 subjects, who were vaccinated with a single dose of Menactra 4 to 6 years before, were to receive 1 dose of Menveo.

• Group Naive: approximately 100 subjects, of similar age to subjects enrolled in other primed groups, with enrollment distributed across all clinical sites, who had not received any meningococcal vaccination, were to receive 1 dose of Menveo.

Randomization / Stratification:

Within each study group, subjects were to be randomized into one of two different blood draw schedules according to a 1:1 ratio, in which subjects were assigned to get blood draws at day 1, day 4 and day 29 or at day 1, day 6 and day 29, respectively.

Outcomes/endpoints

Primary Endpoint:

• Percentage of subjects with hSBA seroresponse against *N meningitidis* serogroups A, C, W and Y at day 29 for Menveo-Menveo and Menactra-Menveo groups.

Seroresponse was defined for this study as follows: For subjects with pre-vaccination titers <4, postvaccination titers ≥ 16; for subjects with pre-vaccination titers ≥4, post vaccination titers at least 4 times the pre-vaccination titers.

Secondary Endpoints:

Immunogenicity endpoints:

The following measures were summarized for Menveo-Menveo, Menactra-Menveo, Naive and the pooled (Menveo-Menveo and Menactra-Menveo) groups:

- Percentage of subjects with hSBA titer ≥ 8 and ≥ 16 against *N meningitidis* serogroups A, C, W and Y at day 1, day 4, day 6 and day 29 and between-group differences;
- Percentages of subjects with hSBA seroresponse against *N meningitidis* serogroups A, C, W and Y at day 4, day 6 and day 29 and between-group differences;
- hSBA GMTs against *N meningitidis* serogroup A, C, W and Y at day 1, day 4, day 6 and day 29;
- Ratios of hSBA GMTs at day 1, day 4, day 6 and day 29 (between study groups);
- hSBA Geometric Mean Ratios (GMRs) at day 4, day 6, and day 29 compared to day 1 (within study groups).

Safety endpoints:

Safety of the study vaccine was assessed in the Menveo-Menveo and Menactra-Menveo groups and the pooled vaccine groups (Menveo-Menveo and Menactra - Menveo) and the vaccine-naive group in terms of the frequencies (percentages) of reported AEs including:

1. Any unsolicited AEs reported within 30 minutes after vaccination;
2. Solicited local and systemic AEs reported from day 1 (6 hours) through day 7 after vaccination;
3. Other indicators of reactogenicity (eg, use of analgesics / antipyretics, body temperature) within 7 days after vaccination;
4. All unsolicited AEs reported from day 1 through day 29 after vaccination;
5. Medically-attended AEs, AEs leading to withdrawal and SAEs reported from day 1 through day 181 (during the entire study period).

Statistical Methods

Primary Immunogenicity Objective

The primary population for the analysis of sufficient immune response was the per protocol set (PPS), and consisted of the Menveo-Menveo group (n=270 evaluable subjects) and Menactra-Menveo group (n=270 evaluable subjects).

For each individual vaccine group (Menveo-Menveo and Menactra-Menveo) and each A, C, W, and Y serogroup, the percentage of subjects with seroresponse were computed, along with associated two-sided 95% Clopper-Pearson CIs.

To demonstrate immune response sufficiency after Menveo booster vaccine administration, the lower limit of the one-sided 97.5% CI for the percentage of subjects with hSBA seroresponse against each of serogroups A, C, W and Y had to be greater than 75%. This was to be tested sequentially first in the group of subjects who received primary vaccination with Menveo and, if met, also in the group of subjects who received primary vaccination with Menactra.

Secondary Immunogenicity Objectives

The primary population for the analysis of the secondary immunogenicity objectives was the PPS.

Seroresponse (day 4, day 6 and day 29) and Percentage of subjects with hSBA titer≥ 8 and ≥ 16 (day 1, day 4, day 6, and day 29):

> The percentage of subjects with seroresponse, the percentage of subjects with hSBA titer ≥ 8 and ≥ 16, and their associated two-sided 95% Clopper-Pearson CIs were computed by group (Menveo-Menveo, Menactra-Menveo, Naive, and pooled Menveo-Menveo and Menactra-Menveo) and by N meningitidis serogroup. Differences in percentages and associated 95% CIs between study groups were calculated using the Miettinen & Nurminen score method.
>
> In a descriptive fashion - using the difference in percentages and 95% CIs - each of the previously vaccinated groups (individually and pooled) was compared to the Naive group. Also the two previously vaccinated study groups were compared to each other.

Between-group ratios of GMTs (adjusted and unadjusted):

> The between-group ratio of hSBA GMTs and corresponding 95% CI, at each of visit day 1 (persistence), day 4, day 6 and day 29 against each N meningitidis serogroup were obtained by exponentiating the mean between-group differences in log-transformed titers and the corresponding 95% CIs at each of the timepoints specified.
>
> Additionally, adjusted ratios of GMTs were obtained from Analysis of Covariance models including pre-vaccination titer as factor in the model. The previously vaccinated groups (individually and pooled Menveo-Menveo and Menactra-Menveo) were compared to the Naive group at each timepoint – descriptively – using the ratios of GMTs.
>
> The two previously vaccinated groups were also compared to each other at each time point using GMT ratios.

Within-group GMRs (adjusted and unadjusted):

> Within each study group and for each serogroup, GMRs were calculated, as applicable, at:
>
> • Visit day 4 versus at Visit day 1;
>
> • Visit day 6 versus at Visit day 1; and
>
> • Visit day 29 versus at Visit day 1.
>
> The unadjusted GMRs and 95% CIs were constructed by exponentiating the mean within-group differences in log-transformed titers and the corresponding 95% CIs.

Secondary Safety Objectives

Solicited AEs:

The analyses of post-vaccination solicited AEs reported from day 1 to day 7 were performed based on 3 intervals: 6 hours-day 3, day 4-day 7 and 6 hours-day 7. The analyses of solicited AEs were done separately for 30 minutes.

Unsolicited AEs:

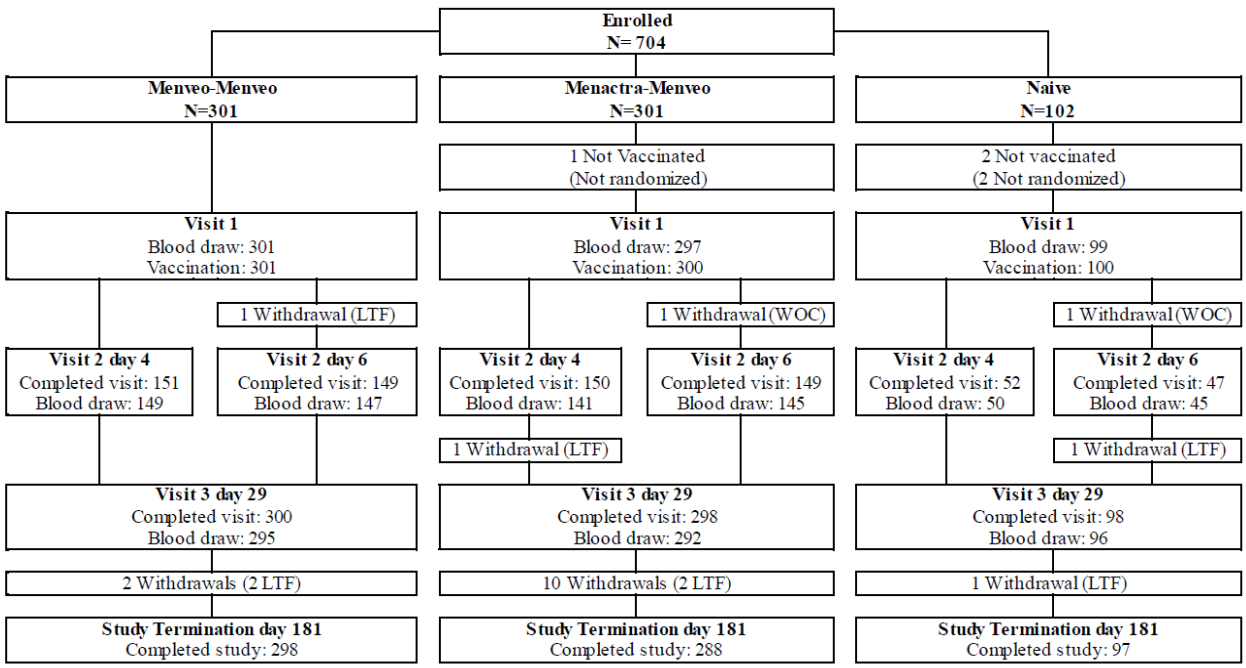
All the unsolicited AEs occurring during the study, judged either as probably related, possibly related, or not related to vaccination by the investigator, were recorded. The original verbatim terms used by investigators to identify AEs in the case report forms were mapped to preferred terms (PTs) using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. The unsolicited AEs were then grouped by MedDRA preferred terms into frequency tables according to system organ class (SOC). AEs judged by the investigator as at least possibly related to study vaccine were summarized by vaccine group, according to SOC and preferred term within SOC.

Results

Recruitment/ Number analysed

The first subject was enrolled on 08-12-2016; the last subject completed on 07-12-2017. A total of 704 subjects (301 in the Menveo-Menveo group, 301 in the Menactra-Menveo group and 102 in the Naive group) who provided informed consent were enrolled in the study. One subject in the Menactra-Menveo group and 2 subjects in the Naive group did not receive study vaccination because they could not be randomized. All other subjects received study vaccination. In total, 18 subjects withdrew from the study prematurely after they received study vaccination: 16 (2%) were lost to follow-up and 2 (< 1%) withdrew consent.

The subject disposition flowchart (page 67 Clinical Study Report):



Source: Table 14.1.1.5; Table 14.1.1.2; Table 14.1.1.6; Appendix16.2.1.1.
Abbreviations: LTF, lost to follow-up; WOC, withdrawal of consent.
Note: the numbers of subjects provided for "Blood draw" refer to the numbers of subjects who had their blood draw within the pre-specified window.

A total of 37 (5%) subjects had protocol deviations: 10 (3%) in the Menveo-Menveo group, 19 (6%) in the Menactra-Menveo group, and 8 (8%) in the Naive group. The most common reason for deviating from the protocol was "subject did not comply with blood draw schedule", reported by a total of 13 (2%) subjects.

Immunogenecity analysis were performed on the per protocol set (PPS) and on the full analysis set (FAS). Overview of population analysed (see page 82 of the Clinical Study Report):

Study Groups	Menveo-Menveo	Menactra-Menveo	Naive	Total
Population	**N=301**	**N=301**	**N=102**	**N=704**
Enrolled	301 (100%)	301 (100%)	102 (100%)	704 (100%)
Immunogenicity PPS				
day 1	298 (99%)	291 (97%)	96 (94%)	685 (97%)
day 29	290 (96%)	282 (94%)	93 (91%)	665 (94%)
Immunogenicity FAS				
day 1	301 (100%)	298 (99%)	97 (95%)	696 (99%)
day 29	297 (99%)	296 (98%)	96 (94%)	689 (98%)

Source: Table 14.1.1.1
Abbreviations: N, total number of subjects; FAS, full analysis set; PPS, per protocol set.

Baseline characteristics (page 83 Clinical Study Report):

Study Groups	Menveo-Menveo	Menactra-Menveo	Naive	Total
	N=301	**N=301**	**N=102**	**N=704**
Age (years) ± SD	17.1 ± 3.66	17.8 ± 4.53	38.8 ± 10.49	20.6 ± 9.32
Gender:				
Female	144 (48%)	156 (52%)	68 (67%)	368 (52%)
Male	157 (52%)	145 (48%)	34 (33%)	336 (48%)
Race				
American Indian or Alaska Native	2 (1%)	6 (2%)	1 (1%)	9 (1%)
Asian	4 (1%)	14 (5%)	3 (3%)	21 (3%)
Black or African American	24 (8%)	23 (8%)	12 (12%)	59 (8%)
Native Hawaiian or other Pacific Islander	3 (1%)	1 (< 1%)	0	4 (1%)
Other	17 (6%)	23 (8%)	5 (5%)	45 (6%)
White	251 (83%)	234 (78%)	81 (79%)	566 (80%)
Ethnic origin:				
Hispanic or Latino	40 (13%)	75 (25%)	11 (11%)	126 (18%)
Not Hispanic or Latino	258 (86%)	223 (74%)	91 (89%)	572 (81%)
Not reported	3 (1%)	3 (1%)	0	6 (1%)
Weight (kg) ± SD	72.8 ± 21.61	72.6 ± 20.00	89.4 ± 25.41	75.2 ± 22.30
Height (cm) ± SD	171.2 ± 9.21	169.8 ± 10.35	169.2 ± 9.78	170.3 ± 9.81
Met entry criteria	298 (99%)	296 (98%)	101 (99%)	695 (99%)

Source: Table 14.1.1.3.
Abbreviation: SD, standard deviation.
Categorical parameters: Number (%) of subjects; non-categorical parameters: mean ± standard deviation.

Demographic and baseline characteristics were generally balanced between both primed groups (Menveo-Menveo and Menactra-Menveo). The mean age of subjects enrolled in the study was 17.1±3.66 years in the Menveo-Menveo group and 17.8±4.53 years in the Menactra-Menveo group. The Naive group enrolled mostly adults (mean age: 38.8±10.49), and more female (67%) than male (33%) subjects. The age difference between the subjects in the primed groups and those in the Naive group is in line with expected enrolment, given the ACIP recommendation for a universal vaccination with a quadrivalent conjugated meningococcal vaccine at 11-12 years of age.

Assessor's comment

Based on the inclusion criteria, the age difference between the primed subjects and the vaccine naïve subjects is understandable. However, this difference will hamper a fair comparison between primed and naïve subjects because of possible differences in natural exposure and vaccine response could be attributable to age.

Efficacy results

Primary efficacy outcome

1. At day 29 after the Menveo booster dose the percentage of subjects with hSBA seroresponse for serogroups A, C, W, and Y ranged from 95.49% to 96.86% across serogroups in the Menveo-Menveo group. The lower limits of the 1-sided 97.5% CI for the percentages of subjects in the Menveo-Menveo group with hSBA seroresponse were greater than 75% for all serogroups. This demonstrates a sufficient immune response following a booster dose of Menveo vaccine, given to subjects who previously received Menveo.

2. At day 29 after the Menveo booster dose the percentage of subjects with hSBA seroresponse for serogroups A, C, W, and Y ranged from 93.24% to 96.45% across serogroups in the Menactra-Menveo group. The lower limits of the 1-sided 97.5% CI for the percentages of subjects in the Menactra-Menveo group with hSBA seroresponse were greater than 75% for all serogroups. This demonstrates a sufficient immune response following a booster dose of Menveo vaccine, given to subjects who previously received Menactra.

Thus for both primary immunogenicity objectives, the criterion to demonstrate a sufficient immune response following a booster dose of Menveo was met. Primary efficacy outcome (see page 85 of the Clinical Study Report):

Table 11.4.1-1 Numbers and Percentages of Subjects (95% CI) with hSBA Seroresponse against *N meningitidis* serogroups A, C, W and Y at day 29 After Vaccination, (Per Protocol Set, day 29[a])

Study Groups	Menveo-Menveo	Menactra-Menveo	Met success criteria for both groups
	N=290	N=282	Yes/No
SerogroupA	279 (96.54%) (**93.73%** -98.33%) N=289	272 (96.45%) (**93.58%** -98.29%)	Yes
SerogroupC	275 (95.49%) (**92.40%** -97.57%) N=288	269 (96.07%) (**93.08%** -98.02%) N=280	Yes
SerogroupW	277 (95.85%) (**92.86%** -97.84%) N=289	262 (93.24%) (**89.64%** -95.88%) N=281	Yes
SerogroupY	278 (96.86%) (**94.13%** -98.56%) N=287	264 (94.29%) (**90.89%** -96.70%) N=280	Yes

Secondary efficacy outcomes

Percentage of subjects with hSBA seroresponse at day 4, day 6, and day 29

A booster dose of Menveo induced an anamnestic immune response in subjects who previously received either Menveo or Menactra, as shown by the higher percentages of subjects with hSBA seroresponse against N meningitidis serogroups A, C, W, and Y in the Menveo-Menveo, Menactra-Menveo, and pooled Menveo/Menactra-Menveo groups compared to subjects who received a first dose of Menveo (Naive group) observed from day 6 (see table below, Clinical Study Report page 87). By day 29, across serogroups

93.24%-96.86% of subjects in the Menveo-Menveo and Menactra-Menveo groups had hSBA seroresponse, compared to 35.87%-65.59% of subjects in the Naive group.

Table 11.4.1-2 **Numbers and Percentages of Subjects (95% CI) with hSBA Seroresponse against *N meningitidis* serogroups A, C, W and Y at day 4, day 6 and day 29 after Vaccination (Per Protocol Set, day 29)**

Study group		Menveo-Menveo	Menactra-Menveo	Pooled Menveo/ Menactra-Menveo	Naive
	Study day	N=290	N=282	N=572	N=93
Serogroup A	day 4	2 (1.39%) (0.17%-4.93%) N=144	3 (2.17%) (0.45%-6.22%) N=138	5 (1.77%) (0.58%-4.09%) N=282	0 (0%) (0%-7.40%) N=48
	day 6	57 (39.31%) (31.31%-47.76%) N=145	44 (31.43%) (23.85%-39.81%) N=140	101 (35.44%) (29.89%-41.30%) N=285	2 (4.55%) (0.56%-15.47%) N=44
	day 29	279 (96.54%) (93.73%-98.33%) N=289	272 (96.45%) (93.58%-98.29%)	551 (96.50%) (94.64%-97.85%) N=571	61 (65.59%) (55.02%-75.14%)
Serogroup C	day 4	4 (2.80%) (0.77%-7.01%) N=143	12 (8.76%) (4.61%-14.80%) N=137	16 (5.71%) (3.30%-9.11%) N=280	3 (6.25%) (1.31%-17.20%) N=48
	day 6	74 (51.39%) (42.92%-59.80%) N=144	67 (48.20%) (39.65%-56.83%) N=139	141 (49.82%) (43.85%-55.80%) N=283	5 (11.36%) (3.79%-24.56%) N=44
	day 29	275 (95.49%) (92.40%-97.57%) N=288	269 (96.07%) (93.08%-98.02%) N=280	544 (95.77%) (93.78%-97.27%) N=568	53 (56.99%) (46.31%-67.22%)
Serogroup W	day 4	4 (2.78%) (0.76%-6.96%) N=144	14 (10.14%) (5.66%-16.44%) N=138	18 (6.38%) (3.83%-9.90%) N=282	3 (6.25%) (1.31%-17.20%) N=48
	day 6	73 (50.34%) (41.93%-58.75%) N=145	69 (49.29%) (40.74%-57.86%) N=140	142 (49.82%) (43.87%-55.78%) N=285	5 (11.36%) (3.79%-24.56%) N=44
	day 29	277 (95.85%) (92.86%-97.84%) N=289	262 (93.24%) (89.64%-95.88%) N=281	539 (94.56%) (92.37%-96.28%) N=570	33 (35.87%) (26.13%-46.54%) N=92
Serogroup Y	day 4	11 (7.75%) (3.93%-13.44%) N=142	6 (4.38%) (1.62%-9.29%) N=137	17 (6.09%) (3.59%-9.58%) N=279	0 (0%) (0%-7.40%) N=48
	day 6	70 (48.95%) (40.51%-57.44%) N=143	80 (57.14%) (48.51%-65.47%) N=140	150 (53.00%) (47.01%-58.94%) N=283	4 (9.09%) (2.53%-21.67%) N=44
	day 29	278 (96.86%) (94.13%-98.56%) N=287	264 (94.29%) (90.89%-96.70%) N=280	542 (95.59%) (93.56%-97.13%) N=567	48 (51.61%) (41.01%-62.11%)

Percentage of subjects with hSBA titers ≥ 8 (and ≥ 16) at Day1, day 4, day 6, and day 29

The anamnestic immune response to a booster dose of Menveo in subjects who previously received either Menveo or Menactra was also shown by the higher percentages of subjects with hSBA titers ≥ 8 and ≥ 16 against N meningitides serogroups A, C, W, and Y in the Menveo-Menveo, Menactra-Menveo, and pooled Menveo/Menactra-Menveo groups compared to the Naive group observed from day 4, with non-overlapping 95% CIs between primed and Naive groups observed starting from day 6. By day 29, at least 98.62% of subjects in the primed groups had hSBA titers ≥ 8 against any serogroup (100% against serogroup W in both primed groups), and at least 97.52% had hSBA titers ≥ 16 against any serogroup.

Percentage of subjects with hSBA titers ≥ 8 (see page 89 of the Clinical Study Report):

Table 11.4.1-3 **Numbers and Percentages of Subjects (95% CI) with hSBA titer ≥ 8 against *N meningitidis* serogroups A, C, W and Y at day 1, day 4, day 6 and day 29 after Vaccination (Per Protocol Set, day 29)**

Study Groups		Menveo-Menveo	Menactra-Menveo	Pooled Menveo/Menactra -Menveo	Naive
	Study day	N=290	N=282	N=572	N=93
Serogroup A	day 1	36 ((12.46%) (8.88%-16.83%) N=289	42 (14.89%) (10.95%-19.59%)	78 (13.66%) (10.95%-16.75%) N=571	4 (4.30%) (1.18%-10.65%)
	day 4	16 (11.11%) (6.49%-17.42%) N=144	18 (13.04%) (7.92%-19.83%) N=138	34 (12.06%) (8.50%-16.44%) N=282	2 (4.17%) (0.51%-14.25%) N=48
	day 6	78 (53.42%) (44.99%-61.71%) N=146	66 (47.14%) (38.66%-55.75%) N=140	144 (50.35%) (44.40%-56.29%) N=286	4 (9.09%) (2.53%-21.67%) N=44
	day 29	286 (98.62%) (96.51%-99.62%)	279 (98.94%) (96.92%-99.78%)	565 (98.78%) (97.49%-99.51%)	66 (70.97%) (60.64%-79.92%)
Serogroup C	day 1	176 (61.11%) (55.22%-66.77%) N=288	151 (53.74%) (47.72%-59.68%) N=281	327 (57.47%) (53.29%-61.57%) N=569	31 (33.33%) (23.89%-43.87%) N=93
	day 4	102 (70.83%) (62.68%-78.10%) N=144	83 (60.14%) (51.47%-68.38%) N=138	185 (65.60%) (59.74%-71.13%) N=282	21 (43.75%) (29.48%-58.82%) N=48
	day 6	127 (87.59%) (81.09%-92.47%) N=145	128 (92.09%) (86.28%-95.98%) N=139	255 (89.79%) (85.66%-93.05%) N=284	19 (43.18%) (28.35%-58.97%) N=44
	day 29	290 (100%) (98.74%-100%)	280 (99.64%) (98.03%-99.99%) N=281	570 (99.82%) (99.03%-100.00%) N=571	81 (87.10%) (78.55%-93.15%)
Serogroup W	day 1	218 (75.43%) (70.05%-80.29%) N=289	217 (76.95%) (71.59%-81.74%)	435 (76.18%) (72.47%-79.62%) N=571	57 (61.29%) (50.62%-71.22%)
	day 4	118 (81.94%) (74.67%-87.85%) N=144	114 (82.61%) (75.24%-88.53%) N=138	232 (82.27%) (77.30%-86.54%) N=282	30 (62.50%) (47.35%-76.05%) N=48
	day 6	137 (93.84%) (88.62%-97.14%) N=146	137 (97.86%) (93.87%-99.56%) N=140	274 (95.80%) (92.79%-97.81%) N=286	28 (63.64%) (47.77%-77.59%) N=44
	day 29	290 (100%) (98.74%-100%)	281 (100%) (98.70%-100%) N=281	571 (100%) (99.36%-100%) N=571	78 (84.78%) (75.79%-91.42%) N=92
Serogroup Y	day 1	155 (54.01%) (48.05%-59.88%) N=287	132 (46.98%) (41.02%-52.99%) N=281	287 (50.53%) (46.33%-54.72%) N=568	30 (32.26%) (22.93%-42.75%)
	day 4	79 (55.24%) (46.71%-63.56%) N=143	77 (55.80%) (47.10%-64.24%) N=138	156 (55.52%) (49.50%-61.42%) N=281	16 (33.33%) (20.40%-48.41%) N=48
	day 6	124 (85.52%) (78.72%-90.81%) N=145	123 (87.86%) (81.27%-92.76%) N=140	247 (86.67%) (82.16%-90.39%) N=285	20 (45.45%) (30.39%-61.15%) N=44
	day 29	290 (100%) (98.74%-100%)	280 (99.64%) (98.03%-99.99%) N=281	570 (99.82%) (99.03%-100.00%) N=571	72 (77.42%) (67.58%-85.45%)

hSBA GMTs at day 1, day 4, day 6, and day 29

In subjects who previously received either Menveo or Menactra, also hSBA GMTs against N meningitidis serogroups A, C, W, and Y were higher compared to subjects who received a first dose of Menveo (Naive group) from day 6. By day 29, hSBA GMTs against all serogroups had further increased in all study groups, with GMRs compared to day 1 ranging between 63.63-123.41 across serogroups in the Menveo-Menveo and Menactra-Menveo groups, and between 4.57-14.14 across serogroups in the Naive group.

hSBA GMTs (see page 94 of the Clinical Study Report):

Table 11.4.1-5 hSBA GMTs (95% CI) against *N meningitidis* serogroups A, C, W and Y and Vaccine Group Ratios of hSBA GMTs at day 1, day 4, day 6 and day 29 after Vaccination (Per Protocol Set, day 29)

		Vaccine Groups				Vaccine Group Ratio			
	Study Groups	Menveo-Menveo	Menactra-Menveo	Pooled Menveo/ Menactra-Menveo	Naive	Menveo-Menveo : Menactra-Menveo	Menveo-Menveo : Naive	Menactra-Menveo : Naive	Pooled Menveo/ Menactra-Menveo : Naive
	Study day	N=290	N=282	N=572	N=93				
Serogroup A	day 1	2.81 (2.54-3.11) N=289	2.95 (2.67-3.27)	2.88 (2.68-3.09) N=571	2.27 (1.90-2.71)				
	day 4	2.83 (2.43-3.29) N=144	3.00 (2.57-3.51) N=138	2.91 (2.61-3.25) N=282	2.25 (1.73-2.93) N=48	0.94 (0.76-1.17)	1.26 (0.93-1.70)	1.34 (0.98-1.82)	1.29 (0.97-1.72
	day 6	12.87 (9.63-17.19) N=146	10.17 (7.57-13.66) N=140	11.47 (9.32-14.10) N=286	2.48 (1.46-4.20) N=44	1.27 (0.84-1.91)	5.19 (2.84-9.47)	4.10 (2.24-7.50)	4.62 (2.62-8.15)
	day 29	210.10 (181.07-243.78)	236.69 (203.56-275.20)	222.81 (200.43-247.70)	32.11 (24.70-41.76)	0.89 (0.72-1.10)	6.54 (4.84-8.85)	7.37 (5.44-9.98)	6.94 (5.23-9.21)
Serogroup C	day 1	16.11 (13.28-19.54) N=288	10.72 (8.82-13.03) N=281	13.17 (11.48-15.12) N=569	5.06 (3.60-7.10)				
	day 4	22.96 (17.31-30.45) N=144	14.29 (10.71-19.07) N=138	18.21 (14.86-22.31) N=282	6.69 (4.10-10.90) N=48	1.61 (1.07-2.40)	3.43 (1.95-6.04)	2.14 (1.21-3.77)	2.72 (1.60-4.64)
	day 6	92.27 (68.91-123.56) N=145	90.06 (66.84-121.35) N=139	91.18 (74.04-112.30) N=284	6.71 (3.95-11.40) N=44	1.02 (0.67-1.56)	13.75 (7.51-25.19)	13.42 (7.31-24.66)	13.59 (7.70-24.00)
	day 29	1159.93 (977.33-1376.63)	1057.66 (888.74-1258.68) N=281	1108.42 (981.09-1252.27) N=571	59.70 (44.12-80.78)	1.10 (0.86-1.40)	19.43 (13.73-27.51)	17.72 (12.50-25.12)	18.57 (13.40-25.73)
Serogroup W	day 1	22.07 (18.54-26.29) N=289	23.46 (19.66-28.00)	22.75 (20.09-25.76) N=571	12.21 (8.98-16.62)				
	day 4	25.90 (20.13-33.32) N=144	33.87 (26.18-43.82) N=138	29.53 (24.66-35.37) N=282	13.80 (8.92-21.35) N=48	0.76 (0.53-1.10)	1.88 (1.13-3.11)	2.46 (1.48-4.08)	2.14 (1.33-3.44)
	day 6	112.49 (86.26-146.71) N=146	143.75 (109.61-188.54) N=140	126.84 (104.90-153.37) N=286	15.98 (9.85-25.93) N=44	0.78 (0.54-1.14)	7.04 (4.05-12.22)	8.99 (5.16-15.66)	7.94 (4.72-13.35)
	day 29	1394.65 (1176.59-1653.11)	1883.96 (1585.12-2239.15) N=281	1617.11 (1431.93-1826.23) N=571	55.31 (40.90-74.80) N=92	0.74 (0.58-0.94)	25.21 (17.83-35.65)	34.06 (24.06-48.23)	29.24 (21.09-40.52)
Serogroup Y	day 1	9.24 (7.81-10.94) N=287	8.22 (6.93-9.75) N=281	8.72 (7.74-9.83) N=568	4.56 (3.39-6.13)				
	day 4	10.87 (8.26-14.32) N=143	12.12 (9.16-16.04) N=138	11.47 (9.43-13.95) N=281	4.63 (2.88-7.44) N=48	0.90 (0.61-1.33)	2.35 (1.36-4.07)	2.62 (1.51-4.54)	2.48 (1.48-4.14)
	day 6	63.30 (47.73-83.95) N=145	61.56 (46.18-82.05) N=140	62.44 (51.06-76.34) N=285	6.44 (3.86-10.76) N=44	1.03 (0.69-1.54)	9.82 (5.47-17.64)	9.55 (5.31-17.19)	9.69 (5.59-16.79)
	day 29	1066.66 (900.67-1263.25)	1007.62 (848.53-1196.54) N=281	1037.19 (919.46-1169.98) N=571	37.40 (27.75-50.42)	1.06 (0.83-1.35)	28.52 (20.23-40.20)	26.94 (19.09-38.02)	27.73 (20.10-38.26)

Percentage of subjects with hSBA titers ≥ 8 at day 1 (persistence)

Percentages of subjects with hSBA titers ≥ 8 at day 1 were 12.46% and 15.46% against serogroup A in Menveo-Menveo and Menactra-Menveo groups, and were higher than in the Naive group, with a vaccine group difference between the Menveo-Menveo and Menactra-Menveo groups vs. the Naive group of 8.29% (95% CI: 1.55%-13.44%) and 11.30% (95% CI: 4.40%-16.78%), respectively. For the other serogroups percentages ranged from 53.63% to 61.82% for serogroup C, from 76.09% to 76.63% for serogroup W, and from 47.24% to 53.90% for serogroup Y, across subjects primed 4 to 6 years before, percentages that were higher in the Menveo-Menveo and Menactra-Menveo groups than those seen in the Naive group, with vaccine group differences between Menveo-Menveo and Menactra-Menveo group vs. the Naive group ranging between 14.64%-26.41% across serogroups (LLs of the 95% CIs all > 0).

Assessor's comment

The seroresponses for the different serogroups and study groups, started to increase between day 4 to 6 after vaccination, with highest seroresponses measured at day 29 (last blood draw). This trend was observed across the different immunogenicity analyses (hSBA, GMT's, GMR's and the reverse cumulative distribution curves of hSBA titers). Higher responses were observed in subjects that had been primed with Menactra or Menveo, compared to vaccine-naïve subjects, indicating that there is an anamnestic response.

Relatively many vaccine naïve subjects had hSBA titers ≥8 before vaccination, which is in line with previous studies and is considered an indication that these individuals previously experienced natural boosting. After vaccination however a true booster response could not be observed. For example 61.29% of naïve subjects had pre-vaccination hSBA titers for serogroup W ≥8, compared to 75.43%, 76.95% and 76.18% of Menveo, Menactra and pooled Menveo/Menactra subjects. At day 29, 84.78% of the vaccine naïve subjects had hSBA titers for serogroup W ≥8, compared to 100% of the vaccine primed subjects. For serogroup W, the day 29 GMT for the vaccine naïve subjects only reached 55.31, while GMT's for vaccine primed subjects ranged from 1394.65 to 1883.96. This raises the question whether these subjects were true seropositives, i.e. actually had protective levels of bactericidal antibodies, or whether there is an inflation of some sort in the assay. The MAH should present the immune response (hSBA and GMT) in vaccine naïve subjects stratified by baseline seropostivity and critically discuss their findings.

Furthermore, hSBA GMT's for serogroups A and Y obtained from the Menveo primed subjects at day 29 are 210.10 and 1066.66 respectively (see hSBA GMT table presented above). These GMT's are significantly lower than the GMT's presented in table 8 of the valid SmPC (819 and 2092 respectively, 28 days after a booster dose of Menveo and 5 years after first Menveo vaccination). Although hSBA titers ≥8 are measured in 98-100% of subjects in the current study, the Applicant should discuss the observed differences in the GMT responses.

hSBA GMTs at Day1 (persistence)

At baseline (day 1), hSBA GMTs ranged between 2.80 (against serogroup A in the Menveo-Menveo group) and 23.33 (against serogroup W in the Menactra-Menveo group) in the primed groups, and were higher than those observed at day 1 in the Naive group (ranging from 2.26 against serogroup A to 12.33 against serogroup W).

Assessor's comment

The data on persistence of the immune response show some differences between study V59_77 and the data in the valid SmPC. Table 8 (section 5.1 of the SmPC) presents the results obtained from study V59P6E1 in 49 subjects. In this study, 29% of subjects had hSBA titers ≥8 before the booster dose and 5 years after vaccination (corresponding GMT 5.16). The current study presents the results obtained from 290 Menveo primed subjects of whom 12.46% had hSBA titers ≥8 (serogroup A), before the booster dose and 4-6 years after vaccination with Menveo (corresponding GMT 2.81). The same applies to the persistence of hSBA titers for serogroup Y. Whereas the valid SmPC table 8 describes hSBA titers ≥8 in 78% of subjects (corresponding GMT 28), the current study describes hSBA titers ≥8 in 54% of subjects (corresponding GMT 9.24). These observations imply that persistence for serogroups A and Y is less than previously reported and they do have implications for sections 4.4 and 5.1 of the SmPC.

Statistical/analytical issues

- As primary analyses, vaccine-group effects were not adjusted. As secondary analyses, vaccine-group effects were adjusted for the log-transformed pre-vaccination antibody titer. The group titers of Naive subjects were always summarized without any adjustment (ie unadjusted GMTs and percentages).

- Missing immunogenicity values were considered not informative. No imputation methods were used to address missing immunogenicity or safety data.
- There were no planned interim analyses for this study. No DMC was used for this study.
- The two hypotheses associated to the primary objective were tested in a hierarchical manner; therefore, no adjustment for multiplicity was needed.
- Using the PPS (day 29), the analysis of the hSBA seroresponse against N meningitides serogroups A, C, W, and Y was replicated by sex and race. There was no meaningful effect of these factors seen on the percentages of subjects with hSBA seroresponse against any of the serogroups. However, there were very few subjects enrolled in some of the race categories, making the assessment difficult.

Safety results

Solicited AEs and Other Indicators of Reactogenicity

• Between 6 hours through day 7, at least 1 solicited AE was reported in 65% of primed subjects (pooled Menveo/Menactra-Menveo group) and 55% subjects in the Naïve group. Solicited local AEs were reported by 36% of primed subjects and 42% of vaccine-naive subjects, and solicited systemic AEs by 52% of primed subjects and 36% of vaccine-naive subjects.

• The most frequently reported solicited local AEs was injection site pain, both for primed subjects (36%) and vaccine-naive subjects (41%) and the most frequently reported systemic reactions was fatigue (38% of primed subjects and 20% of vaccine-naive subjects).

• Most of the solicited AEs were mild to moderate in intensity, had their onset between 6 hours and day 3 after vaccination and resolved within 3 days from onset.

• Fever (body temperature ≥ 38.0° C) was reported in 7 (1%) primed subjects and by none of the subjects in the Naive group. All cases of fever resolved within 2 days after vaccination. Fever with a body temperature ≥ 40.0° C was not reported by any subject in the study.

• Both in the pooled Menveo/Menactra-Menveo and in the Naive group, 5% of subjects used antipyretics and/or analgesics for prevention of pain and/or fever; 7% and 10% of primed and vaccine-naive subjects, respectively, used antipyretics and/or analgesics for the treatment of pain and/or fever.

Solicited local AE's (page 109 Clinical Study Report):

Table 12.2.3-1 Numbers and Percentages of Subjects With Any and Severe Solicited Local AEs with Onset from 6 hours through day 7 After Vaccination – Solicited Safety Set (6 hours – day 7)

Study Groups		Pooled Menveo/ Menactra-Menveo	Naive
		N=592	N=97
Injection site erythema (mm)	Any	20 (3%) N=573	10 (11%) N=92
	> 100 mm	0 N=573	2 (2%) N=92
Injection site induration (mm)	Any	24 (4%) N=572	8 (9%) N=92
	> 100 mm	0 N=572	0 N=92
Injection site pain	Any	210 (36%) N=588	40 (41%)
	Severe	11 (2%) N=588	2 (2%)

Source: Table 14.3.1.1; Table 14.3.1.2.
Abbreviation: AEs, adverse events.

Solicited systemic AE's (page 111 Clinical Study Report):

Table 12.2.3-2 Numbers and Percentages of Subjects With Any Or Severe Solicited Systemic AEs and Other Indicators of Reactogenicity with Onset from 6 hours up to day 7 After Vaccination – Solicited Safety Set (6 hours – day 7)

Study Groups		Pooled Menveo/ Menactra-Menveo N=592	Naive N=97
Systemic AEs			
Chills	Any	69 (12%) N=589	10 (10%)
	Severe	2 (< 1%) N=589	1 (1%)
Nausea	Any	92 (16%) N=588	13 (13%)
	Severe	6 (1%) N=588	2 (2%)
Myalgia	Any	109 (18%) N=590	15 (15%)
	Severe	11 (2%) N=590	2 (2%)
Arthralgia	Any	82 (14%) N=589	13 (14%) N=96
	Severe	6 (1%) N=589	2 (2%) N=96
Headache	Any	182 (31%) N=589	21 (22%)
	Severe	21 (4%) N=589	2 (2%)
Fatigue	Any	223 (38%) N=591	19 (20%)
	Severe	19 (3%) N=591	2 (2%)
Loss of appetite	Any	83 (14%) N=590	6 (6%)
	Severe	6 (1%) N=590	2 (2%)

Assessor's comment

Systemic solicited AE's occurred relatively more often in the primed group. This is currently not acknowledged by the MAH. The MAH should discuss this trend and substantiate whether or not to mention it in the SmPC.

Furthermore, fatigue was reported very often as a solicited AE in the current study. Fatigue should be added to the frequency table in section 4.8.

Also, arthralgia was reported very often as a solicited AE in the current study. Based on this finding, the MAH should re-evaluate the frequency of arthralgia amongst the total number of subjects exposed to Menveo.

Unsolicited AEs

• Overall, 9 subjects (8 primed subjects [pooled Menveo/Menactra-Menveo group] and 1 in the Naive group) reported at least 1 unsolicited AE within 30 minutes after vaccination.

• Overall, 25% of primed subjects and 22% of subjects in the Naive group reported any unsolicited AE between day 1 and day 29 after vaccination. The most frequently reported unsolicited AE between day 1 and day 29 after vaccination, by preferred term, was headache (reported in 3% of primed and vaccine-naive subjects).

• Overall, 8% of primed subjects and 11% of subjects in the Naive group reported at least 1 possibly related unsolicited AE between day 1 and day 29 after vaccination. The only at least possibly related AEs reported in more than 1% of subjects in either the pooled Menveo/Menactra-Menveo or the Naïve group were fatigue

(reported in 2% of primed subjects), injection site erythema (4% in the Naive group), and injection site pruritus (2% in the Naive group).

• Medically attended AEs were reported in 30% of primed subjects and 19% of vaccine-naive subjects, respectively. Overall, across primed and vaccine-naive subjects, 5 subjects reported medically attended AEs that were considered at least possibly related to the study vaccine by the investigator.

• Few SAEs were reported during the study: 5 (1%) primed subjects and 3 (3%) vaccine-naive subjects reported at least 1 SAE; none of the SAEs reported in this study was considered at least possibly related to the study vaccine.

• There were no AEs leading to premature withdrawal from the study or deaths reported in this study.

Assessor's comment

No deaths occurred and no AEs occurred leading to withdrawal from the study. The 13 serious adverse events reported by 8 subjects, were judged not to be related to the study drug. These findings further support what is already known about the safety profile of Menveo.

The MAH should discuss whether the possibly related medically attended AEs must be added to section 4.8 of the SmPC.

2.3.3. Discussion on clinical aspects

The current study aimed to evaluate the safety and antibody response following a single booster dose of Menveo administered to healthy adolescents and adults, 15-55 years of age, given approximately 4-6 years after primary MenACWY vaccination (Menveo or Menactra) and to assess the safety and antibody response to a single dose of Menveo given to vaccine-naïve subjects (subjects who did not receive any meningococcal vaccination prior to participation to this trial). This is a relatively large study where persistence of the immune response to Menveo is measured in 589 individuals for up to 4-6 years and the effect of a booster response is measured in 572 individuals. The information currently contained in the SmPC regarding the persistence of immunity in adolescents and the response to a booster in this age group is based upon far more limited data, in approximately 50 individuals.

The vaccine naïve group was significantly older than the vaccine primed groups (38.8±10.49 years vs. 17.1±3.66 years Menveo-Menveo and 17.8±4.53 years Menactra-Menveo). This hampers any between group comparisons, as age can affect the immune response to vaccination and the background exposure to *Neisseria meningitidis* can be expected to increase with age. These observations will not have any impact on the current SmPC, the issue is not further pursued here.

Booster response

The study demonstrated that a single booster dose of Menveo induced an immune response for which the lower limit of the one-sided 97.5% CI for the percentage of subject with hSBA seroresponse at day 29 against serogroups A, C, W, and Y was greater than 75%, irrespective of the meningococcal quadrivalent conjugated vaccine used for priming (Menveo or Menactra). The response to the booster dose was anamnestic, as evidenced by exponentially higher hSBA titers after a booster dose in primed subjects (GMRs at day 29 compared to day 1 ranging 63.63-123.41 across serogroups) compared with vaccine naïve individuals given a first dose of meningococcal vaccine (GMRs at day 29 compared to day 1 ranging 4.57-14.14). Percentages of primed subjects with hSBA titre $\geq$ 8 ranged from 47.14%-97.86% already at study day 6.

Questions were raised relating to relatively large proportion of vaccine naïve subjects who are seropositive at baseline to different serogroups, in particular serogroup W, however in whom no booster response was

observed. The MAH clarified that the immune response and memory in naturally primed individuals will not be similar to the response in individuals primed with a conjugate vaccine, explaining the differences in response.

Persistence

Persistence of immune responses at 4-6 years after primary vaccination was measured by percentages of subjects with hSBA ≥ 8 and GMTs at day 1 (pre-vaccination). Percentages of subjects with hSBA ≥ 8 were 12.46% (Menveo-Menveo) and 15.46% (Menactra-Menveo) for serogroup A, 61.82% and 53.63% for serogroup C, 76.09% and 76.63% for serogroup W, and 53.90% and 47.24% for serogroup Y. GMTs were higher in primed subjects compared to vaccine-naive controls, especially against serogroup C, W and Y.

The results concerning persistence of seroresponse 4-6 years after primary vaccination are not entirely in line with the data that are presented in table 8 of the current SmPC. Although persistence in serogroup A is known to be poor, the current SmPC describes hSBA ≥ 8 in 29%, whereas only 12.46% of 290 subjects had hSBA ≥ 8 in the current study. Moreover, persistence data in serogroup Y are worrying as the data presented here describe hSBA ≥ 8 in 54% of subjects, while the SmPC currently describes 78%.

Following a request for clarification, the MAH pointed out that the data from the present study represent the immune response 4-6 years after a single dose, in line with the dosing recommendations in the SmPC, with no insight in to the response to the primary vaccination course which limits the ability to determine the waning of antibodies. The comparison with the vaccine naïve group in study V59_77 also has its limitations, further limiting the ability to conclude on the waning of antibodies. Finally, a direct comparison to other studies with Menveo also comes with limitations due to differences in populations, natural circulation of meningococcal strains and potential assay variability. Therefore the data are insufficient to single out whether there is a real issue with waning protection against MenY.

Safety

Overall, the safety profile did not reveal any major safety concerns. A trend towards more systemic solicited AE's in the primed group compared to the naïve group could be observed, which is likely due to the differences in age between the two groups. The frequencies of unsolicited AEs reported within 1 month after vaccination were balanced between all study groups, and few at least possibly related unsolicited AEs were reported across groups. All reported SAEs (13 in 8 subjects) were considered not related to study vaccination. No deaths or AEs leading to withdrawal from the study were reported. Few medically attended, possibly related AEs were observed. *Lymphadenopathy* is not yet listed in the SmPC and should be included in section 4.8.

3. Additional clarification requested

Based on the data submitted, the MAH should address the following questions as part of this procedure:

- Efficacy
    - Many vaccine naïve subjects had hSBA ≥ 8 for one or more serogroups, which is not unexpected perse and in line with baseline immunity seen in different studies. However it appears that after vaccination these subjects did not experience a true booster response which is unexpected. The MAH is asked to discus this matter and to illustrate it by performing the hSBA and GMT immunogenicity analyses in the naïve group separated into a group with seropositive and a group with seronegative subjects.
    - Some significant differences were observed between persistence data for serogroups A and Y, presented in the current study V59_77 (in 290 Menveo primed subjects) and persistence data presented in Table 8 of the current SmPC (based on study V59P6E1 in 49 Menveo primed subjects).

These observations imply that persistence in both serogroups A and Y is poor and they do have implications for sections 4.4 and 5.1 of the SmPC.

- Safety
  - Systemic solicited AE's occurred relatively more often in the primed group. The Applicant is asked to discuss this trend and substantiate whether or not to mention it in the SmPC.
  - Fatigue was reported very often by the current population and should be added to the frequency table in section 4.8.
  - The SmPC currently describes that arthralgia occurs often. In the data presented here, arthralgia is described to occur very often. It is suggested to re-evaluate the frequency of arthralgia amongst the total number of subjects that have been exposed to Menveo.
  - Regarding the medically attended, possibly related AEs, the MAH should discuss whether these should be added to section 4.8.
  - Since the above changes to section 4.8 require a type II variation procedure, the MAH should consider to merge the separate frequency tables for children aged 2-10 years old and children and adults aged 11 years and older, in order to improve readability.

The timetable is a 30 day response timetable with clock stop.

MAH responses to Request for supplementary information

Efficacy

Rapporteur's Request

Many vaccine naïve subjects had hSBA $\geq$ 8 for one or more serogroups, which is not unexpected per se and in line with baseline immunity seen in different studies. However, it appears that after vaccination these subjects did not experience a true booster response which is unexpected. *The MAH is asked to discuss this matter and to illustrate it by performing the hSBA and GMT immunogenicity analyses in the naïve group separated into a group with seropositive and a group with seronegative subjects.*

Company Response:

As requested by the Agency, immune responses by baseline serostatus in vaccine-naïve subjects from study V59_77 are presented in Table 1 (GMTs) and Table 2 (percentages of subjects with hSBA titers $\geq$ 8). Of note, the number of vaccine-naïve subjects seropositive at baseline (subjects with pre-vaccination hSBA titer $\geq$ 4) varied across the serogroups and was particularly low for *N. meningitidis* serogroup A (N=8; 8.60%), preventing drawing conclusions. Nevertheless, the data do show an increase in bactericidal titers against all 4 serogroups in vaccine-naïve subjects seropositive at baseline after a single dose of Menveo. In vaccine-naïve subjects seropositive at baseline hSBA GMTs were higher at Day 29 than at Day 1, as shown by the geometric mean ratios (GMRs [Day 29/Day 1]) for *N. meningitides* serogroups A (12.48), C (10.00), W (2.60), and Y (4.50; Table 1). hSBA GMTs at Day 29 were higher against all serogroups in subjects seropositive when compared to those seronegative at baseline. The same was observed for the percentages of subjects with hSBA titers $\geq$ 8, which were higher at Day 29 when compared to Day 1 irrespectively of the baseline serostatus, and at Day 29 higher in subjects seropositive at baseline than those seronegative (Table 2).

Table 1 hSBA GMTs (95% CI) against *N. meningitidis* serogroups A, C, W and Y at Day 1, Day 4, Day 6 and Day 29 after vaccination (per protocol set, Day 29) and Day29/Day1 GMRs (95% CI), by baseline serostatus, Naive group

	Study day	Seronegative subjects (pre-vaccination hSBA titer < 4)	Seropositive subjects (pre-vaccination hSBA titer ≥ 4)
Serogroup A	GMT Day 1	2.00 (2.00-2.00) N=85	8.80 (4.65-16.65) N=8
	GMT Day 4	2.00 (1.73-2.32) N=45	13.05 (2.84-59.88) N=3
	GMT Day 6	2.15 (1.26-3.69) N=39	7.46 (2.04-27.28) N=5
	GMT Day 29	28.61 (21.68-37.74) N=85	109.77 (53.66-224.56) N=8
	GMR (Day 29/ Day 1)	14.30 (10.84-18.87) N=85	12.48 (5.49-28.32) N=8
Serogroup C	Day 1	2.00 (2.00-2.00) N=43	11.23 (7.72-16.32) N=50
	Day 4	2.38 (1.62-3.49) N=20	14.00 (8.17-24.00) N=28
	Day 6	3.16 (1.41-7.07) N=23	15.32 (7.85-29.92) N=21
	Day 29	28.65 (19.49-42.13) N=43	112.23 (73.78-170.71) N=50
	GMR (Day 29/ Day 1)	14.33 (9.79-20.97) N=43	10.00 (6.55-15.25) N=50
Serogroup W	Day 1	2.00 (2.00-2.00) N=33	33.04 (25.52-42.76) N=60
	Day 4	3.79 (2.08-6.89) N=17	28.04 (17.96-43.76) N=31
	Day 6	5.46 (2.22-13.46) N=16	29.53 (17.40-50.12) N=28
	Day 29	25.08 (14.19-44.33) N=33	86.08 (60.65-122.17) N=59
	GMR (Day 29/ Day 1)	12.54 (7.09-22.19) N=33	2.60 (1.73-3.91) N= 59
Serogroup Y	Day 1	2.00 (2.00-2.00) N=54	14.25 (10.19-19.93) N=39
	Day 4	2.00 (1.36-2.94) N=27	13.61 (7.30-25.36) N=21
	Day 6	3.28 (1.65-6.53) N=27	18.85 (9.01-39.42) N=17
	Day 29	25.36 (16.89-38.06) N=54	64.07 (41.50-98.94) N=39
	GMR (Day 29/ Day 1)	12.68 (8.43-19.07) N=54	4.50 (2.74-7.37) N=39

Abbreviations: hSBA, human serum bactericidal assay; GMT, geometric mean titer; CI, confidence interval; GMR, geometric mean ratio.

Table 2 **Numbers and percentages (95% CI) of subjects with hSBA titer ≥ 8 against *N meningitidis* serogroups A, C, W and Y at Day 1, Day 4, Day 6 and Day 29 after vaccination (per protocol set, Day 29), by baseline serostatus, Naive group**

	Study day	Seronegative subjects (pre-vaccination hSBA titer < 4)	Seropositive subjects (pre-vaccination hSBA titer ≥ 4)
Serogroup A	Day 1	0 (0%) (0%-4.25%) N=85	4 (50.00%) (15.70%-84.30%) N=8
	Day 4	0 (0%) (0%-7.87%) N=45	2 (66.67%) (9.43%-99.16%) N=3
	Day 6	1 (2.56%) (0.06%-13.48%) N=39	3 (60.00%) (14.66%-94.73%) N=5
	Day 29	59 (69.41%) (58.47%-78.95%) N=85	7 (87.50%) (47.35%-99.68%) N=8
Serogroup C	Day 1	0 (0%) (0%-8.22%) N=43	31 (62.00%) (47.17%-75.35%) N=50
	Day 4	1 (5.00%) (0.13%-24.87%) N=20	20 (71.43%) (51.33%-86.78%) N=28
	Day 6	3 (13.04%) (2.78%-33.59%) N=23	16 (76.19%) (52.83%-91.78%) N=21
	Day 29	32 (74.42%) (58.83%-86.48%) N=43	49 (98.00%) (89.35%-99.95%) N=50
Serogroup W	Day 1	0 (0%) (0%-10.58%) N=33	57 (95.00%) (86.08%-98.96%) N=60
	Day 4	3 (17.65%) (3.80%-43.43%) N=17	27 (87.10%) (70.17%-96.37%) N=31
	Day 6	4 (25.00%) (7.27%-52.38%) N=16	24 (85.71%) (67.33%-95.97%) N=28
	Day 29	20 (60.61%) (42.14%-77.09%) N=33	58 (98.31%) (90.91%-99.96%) N=59
Serogroup Y	Day 1	0 (0%) (0%-6.60%) N=54	30 (76.92%) (60.67%-88.87%) N=39
	Day 4	0 (0%) (0%-12.77%) N=27	16 (76.19%) (52.83%-91.78%) N=21
	Day 6	4 (14.81%) (4.19%-33.73%) N=27	16 (94.12%) (71.31%-99.85%) N=17
	Day 29	35 (64.81%) (50.62%-77.32%) N=54	37 (94.87%) (82.68%-99.37%) N=39

Abbreviations: CI, confidence interval; hSBA, serum bactericidal assay using human complement.

These immunogenicity results in vaccine-naive subjects seropositive at baseline cannot, however, be directly compared with immune responses seen after a booster dose in previously vaccinated subjects in study V59_77, as there are several unknown factors that may influence the magnitude and kinetics of the immune response in subjects seropositive at baseline, including:

- Time since exposure
- Strength of exposure (duration, degree of contact)

- Serogroup, strain or species (potentially non-invasive) of exposure
- Status of nasal colonization

In addition, the immune response and memory in naturally primed individuals may not be similar to the response in individuals primed with a conjugate vaccine. Encapsulated bacteria such as *N. meningitidis* generally induce a T-cell independent response, primarily of the (low-affinity) immunoglobulin M isotype. The surface polysaccharide antigens do not require T-cells to elicit antibody production and, therefore, immunological memory is limited [Weintraub, 2003; Klouwenberg. 2008].

On the other hand, protein-conjugated polysaccharide vaccines such as Menveo induce a T-cell dependent immune response, which is characterized by longer immunological memory based on functional avidity maturation and production of higher-affinity antibodies (primarily IgG) by B-cells due to T-cell stimulation [Klouwenberg. 2008; Blanchard-Roehner, 2008; Ada, 2003].

Therefore, it can be expected that the immune response to a booster dose in subjects primed with a conjugate meningococcal vaccine that is designed to elicit specific, robust and long-lasting immune responses against multiple serogroups, may be higher and different than that seen after a first dose in subjects who may have been exposed to one or more strains of the pathogen.

Assessor's comment
It is agreed with the MAH that the immune response and memory in naturally primed individuals may not be similar to the response in individuals primed with a conjugate vaccine.

Conclusion
Issue solved

Rapporteur's Request

Some significant differences were observed between persistence data for serogroups A and Y, presented in the current study V59_77 (in 290 Menveo primed subjects) and persistence data presented in Table 8 of the current SmPC (based on study V59P6E1 in 49 Menveo primed subjects). These observations imply that persistence in both serogroups A and Y is poor and they do have implications for sections 4.4 and 5.1 of the SmPC.

Company Response

GSK acknowledges the observations made by the Agency that hSBA GMTs and percentages of subjects with hSBA titers $\geq$ 8 against *N. meningitidis* serogroups A and Y in study V59_77 appeared to be lower than those previously observed at a similar time point in study V59P6E1. However, these results do not automatically indicate lower persistence or waning of antibody titers.

The results at Day 1 from study V59_77 represent a snapshot of the immune response to Menveo at 4-6 years after a single vaccination. Since there was no assessment of antibody titers before and after the initial (priming) Menveo dose, which was administered according to field conditions, no conclusions regarding waning of antibody titers can be drawn for primed subjects in study V59_77.

Nevertheless, the data from study V59_77 do suggest persistence of a specific immune response against serogroups A and Y up to 4-6 years after a single vaccination with Menveo, as shown by:

- Higher hSBA titers before (booster) vaccination in study V59_77 in primed subjects (serogroup A: 2.80, serogroup Y: 9.12) compared to vaccine-naïve controls (serogroup A: 2.26, serogroup Y: 4.44; V59_77 Report Table 11.4.1-8). The same was observed when comparing the percentages of subjects with hSBA titers $\geq$ 8 against serogroups A (primed: 12.46%; vaccine-naïve controls: 4.17%) and Y (primed: 53.90%; vaccine-naïve controls: 31.25%) before vaccination in study V59_77 (V59_77 Report Table 11.4.1-7).

- The anamnestic response to a booster dose of Menveo: higher hSBA GMT increase in Menveo primed subjects compared to vaccine-naïve controls as early as 5 days after the day of vaccination in study V59_77 and several-fold higher hSBA GMTs in Menveo primed subjects at day 29 after the booster than in vaccine-naive controls after a first dose.

Furthermore, it is worth mentioning that low persistence of antibody titers does not automatically correlate with lack of protection [Baxter, 2016]. The correlate of protection routinely used in Menveo clinical trials is a more conservative extrapolation from the original correlate of protection (hSBA titer $\geq$ 4) determined by Goldschneider et al. for serogroup C [Goldschneider, 1969a; Goldschneider, 1969b], and therefore hSBA titers lower than 1:8 do not necessarily indicate lack of protection.

Moreover, in a large field trial assessing a serogroup A conjugate vaccine used in a mass vaccination campaign in several countries in Africa, persistence of hSBA titers was low at 1 year after vaccination, but protection against disease remained high as evidenced by very low incidence of invasive meningococcal disease cases due to serogroup A [Kristiansen, 2014; Daugla, 2014].

In conclusion, the Company believes that the results of the V59_77 study do not indicate low persistence of antibodies to *N. meningitidis* serogroups A and Y despite lower titers than seen in previous studies, as the lack of baseline assessment (at the time of priming) makes it impossible to assess waning or lack of waning of antibodies. Based on the above, GSK believes that the V59_77 clinical data do not lead to any new conclusion on persistence of the immune response and that sections 4.4 and 5.1 of the SmPC currently contain all the relevant information for prescribers. Thus, GSK believes that no revision of sections 4.4 and 5.1 of the SmPC is needed.

Assessor's comment

The response of the MAH is not entirely agreed. The data currently in the SmPC is more limited than the data from the present study, and paints a slightly different picture as in that persistence is worse for MenY as well as for MenA. The poor persistence for MenA is currently included in the warning in section 4.4, therefore we can agree that no changes are needed for MenA, however the poor persistence for MenY is not. The MAH argues that protection may be better than suggested by the hSBA cut off applied, this can be agreed that this is possible however how much better? Applying a cut-off of hSBA >1:4 would still indicate a potential issue. Furthermore, it has been established that circulating bactericidal Ab's are needed for sustained protection against IMD – therefore we have to assume that absence of measurable antibodies indicates an absence of protection. Considering the severity of the disease, it is preferred to err on the side of caution.
The MAH however also points out that the data represent the immune response 4-6 years after a single dose, in line with the dosing recommendations in the SmPC, with no insight in to the response to the primary vaccination course which limits the ability to determine the waning of antibodies. Further, it can be agreed that comparison with the vaccine naïve group in study V59_77 also has its limitations, further limiting the ability to conclude on the waning of antibodies. Finally, a direct comparison to other studies with Menveo also comes with limitations due to differences in populations, natural circulation of meningococcal strains and potential assay variability. Therefore the data are insufficient to single out whether there is a real issue with waning protection against MenY.

In conclusion, we can agree with the company that an SmPC update based upon these data might not be necessary as the data will not significantly add to the information already reflected in the SmPC.

Conclusion

Issue solved

Safety

Rapporteur's Request

Systemic solicited AE's occurred relatively more often in the primed group. The Applicant is asked to discuss this trend and substantiate whether or not to mention it in the SmPC.

Company Response

GSK acknowledges the observations made by the Agency that systemic AEs occurred relatively more often in the primed group (52%) than in vaccine-naïve subjects (36%; V59_77 Report Table 12.2.1-1).

The mean age of subjects enrolled in the study was 17.1±3.66 years in the Menveo-Menveo group and 17.8±4.53 years in the Menactra-Menveo group. The Naïve group enrolled mostly adults, with a mean age of 38.8±10.49 years. The age difference between the subjects in the primed groups and those in the Naïve group is in line with expected enrolment, given the ACIP recommendation for a universal vaccination with a quadrivalent conjugated meningococcal vaccine at 11-12 years of age and the subsequent recommendation for a booster dose approximately 5 years later. The difference in the percentages of subjects who reported systemic solicited AEs could have been caused by the difference in age between primed and vaccine-naïve subjects. It is generally expected that adolescents are more likely to have concomitant infectious diseases, which may have contributed to more frequent reported systemic solicited AEs in the primed group. Indeed, primed subjects more frequently reported unsolicited AEs in the system organ class "Infections and infestations" than vaccine-naïve subjects (pooled Menveo/Menactra-Menveo group: 20%; Naive group: 13%), that are commonly associated with fatigue and headache, which were the 2 solicited systemic AEs that contributed most to the difference in the overall percentages of subjects who reported solicited systemic AEs between the primed and the Naive groups. Therefore, it is clinically plausible that the difference in the percentages of subjects who reported systemic solicited AEs could have been caused by the differences in age of those enrolled, rather than a difference in priming status between primed and vaccine-naïve subjects. Thus, we cannot conclude that the differences in reporting rates of solicited systemic AEs between the groups is related to the vaccination status of subjects, due to potential differences in reporting rates across different age groups.

Assessor's comment
It is agreed with the MAH that the age difference between the groups could possibly explain the differences in reporting rates.

Conclusion
Issue solved

Rapporteur's Request

Fatigue was reported very often by the current population and should be added to the frequency table in section 4.8.

Company Response

GSK acknowledges that fatigue was reported by 38% of primed subjects and 20% of vaccine-naïve subjects in study V59_77, which would correspond to the frequency "very common" in the SmPC.

Although 'fatigue' is not included as a standalone term, GSK believes that it is already covered in the Menveo SmPC. The Menveo SmPC indeed includes "malaise" as a very common adverse reaction in individuals 11 to 65 years of age. Malaise is a broader term which includes fatigue in its spectrum [Greenberg, 2002].

Considering the above, GSK considers an update of the SmPC not needed.

Assessor's comment

Both terms are separate MedDRA LLTs. It is acknowledged however that there is some overlap. The MAH is urged to be consistent in studies as to which terminology they use, and what definitions they apply. There is no need to include fatigue as likely this is encompassed by the 'malaise' already listed.

Conclusion

Issue solved.

Rapporteur's Request

The SmPC currently describes that arthralgia occurs often. In the data presented here, arthralgia is described to occur very often. It is suggested to re-evaluate the frequency of arthralgia amongst the total number of subjects that have been exposed to Menveo.

Company Response

GSK acknowledges the Rapporteur's request and has re-evaluated the frequency of arthralgia, considering all clinical trials that enrolled subjects 11 to 65 years of age. Table 3 below provides the number and percentages of subjects who reported arthralgia after any dose (primary or booster) of Menveo in clinical trials that enrolled subjects 11 to 65 years of age.

Overall, 9.77% of subjects reported arthralgia. This is in line with what is currently reported in the Menveo SmPC, which reports arthralgia as "common", i.e. ≥1% to <10%. Therefore, no update of the SmPC regarding the frequency of arthralgia is foreseen.

Table 3 **Number and percentages of subjects 11 through 65 years of age who received *Menveo* vaccination and reported arthralgia after any dose in *Menveo* clinical trials**

Study	Number of subjects who received at least one dose of *Menveo*	Number (%) of subjects who reported arthralgia
V59_P17	1588	118 (7.43%)
V59_P18	1583	208 (13.14%)
V59_P11	716	97 (13.55%)
V59_P6	151	12 (7.95%)
V59_P13	2643	197 (7.45%)
V59_77	685	95 (13.87%)
V59_P6E1	153	14 (9.15%)
V59_P20E1	162	12 (7.41%)
V59_P13E1	160	13 (8.13)
Total	**7841**	**766 (9.77%)**

Assessor's comment

The percentage of 9.77% is just inside the 10% threshold, therefore the rate can be considered 'common' rather than 'very common'.

Conclusion

Issue solved.

Rapporteur's Request

Regarding the medically attended, possibly related AEs, the MAH should discuss whether these should be added to section 4.8.

Company Response

The following at least possibly related medically attended AEs (all non-serious) were reported following Menveo vaccination in study V59_77: urticaria (2 cases reported by 1 subject), fatigue, headache, and myalgia (1 case each, all in the same subject), anxiety (1 case in 1 subject), pyrexia (1 case in 1 subject), and lymphadenopathy (1 case in 1 subject).

Except for urticaria (which is a symptom of hypersensitivity reactions) and lymphadenopathy, all these AEs are already reported in the Menveo SmPC. Urticaria and lymphadenopathy were only reported by 1 subject in study V59_77. GSK is of the opinion that this does not warrant an update of the SmPC.

Assessor's comment
The position of the MAH is not agreed. Urticaria is a known adverse reaction to many vaccines and causality is therefore possible, however it can be accepted that it falls under hypersensitivity reactions. The same does not hold for lymphadenopathy, which is not currently covered by the information in the SmPC. Therefore this should be listed in section 4.8 of the SmPC.

Conclusion
Issue not solved. The MAH is expected to submit a type II variation to include lymphadenopathy in 4.8.

Rapporteur's Request

Since the above changes to section 4.8 require a type II variation procedure, the MAH should consider to merge the separate frequency tables for children aged 2-10 years old and children and adults aged 11 years and older, in order to improve readability.

Company Response

As indicated in the above responses to the Rapporteur's requests, GSK does not foresee an update of section 4.8 of the Menveo SmPC.

With regards to the request to merge the safety information for children 2 to 10 years of age and individuals 11 to 65 years of age, GSK is of the opinion that applying this change will not improve the readability of the SmPC. On the contrary, due to differences in reactions usually reported by subjects in the different age groups (children, adolescents and adults) presenting all adverse reactions together will deprive health care providers of tools to make a risk assessment for subjects from different age groups. Therefore, GSK does not foresee any changes to the Section 4.8 of the SmPC.

Assessor's comment
The Rapporteur remains of the opinion that the two tables creates redundancy, but will not further pursue this issue. A type II variation to include urticaria and lymphadenopathy is still expected.

Conclusion
Issue solved.

4. Rapporteur's overall conclusion and recommendation

In conclusion, a single Menveo booster dose induced an anamnestic response within 5 days after vaccination in individuals primed with a quadrivalent conjugate meningococcal vaccine 4-6 years earlier. The company states that the data provided do not influence the benefit risk balance. This is agreed.

The MAH is expected to submit a type II variation to include lymphadenopathy in section 4.8.

☒ **Fulfilled**