London, 23 February 2017
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Committee for Medicinal Products for Human Use (CHMP)

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/P46/034

Note

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

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1. Introduction

On 27 June 2016, the MAH submitted 4 completed paediatric studies for Menveo, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

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 the following 4 studies:

- **V102_02**: Phase 2, Observer Blinded, Controlled, Randomized Multi-Centre Study in Adolescents, to Evaluate Safety, Tolerability and Immunogenicity of Four Different rMenB plus MenACWY Formulations.
- **V102_02E1**: Phase 2, Observer-Blind, Controlled, Randomized, Multi-Centre Extension Study to Evaluate Safety, Tolerability and Immunogenicity of a Third Dose of One of Four Different Formulations of rMenB + MenACWY in Adolescents Who Previously Received the Same Study Vaccines.
- **V102_03**: Phase 2, Observer Blinded, Controlled, Randomized Multi-Centre Study in Adolescents and Young Adults to Evaluate Safety and Immunogenicity of Two Different rMenB with OMV + MenACWY Combination Vaccination Formulations.
- **V102_03E1**: Phase 2, Observer-Blind, Placebo-Controlled, Randomized, Multi-Centre Extension Study to Evaluate the Safety and Immunogenicity of a Booster Dose of a MenABCWY Vaccine Administered 24 Months Following the Primary Series to Adolescents and Young Adults Who Participated in V102_03.

were conducted as part of the development program of the investigational meningococcal combination vaccine MenABCWY, intended to protect against the five most common *Neisseria meningitides* serogroups (A, B, C, W and Y) responsible for invasive meningococcal disease worldwide. MenABCWY combination vaccine is based upon two established GSK vaccines components, Menveo and Bexsero.

Assessor's comment

Menveo was used in submitted studies as control vaccine. The study population and single dose administration is conform the currently accepted indication and posology of Menveo.

2.2. Information on the pharmaceutical formulation used in the studies

In studies V102_02, V102_02E1, V102_03 and V102_03E1, GSK's MenACWY vaccine (Menveo) was used with or without addition of one of the formulations of the MenB vaccine. Menveo consists of

powder and solution for injection in vial/vial presentations. The vaccine is a conjugate vaccine, containing bacterial capsular oligosaccharides for serogroup A, C, W and Y of *Neisseria meningitides*, each separately conjugated to *Corynebacterium diphtheriae* cross reactive material 197 (CRM-197) – a non-toxic mutant of diphtheria toxin.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted final reports for:

- **V102_02**: Phase 2, Observer Blinded, Controlled, Randomized Multi-Centre Study in Adolescents, to Evaluate Safety, Tolerability and Immunogenicity of Four Different rMenB plus MenACWY Formulations;
- **V102_02E1**: Phase 2, Observer-Blind, Controlled, Randomized, Multi-Centre Extension Study to Evaluate Safety, Tolerability and Immunogenicity of a Third Dose of One of Four Different Formulations of rMenB + MenACWY in Adolescents Who Previously Received the Same Study Vaccines;
- **V102_03**: Phase 2, Observer Blinded, Controlled, Randomized Multi-Centre Study in Adolescents and Young Adults to Evaluate Safety and Immunogenicity of Two Different rMenB with OMV + MenACWY Combination Vaccination Formulations;
- **V102_03E1**: Phase 2, Observer-Blind, Placebo-Controlled, Randomized, Multi-Centre Extension Study to Evaluate the Safety and Immunogenicity of a Booster Dose of a MenABCWY Vaccine Administered 24 Months Following the Primary Series to Adolescents and Young Adults Who Participated in V102_03.

2.3.2. Clinical studies

V102_02: Phase 2, Observer Blinded, Controlled, Randomized Multi-Centre Study in Adolescents, to Evaluate Safety, Tolerability and Immunogenicity of Four Different rMenB plus MenACWY Formulations

Description

This was a phase 2, observer blinded, multicentre, controlled, randomized (1:1:1:1:1:1) study in healthy adolescents 11 to 18 years of age at time of enrolment. The study was conducted in Panama, Columbia and Chile. Subjects were randomized to one of the following 6 groups:

- Group I (MenABCWY): Meningococcal B Recombinant Vaccine (rMenB, vaccine containing serogroup B only, no Outer Membrane Vesicle (OMV))+MenACWY at a 0, 2-month schedule;
- Group II (MenAB (X2)CWY): rMenBx2doses (no OMV)+MenACWY at a 0, 2-month schedule;
- Group III (MenABCWY+OMV): rMenB+OMV NZ+MenACWY at a 0, 2-month schedule;
- Group IV (MenABCWY+¼OMV): rMenB+ MenACWY+¼OMV NZ at a 0, 2-month schedule;
- Group V (MenB): rMenB at a 0, 2-month schedule;
- Group VI (MenACWY/Placebo): One dose of MenACWY, one dose of placebo, respectively at 0,2 months schedule.

Assessor's comment:

In this AR, only the methods and data relevant for Menveo (MenACWY) will be discussed.

Methods

Objective(s)

In this study MenACWY vaccine was not included in any of the immunogenicity or safety study objectives. However immunogenicity and safety for MenACWY was analysed, as described below (under Outcomes/endpoints).

Study design

Phase 2, randomized, observer-blind, controlled, multicentre study.

Study population /Sample size

Inclusion criteria were: Healthy male and female subjects, 11 to 18 years of age at time of enrolment, generally in good health, and available for all study visits, whose parents/legal guardians had given written informed consent at the time of enrolment.

A total of 495 subjects were enrolled, 83 of which were randomized to Group VI (MenACWY/Placebo).

Main exclusion criteria were:

- Serious, acute, or chronic illnesses.
- Previous or suspected disease caused by *N meningitidis.*
- Previous immunization with any meningococcal vaccine.
- Exposure to individuals with clinically proven meningococcal disease or clinical bacterial meningitis without further microbiologic characterization.
- Pregnancy or nursing (breastfeeding) mothers.

Treatments

Subjects randomized to Group VI (MenACWY/Placebo) received one dose of MenACWY (final quantity/dose: 10 µg MenA, 5 µg MenC, 5 µg MenW, 5 µg MenY) at month 0, and one dose of placebo (aluminium hydroxide: 1,5 mg/dose) at month 2 of the study. Total follow-up was 3 months (study termination 30 days after the second vaccination).

Outcomes/endpoints

Relevant outcomes/endpoints for MenACWY were:

Immunogenicity:

One month after vaccination with MenACWY (first vaccination in group MenACWY/Placebo):

- The percentages of subjects with seroresponse[1] against *N. meningitidis* serogroups A, C, W, and Y, respectively.
- The percentages of subjects with hSBA ≥1:8 against *N. meningitidis* serogroups A, C, W, and Y.
- The geometric mean titres (GMTs) against *N. meningitidis* serogroups A, C, W, and Y.

[1] Seroresponse to *N. meningitidis* serogroups A, C, W and Y was defined as:

- for subjects with a pre-vaccination hSBA <1:4, a post-vaccination hSBA ≥1:8
- for subjects with a pre-vaccination hSBA ≥1:4, an increase in hSBA titre of at least four times the pre-vaccination titre.

Safety:

During this study solicited, all unsolicited adverse events (AEs) and concomitant medications were collected for 7 days after each vaccination. Serious adverse events (SAEs), medically attended AEs, AE leading to withdrawal from the study and concomitant medications used for treatment of aforementioned AEs were collected from day 8 after each vaccination up to next vaccination or to 30 days after last vaccination.

Statistical Methods

The analyses of reactogenicity, immunogenicity and safety were descriptive and hence no statistical tests were performed.

Eighty subjects were to be enrolled in each of the 6 vaccine groups. The sample size has no statistical basis and has been selected in order to obtain preliminary immunogenicity and safety data after vaccination with one of the four investigational formulations of MenB (±OMV) + MenACWY (group I, II, III and IV).

Results

Recruitment/ Number analysed

The first subject first visit (Visit 1) was on 20 December 2010. The last study visit (Visit 4) for the last subject took place on 27 July 2011.

A total of 495 subjects were enrolled at 11 centres in three countries and 494 subjects received at least one dose of the study vaccines.

Of the 495 subjects who were enrolled in the study, 485 subjects completed the study up to Visit 4.

For group VI (MenACWY/placebo), all 83 enrolled subjects completed the study. Of these, all 83 subjects were included in the MITT population, 81 subjects were included in the "PP population – 1 month after the first vaccination", and 82 subjects were included in the "PP population – 1 month after the second vaccination".

Reasons for exclusion of the PP population were randomization error (n=1) and blood draw done but inappropriate clotting duration (n=1).

Baseline data

The demographic and other baseline characteristics were balanced across the different vaccination groups. The majority of the subjects were Hispanic (72% to 76%). Gender distributions were similar across the vaccination groups (male 41%-54% and female 46%-59%). Age, height and weight were similar across the vaccination groups.

Immunogenicity results

One month after vaccination with MenACWY (first vaccination in group MenACWY/Placebo):

- The percentages of subjects with seroresponse were 86%, 68%, 60% and 78% against *N. meningitidis* serogroups A, C, W, and Y, respectively.
- The percentages of subjects with hSBA ≥1:8 against *N. meningitidis* serogroups A, C, W, and Y were 88%, 84%, 98% and 100%.
- Against *N. meningitidis* serogroups A, C, W, and Y the geometric mean titres (GMTs) were 105 (geometric mean ratio 1 month postvaccination to prevaccination [GMR] 77), 59 (GMR 15), 188 (GMR 10) and 77 (GMR 15), respectively.

Of note, one month after the first vaccination, the percentage of subjects with seroresponse in Groups I, II, III, IV (MenABCWY groups) for *N. meningitidis* serogroups were: A (75%- 86%), C (61%-79%), W (56%-67%) and Y (77%-82%) which were generally comparable to those in Group VI (MenACWY; 86%, 68%, 60% and 78%, respectively). In Group V (MenB), the percentages were 26%, 3%, 7% and 3% against the serogroups A, C, W and Y, respectively.

Similar results were obtained when the data was analysed based on the percentages of subjects with hSBA ≥1:8 against *N. meningitidis* serogroups A, C, W, and Y.

One month after the first vaccination, in Groups I, II, III, IV (ABCWY groups) the GMTs ranged as follows: serogroups A (41-73, GMR 32-55), C (54-82, GMR 12-20), W (143- 204; GMR 7.8-12) and Y (67-77; GMR 16-18). In Group VI (MenACWY) the GMTs were 105 (GMR 77), 59 (GMR 15), 188 (GMR 10) and 77 (GMR 15) against the respective serogroups.

Assessor's comment:

Seroresponse (defined as a post-vaccination hSBA ≥1:8 for subjects with a pre-vaccination hSBA <1:4; or an increase in hSBA titre of at least four times the pre-vaccination titre for subjects with a pre-vaccination hSBA ≥1:4) was lower in subjects with a pre-vaccination hSBA ≥1:4 vs in subjects with a pre-vaccination hSBA <1:4 for all serogroups. Overall, the immunogenicity results are in line with those reported in the initial MAA studies in adolescents. Based on the results described above, inclusion of an additional rMenB formulation did not seem to substantially influence the response against the serogroups A, C, W and Y.

Extension Study V102_02E1

Study V102_02E1 was an observer-blind, multicentre, randomized, controlled, extension study in healthy adolescents who participated in the parent study V102_02. This study was designed to evaluate safety, tolerability and immunogenicity of a third dose at month 6 (6 months following the first vaccination in the parent study) of one of four different formulations of MenABCWY vaccine or rMenB vaccine in subjects who previously received two doses of the same study vaccines (for details see description of study groups in parent study V102_02). Subjects previously allocated to groups I–V of the parent study were randomized in a 1:2 ratio to receive in this extension study either a third dose of the same vaccine as in the parent study or a dose of tetanus, diphtheria and acellular pertussis vaccine (Tdap), respectively. The subjects previously randomized to group VI in the parent study (subjects received MenACWY and placebo in the parent study) received only Tdap in this extension study. The study was conducted in Panama, Columbia and Chile.

A total of 440 subjects were enrolled and randomized. In Group VI (1 dose of MenACWY), 73 subjects were enrolled and received study vaccination and 72 subjects completed the extension study following the protocol.

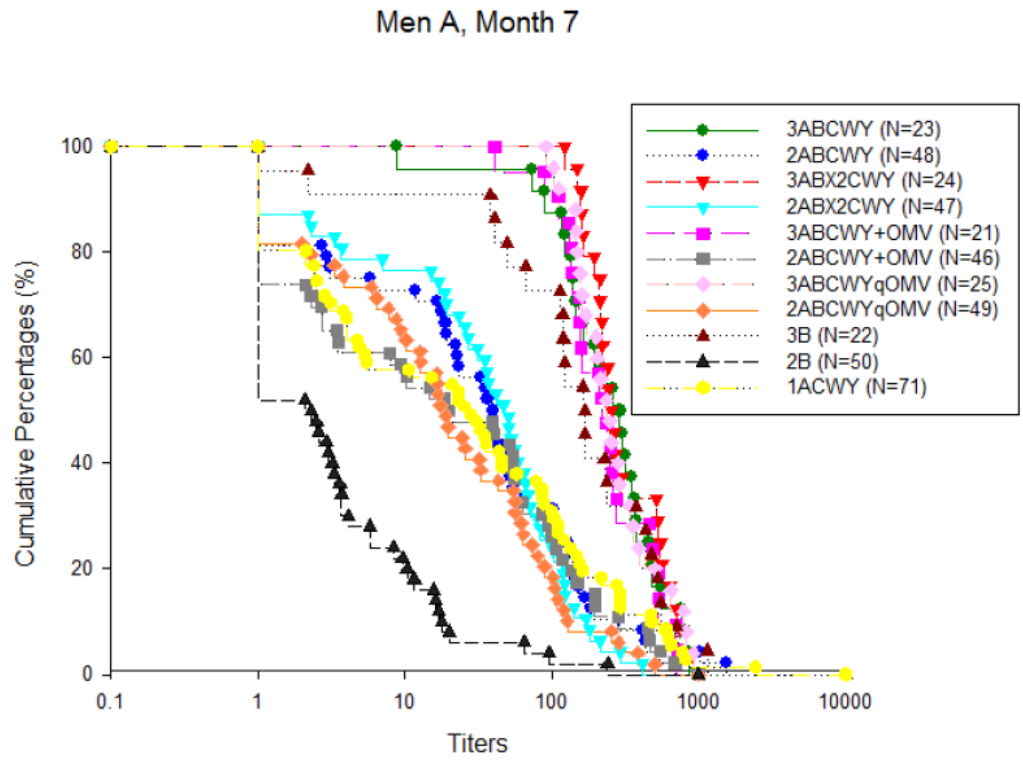
The percentage of subjects with hSBA ≥1:8 against *N. meningitidis* serogroups A, C, W and Y at 6, 7, and 12 months after vaccination with MenACWY in parent study V102_02 is reported below:

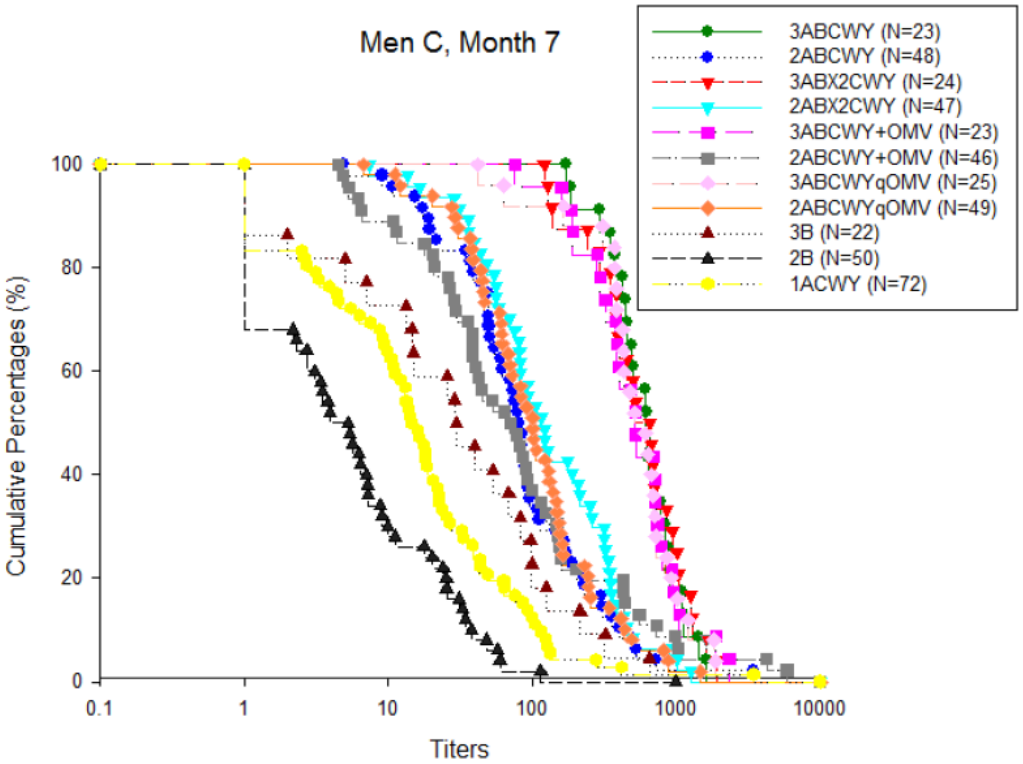
- Six months after administration of MenACWY vaccine in study V102_02, 55%, 76%, 97%, and 85% of subjects had hSBA ≥ 1:8 against *N. meningitidis* serogroups A, C, W, and Y, respectively.
- Seven months after vaccination, 58%, 68%, 96%, and 85% of subjects had hSBA ≥1:8 against *N. meningitidis* serogroups A, C, W, and Y, respectively.
- Twelve months after vaccination, 55%, 60%, 90%, and 80% of subjects had hSBA ≥1:8 against *N. meningitidis* serogroups A, C, W, and Y, respectively.

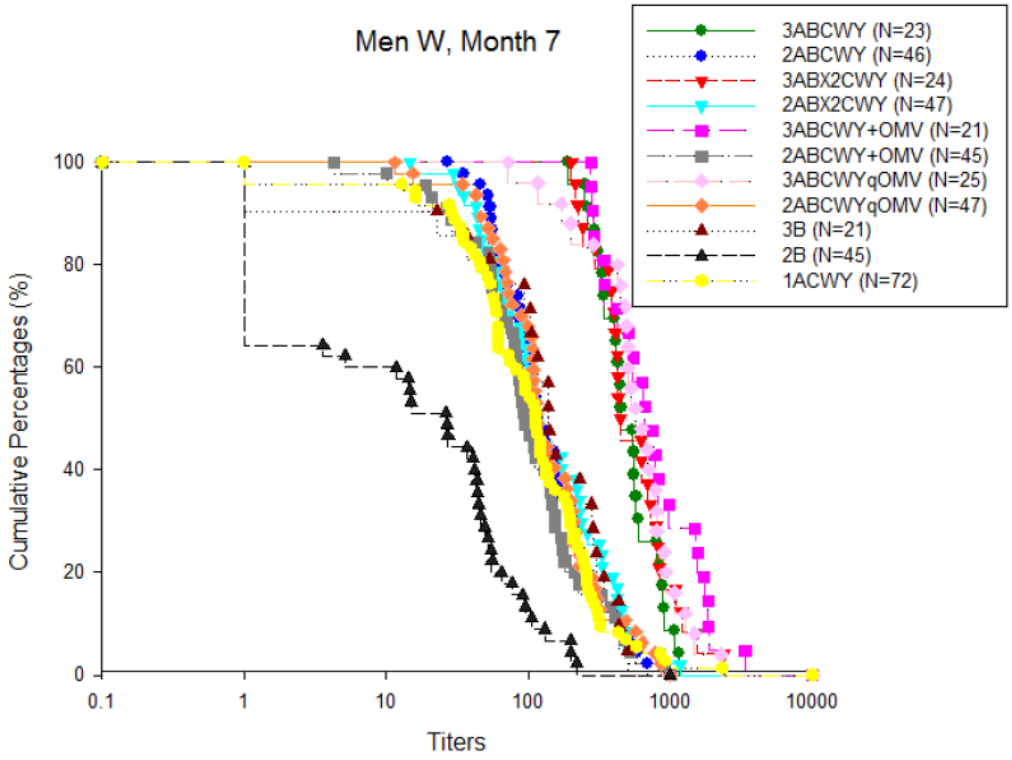
Antibody persistence as measured by the hSBA GMTs against *N. meningitidis* serogroups A, C, W and Y showed the following results:

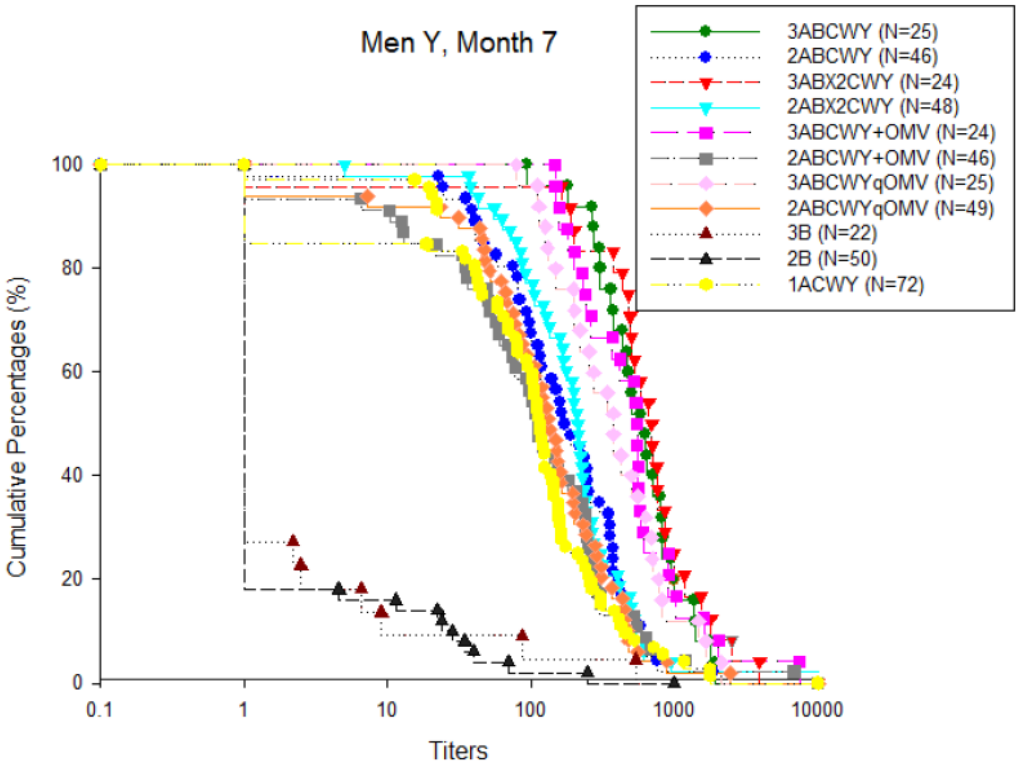
- Six months after administration of MenACWY vaccine in study V102_02, the GMTs were 20, 23, 117 and 84 against *N. meningitidis* serogroups A, C, W, and Y, respectively.
- Seven months after vaccination the GMTs were 21, 18, 121 and 75 against *N. meningitidis* serogroups A, C, W, and Y, respectively.
- Twelve months after vaccination the GMTs were 14, 14, 75 and 47 against *N. meningitidis* serogroups A, C, W, and Y, respectively.

The figures below depict the Reverse Cumulative Distribution Function (RCDF) of hSBA titres 7 months after vaccination against serogroups A, C, W and Y – MITT. In each of the panels, the yellow curve corresponds to data of subjects who received 1 dose of MenACWY.


Men A, Month 7
Cumulative Percentages (%)
Titers
0
20
40
60
80
100
0.1
1
10
100
1000
10000
3ABCWY (N=23)
2ABCWY (N=48)
3ABX2CWY (N=24)
2ABX2CWY (N=47)
3ABCWY+OMV (N=21)
2ABCWY+OMV (N=46)
3ABCWYqOMV (N=25)
2ABCWYqOMV (N=49)
3B (N=22)
2B (N=50)
1ACWY (N=71)


Men C, Month 7
Cumulative Percentages (%)
Titers
0
20
40
60
80
100
0.1
1
10
100
1000
10000
3ABCWY (N=23)
2ABCWY (N=48)
3ABX2CWY (N=24)
2ABX2CWY (N=47)
3ABCWY+OMV (N=23)
2ABCWY+OMV (N=46)
3ABCWYqOMV (N=25)
2ABCWYqOMV (N=49)
3B (N=22)
2B (N=50)
1ACWY (N=72)





Assessor's comment:

Of relevance to determine antibody persistence after a single MenACWY dose is the yellow curve in each of the panels (1ACWY group). The other vaccine groups received either one or two additional

vaccinations (at 2 and 6 months after the first vaccination) and have had their last vaccination 5 months or 1 month ago. Twelve month data was not visualized, but GMTs were described to be 14, 14, 75 and 47 for serogroups A, C, W, and Y, respectively in the 1ACWY group.

It is known that waning of the immune response occurs especially during the first months after vaccination with MenACWY (in particular for MenA) after which it more or less stabilises. As such, the presented results can be considered to be in line with expectations. It does however seem that waning of the MenC response in the current study is (slightly) faster than previously observed.

Safety results

The frequencies of solicited AEs after vaccination with MenACWY were 68%, 60%, and 55% for any, local, and systemic solicited AEs, respectively. The most frequently reported local solicited AE was injection-site pain, reported in 50% of subjects after vaccination with MenACWY; in 9% of subjects, pain was graded as severe. The most frequently reported systemic solicited AEs were headache and myalgia reported in 41%, and 38% of subjects, respectively and in 9%, and 7% of subjects, respectively, they were graded as severe. Rash was reported in 4 (5%) subjects after vaccination with MenACWY, in 2 subjects it was graded as urticarial. In this study rash was additionally assessed by an external expert. In 3 subjects the rash was local and in 1 subject it had a local extension (on the left wrist). According judgement of the external expert in none of these subjects rash was caused by a hypersensitivity reaction.

Assessor's comment:

The safety profile observed in the newly submitted studies is in line with the known safety profile of Menveo, no new safety signals were identified. It is noted that the fraction of subjects reporting (severe) AEs seems higher than observed in the initial MAA studies, but due to the small sample size, no conclusions should be drawn.

V102_03: Phase 2, Observer Blinded, Controlled, Randomized Multi-Centre Study in Adolescents and Young Adults to Evaluate Safety and Immunogenicity of Two Different rMenB with OMV + MenACWY Combination Vaccination Formulations

Description

This was a phase 2, observer-blinded, controlled, randomized (1:1:1:1), multicentre study in healthy adolescents and young adults aged 10 through 25 years to evaluate the safety and immunogenicity of 2 different formulations of MenABCWY vaccine. The study was conducted at 13 sites (8 in the United States and 5 in Poland). MenACWY was used as a control vaccine. Subjects were randomized to 1 of the 4 vaccination groups described below:

- Study group ABCWY+OMV received the MenABCWY+OMV vaccine formulation (containing a 'full dose' of OMV) on a 0, 2-month schedule.
- Study group ABCWY+qOMV received the MenABCWY+qOMV vaccine formulation (containing a 'quarter dose' of OMV) on a 0, 2-month schedule.
- Study group rMenB+OMV received the rMenB+OMV vaccine (containing a 'full dose' of OMV) on a 0, 2-month schedule.

- Study group Placebo/MenACWY received a single dose of placebo and a single dose of MenACWY vaccine, respectively, on a 0, 2-month schedule.

Assessor's comment:

As for study V102_02, only the methods and data relevant for Menveo (MenACWY) will be discussed in this AR.

Methods

Objective(s)

Primary immunogenicity objective:

- To demonstrate immunologic non-inferiority of 2 doses of 2 different formulations of MenABCWY vaccine to a single dose of MenACWY vaccine, as measured by the percentage of subjects with high-throughput assay for human serum bactericidal activity (HT-hSBA) seroresponse against *N. meningitidis* serogroups A, C, W, and Y, at 30 days after the second vaccination, in healthy adolescents and young adults aged 10 through 25 years.

Secondary immunogenicity objective:

- To compare the immunogenicity of 2 doses of 2 different formulations of MenABCWY vaccine with that of a single dose of MenACWY vaccine, as measured by the percentage of subjects with HT-hSBA $\geq$ 1:8 and HT-hSBA GMTs against *N. meningitidis* serogroups A, C, W, and Y, at 30 days after the second vaccination.

No safety objective was defined for the control vaccine MenACWY, however results for solicited and unsolicited adverse events (AEs) were analysed and summarized.

Assessor's comment:

The MAH has chosen as primary immunogenicity objective to demonstrate immunologic **non-inferiority of 2 doses** of 2 different formulations of MenABCWY vaccine **to a single dose** of MenACWY vaccine. As outlined below (Statistical Methods), the non-inferiority of MenABCWY+OMV to MenACWY was tested first (4 hypotheses). Following confirmation of non-inferiority, the non-inferiority of MenABCWY+qOMV (4 hypotheses) was tested. The trial would be considered successful only if all 8 null hypotheses were rejected simultaneously.

Study design

Phase 2, randomized, observer-blind, controlled, multicentre study.

Study population /Sample size

Inclusion criteria were: Healthy male and female subjects, 10 to 25 years of age at time of enrolment, generally in good health, and available for all study visits, who had given their written informed consent or assent (as applicable) at the time of enrolment, and, if the subject was under age 18 at the time of enrolment, the legal parent/guardian of the subject had given their written consent on behalf of the subject.

A total of 484 subjects were enrolled, 121 of which were randomized to Study group Placebo/ MenACWY.

Main exclusion criteria were:

- Serious, acute, or chronic illnesses.
- Current or previous, confirmed or suspected, disease caused by *N meningitidis.*
- Previous immunization with any meningococcal vaccine.
- Exposure to individuals with clinically proven meningococcal disease or clinical bacterial meningitis without further microbiologic characterization.
- Pregnancy or nursing (breastfeeding) mothers.

Treatments

Study group Placebo/MenACWY received one dose of saline placebo at month 0 and one dose of MenACWY (final quantity/dose: 10 µg MenA, 5 µg MenC, 5 µg MenW, 5 µg MenY) at month 2 of the study. Total follow-up was 241 days (study termination 180 days after the second vaccination).

Outcomes/endpoints

Relevant outcomes/endpoints for MenACWY were:

Immunogenicity:

- Percentage of subjects with hSBA seroresponse at day 30 after the second vaccination. Seroresponse to *N. meningitidis* serogroups A, C, W-135 and Y is defined as:

  - For subjects with a prevaccination hSBA < 1:4, a postvaccination hSBA ≥ 1:8;

  - For subjects with a prevaccination hSBA ≥ 1:4, an increase in hSBA titre of at least 4 times the prevaccination titre.
- Percentage of subjects with hSBA ≥ 1:8 to *N. meningitidis* serogroups A, C, W-135, and Y.
- hSBA GMTs for *N. meningitidis* serogroups A, C, W-135, and Y, and pre- to postvaccination geometric mean ratios (GMRs).

High-throughput assays for serum bactericidal activity using human complement (HT-hSBA) were used for *N. meningitidis* serogroups A, C, W-135, and Y and serogroup B test strains.

Safety:

No safety objective was defined for the control vaccine MenACWY, however results for solicited and unsolicited adverse events (AEs) were collected as follows.

During this study solicited AEs were collected for 7 days after each vaccination. From day 8 through day 91 all unsolicited AEs, serious adverse events (SAEs) and concomitant medications were collected; from day 92 through day 241 (i.e., 180 days following the second vaccination) only medically attended AEs, SAEs, and AEs leading to withdrawal from the study were collected.

Statistical Methods

The null hypothesis associated with the primary immunogenicity objective was based on non-inferiority of 2 doses of 2 different formulations of MenABCWY vaccine to a single dose of MenACWY (Menveo), as measured by the percentage of subjects with hSBA seroresponse directed against *N. meningitidis* serogroups A, C, W-135, and Y, at 30 days after the second vaccination.

The number and percentage of subjects with hSBA seroresponse and associated 2-sided 95% Clopper-Pearson confidence intervals (CIs) were computed for each N. meningitides serogroup A, C, W-135,

and Y at 30 days after the second vaccination. For constructing 2-sided 95% CIs for the difference between the ABCWY and Placebo/ACWY groups in the proportion of subjects with seroresponse, the usual normal approximation was not considered to be appropriate because these proportions could be close to 1. Therefore, the associated CIs (for the differences in percentage of subjects with seroresponse) were constructed using the method of Miettinen and Nurminen (known as the MN method [Miettinen and Nurminen, 1985]).

The immune response to 2 doses of MenABCWY vaccine was considered noninferior to the immune response to a single dose of MenACWY if the lower limit of the 2-sided 95% confidence interval (CI) around the difference between the study groups (ABCWY – Placebo/ACWY) in percentage of subjects with seroresponse between the vaccination groups was greater than -10% for each serogroup.

The 8 non-inferiority hypotheses underlying the first primary objective were tested as follows: the non-inferiority of MenABCWY+OMV to MenACWY was tested first (4 hypotheses); following confirmation of non-inferiority, the non-inferiority of MenABCWY+qOMV (4 hypotheses) was tested.

Novartis Vaccines and Diagnostics would consider this trial successful if all 8 null hypotheses were rejected simultaneously, confirming the immunological non-inferiority of 2 doses of the MenABCWY+OMV and of the MenABCWY+qOMV formulations to a single dose of MenACWY at 30 days after the second vaccination.

All subjects who received at least 1 vaccination and provided any safety data were to be considered evaluable for the safety analyses. All safety data were evaluated using descriptive statistics only.

Sample size determination was based on the assumption that the subjects in the study V102_03 would have antibody responses similar to those in earlier studies V59P18 and V59P13 (part of the clinical dossier submitted for Menveo), and there would be no negative influence of combining MenACWY and rMenB on these responses, with N=110 evaluable subjects (i.e., N=120 minus about 8% dropout rate), the non-inferiority criteria for each of the 4 serogroups is satisfied with the power 98.6%, 99%, 96.4%, and 99% according to responses similar to those in V59P18 and 99.9% for all strains assuming responses similar to those observed in V59P13.

Assuming that the results for the 4 serogroups are independent, the overall power for 8 non-inferiority ACWY criteria equals 86.8% assuming responses similar to V59P18, and 92.3% assuming responses similar to V59P13. Calculations were to be done using Nquery.

Results

Recruitment/ Number analysed

The first subject first visit (Visit 1) was on 8 August 2011. The last study visit for the last subject took place on 11 September 2012.

A total of 480 subjects were planned for this study, with 120 subjects in each of the 4 study groups. The actual number of subjects enrolled was 484; of these, a total of 480 subjects received at least one vaccination and were analysed.

For study group Placebo/MenACWY, 107/121 (88.4%) enrolled subjects completed the study. Of these, 105 (87%) subjects were included in the full analysis set for immunogenicity (FASi) population, 76 (63%) subjects were included in the per-protocol set for immunogenicity (PPSi) population.

At one site in Poland, 11 subjects randomized to the Placebo/MenACWY group were vaccinated with the correct vaccines but in the wrong order, that is, the first vaccination was with MenACWY and the second with placebo. Their data were excluded from the PPSi and desirability, and from the Unsolicited

Safety Set, both Solicited Safety Sets (applicable to the first and second vaccinations), and the Restricted Safety Set.

Assessor's comment:

It is noted that a substantial number of subjects were excluded from one or more analysis sets due to protocol deviations. Excluding the above mentioned vaccination error at one of the Polish sites, main reasons for exclusion were: subject did not comply with the protocol-specified window for the second study vaccination (N=37 overall), subject received a vaccine forbidden by the protocol (N=13 overall), and subject provided the visit 3 (day 91) blood sample outside the protocol-specified window (N=15 overall). As a result, only 343 subjects (90 in the ABCWY+OMV group, 85 in the ABCWY+qOMV group, 92 in the rMenB+OMV group, and 76 in the Placebo/ACWY group) were included in the PPSi.

Baseline data

Demographic characteristics were comparable across study groups. The median age was 13 years overall; the minimum age in each group was 10 years, and the maximum was 24 or 25 years. Approximately half of subjects were male (44% to 51% across groups). Median weights were 56 to 57 kg across study groups. Ethnicity was also comparable across groups: 61% of all subjects were Caucasian, 32% were Hispanic, 5% were Black, and the remainder were Asian or of other ethnicities. Approximately one-fourth of subjects were from Poland, with the remainder from the US.

Immunogenicity results

The percentages of subjects with seroresponse against all 4 serogroups at 30 days after the second vaccination in the Placebo/MenACWY group (i.e., one vaccination of MenACWY) were analysed as part of the primary objective. The percentages of subjects with seroresponse against serogroups A, C, W, and Y were 73%, 63%, 65%, and 75% of subjects, respectively.

Immunological non-inferiority of 2 doses of the MenABCWY+OMV formulation vs. a single dose of the MenACWY vaccine was demonstrated for all 4 serogroups: the lower limits of the 2-sided 95% CI for the differences, in percentage of subjects with seroresponse, between study groups were 5%, 21%, 0%, and 5% for serogroups A, C, W-135, and Y, respectively, thereby satisfying the noninferiority criterion (lower limit of the 95% CI was > −10%).

The immune responses against serogroups A, C, W-135, and Y were statistically higher after 2 doses of each of the MenABCWY formulations than after a single dose of the ACWY vaccine, i.e., the lower limits of the 2-sided 95% CIs for the difference between study groups were greater than 0%, except for serogroup W-135 in the ABCWY+OMV group.

The following immunogenicity results for MenACWY (Placebo/MenACWY group) were analysed as part of the secondary objectives:

- Across all study groups, low percentages of subjects had baseline hSBA ≥ 1:8 to serogroups A and Y (1% to 8% and 8% to 18%, respectively), while 32% to 37% of subjects across groups had such baseline hSBA levels to serogroup C and 51% to 66% of subjects had baseline hSBA ≥1:8 to serogroup W-135.
- At 30 days after the second vaccination the percentages of subjects who achieved HThSBA ≥ 1:8 in the Placebo/MenACWY group were 73%, 83%, 89% and 82% against serogroups A, C, W and Y, respectively. The percentages of subjects with hSBA ≥ 1:8 at 30 days after the second vaccination in the ABCWY+OMV and ABCWY+qOMV groups were: 93% and 95%

against serogroup A, respectively, 99% and 100% against serogroup C, respectively, and 100% against serogroup W-135 and 97% against serogroup Y in both study groups.

- At 30 days after the second vaccination in the Placebo/MenACWY group, HT-hSBA GMTs against serogroup A, C, W, and Y were 45, 55, 65, and 46, respectively. At 30 days after the second vaccination, hSBA GMTs against serogroup A in the ABCWY+OMV and ABCWY+qOMV groups were 71 and 77, 214 and 187 against serogroup C, 239 and 288 against serogroup W-135, and 149 and 129 against serogroup Y.

Assessor's comment:

The immunogenicity results are as could be expected, e.g. higher after 2 doses of either one of the MenABCWY vaccines than after a single dose of MenACWY. The results of study group Placebo/MenACWY, albeit not directly comparable due to the different assay used (High-throughput assay), seem to be in line with those reported in the initial MAA studies in subjects 10 through 25 years of age. A separate analysis for adolescents was not provided, but considering the overall mean age was 13 years and all subjects were ≤25 years of age, it is not expected to be different from the overall results.

Extension Study V102_03E1

Study V102_03E1 was a phase 2, observer-blinded, placebo-controlled, randomized, multicentre extension study in healthy adolescents and young adults that participated in the parent study V102_03. The parent study groups were further randomized to receive either one dose of the different MenABCWY vaccine formulations under study or a dose of placebo approximately 24 months after the last vaccination was completed in the V102_03 study. The study was conducted in the US and Poland.

A total of 194 subjects were enrolled and randomly assigned to study groups based on the vaccine received in the parent study. Study group Placebo/MenACWY was further randomized to 3 groups in a 1:1:1 ratio; one group received MenABCWY + full dose of OMV, the second group received MenABCWY+ ¼ dose of OMV and the third group received placebo. These groups were designated as 1M_OMV, 1M_qOMV and 1M_Pbo respectively.

In study group Placebo/ACWY, 120 subjects were planned to be enrolled, 40 in each of the three subgroups. 59 subjects were actually enrolled and received the allocated vaccinations and 57 subjects completed the protocol. A total of 19 subjects received placebo (study group 1M_Pbo) and 18 subjects in this study group completed protocol.

On this study only MenABCWY formulations and placebo were given in this study, but not MenACWY. For this reason only antibody persistence 24 months after vaccination in study V102_03 (only group Placebo/ACWY of study V102_03) on study day 1 before vaccination in study V102_03E1 and antibody persistence 36 months after vaccination in study V102_03 (only for study group 1M_Pbo of study V102_03E1) are relevant for immunogenicity of MenACWY.

All subjects received the study vaccination on day 1 (−60/+150 days) of this extension study ie, approximately 24 months after last primary vaccination. All subjects in the extension study were to be followed for safety and immunogenicity for approximately 12 months after the study vaccination.

The following immunogenicity results for MenACWY vaccine were analysed as part of the secondary objective: Persistence After Primary Vaccination Against Serogroups A, C, W and Y

HT-hSBA Titers ≥ 1:8

- Group placebo/ACWY: At 24 months after primary vaccination, percentages of subjects with HT-hSBA ≥ 1:8 were 31% of subjects against serogroup A, 57% of subjects against serogroup C, 68% of subjects against serogroup W, and 46% of subjects against serogroup Y.
- Group 1M_Pbo: At 36 months after primary vaccination percentages of subjects with HT-hSBA ≥ 1:8 were 35% of subjects against serogroup A, 65% of subjects against serogroup C, 65% of subjects against serogroup W, and 47% of subjects against serogroup Y.

HT-hSBA GMTs

- Group placebo/ACWY: At 24 months after primary vaccination, the GMTs were 4.14 for serogroup A, 10 for serogroup C, 17 for serogroup W, and 6.49 for serogroup Y.
- Group 1M_Pbo: At 36 months after primary vaccination the GMTs were 3.54 for serogroup A, 24 for serogroup C, 16 for serogroup W, and 9.56 for serogroup Y.

Assessor's comment:

Trends in antibody persistence for serogroups W and Y appear lower than previously generated persistence data (study V59P13E1, V59P6E1). After clarifications were requested, the MAH pointed out that small numbers in V102_03E1 make it difficult to draw firm conclusions; the confidence intervals provide some measure of uncertainty, and these overlap between studies. Secondly, in study V102_03E1 a high-throughput [HT]-SBA was used – unlike in previous studies. It is agreed with the MAH that results obtained using different assays, which have different sensitivity aspects, cannot be directly compared.

Safety results

The frequencies of solicited AEs after vaccination with MenACWY were 63%, 53%, and 46% for any, local, and systemic solicited AEs, respectively. The most frequently reported local solicited AE was injection-site pain, reported in 42% of subjects after vaccination with MenACWY; in 8% of subjects, pain was graded as severe. The most frequently reported systemic solicited AEs were myalgia, headache and fatigue reported in 25%, 23%, and 20% of subjects, respectively and in 4%, 3%, and 2% of subjects, respectively, they were graded as severe.

Unsolicited AEs were reported in 7% of subjects within 30 days (day 61 through 91) after vaccination with MenACWY, in 1 subject (1% of subjects) the AE (injection site erythema) was judged by investigator as at least possibly related. The percentage of subjects with at least possibly related unsolicited AEs reported during the entire study period (days 1 through 241) was 6% in the Placebo/MenACWY group, all of them were reported in the period from day 1 through day 91. Injection-site pain was the only AE in this group which was reported in more than 1% of subjects (i.e., in 2% of subject).

In study group Placebo/MenACWY, 28% of subjects reported medically attended AEs from day 92 through day 241 and 3% of subjects reported serious AEs (SAEs) throughout the complete study period (from day 1 through day 241), none of these AEs were judged by investigator as at least possibly related. No AE in this group led to premature withdrawal of subjects, no subject died.

A total of 7 different events of New Onset of Chronic Disease (NOCDs) were reported in group Placebo/ACWY since completion of the parent study V102_03 up to day 1 in study V102_03E1. Obesity was reported by 2 subjects. Myopia, chronic sinusitis, scoliosis, asthma, rhinitis allergic, and hypertension were reported each by 1 subject.

Assessor's comment:

Again, the fraction of subjects reporting (severe) AEs seems higher than observed in the initial MAA studies, but due to the small sample size, no conclusions should be drawn. Overall, the safety profile observed is in line with the known safety profile of Menveo, and no new safety signals were identified.

2.3.3. Discussion on clinical aspects

The MAH submitted 4 studies conducted as part of the development program of the investigational meningococcal combination vaccine MenABCWY, intended to protect against the five most common *Neisseria meningitides* serogroups (A, B, C, W and Y) responsible for invasive meningococcal disease worldwide. MenABCWY combination vaccine is based upon two established GSK vaccines components, Menveo and Bexsero.

Menveo was used in those studies as control vaccine. The study population and single dose administration was conform the currently accepted indication and posology of Menveo. The immunogenicity after vaccination was determined with the hSBA assay (standard assay in studies V102_02+E1, high throughput (HT) assay in V102_03+E1). Due to the HT-assay used in V102_03, the results from this study might not be directly comparable to earlier results, although they seem to be in line. No correlation between the two assays in a single study was provided.

Immunogenicity results against the serogroups A, C, W and Y in subjects vaccinated with Menveo in these studies are in line with those reported in the initial MAA studies in adolescents and young adults.

Upon request the MAH provided an overview of all available persistence data since marketing authorisation for serogroups A, C, W and Y, and placed the findings of particularly study V102_03E1 in perspective of these findings.

The overview provided by the MAH did not provide many new insights. Currently, the SmPC includes persistence data up to 5 years after vaccination in adolescents, children aged 2-10 years. From these data, it can be deducted that persistence is poorer in younger children. The data in the SmPC stem from studies V59P13E1 and V59P20E1. Follow up in study V59P22E1 is poor and the data does not add to what is already described. The findings of study V59P6E1 are in line with data already described. The discrepancies between the hSBA and rSBA have discussed in earlier assessments. Study V59_67 falls outside the indication.

~~In the 2 extension studies, antibody persistence was evaluated at 6 months, 7 months and 1 year (study V102_02E1), or at 2 and 3 years (study V102_03E1) after vaccination with MenACWY. As expected, there was a substantial decrease in hSBA GMTs 6 months to 1 year (study V102_02E1) and HT-hSBA GMTs (study V102_03E1) 2 and 3 years after vaccination. Although substantial waning of the immune response is known, especially for MenA, the decreases observed in the present studies seem to be larger than expected based on results from study V59P13E1. Therefore, the MAH is requested to:~~

~~a) provide an overview of all available persistence data since marketing authorisation for serogroups A, C, W and Y, and~~

~~b) put the results generated in the studies described in the current report in perspective, based upon the provided overview of all available persistence data.~~

The safety data did not raise any unforeseen safety issue.

Overall the results of the 4 studies do not alter the benefit-risk profile of MenACWY vaccine.

The MAH has reviewed the immunogenicity and safety results following MenACWY vaccine administration as control vaccine in studies V102_02, V102_02E1, V102_03, and V102_03E1 and has

concluded that they are in line with the current safety and product information of MenACWY. Therefore, no changes to the considered current SmPC of MenACWY are necessary. This is agreed~~, provided that the additional requested overview of available persistence data does not warrant an update of the currently approved SmPC.~~

3. Rapporteur's overall conclusion and recommendation

☒ Fulfilled:

The immunogenicity and safety findings following MenACWY vaccine administration as control vaccine in studies V102_02, V102_02E1, V102_03, and V102_03E1 are in line with what is known and described in the product information of MenACWY. These findings do not alter the Benefit/Risk and no changes to the current labelling of MenACWY is necessary based on these findings.

☐ Not fulfilled:

~~Based on the data submitted, the MAH is requested to:~~

~~a) provide an overview of all available persistence data since marketing authorisation for serogroups A, C, W and Y, and~~

~~b) put the results generated in the studies described in the current report in perspective, based upon the provided overview of all available persistence data.~~

4. Additional clarification requested

Although substantial waning of the immune response is known, especially for MenA, the decreases observed in the present studies seem to be larger than expected based on results from study V59P13E1. Therefore, the MAH is requested to:

a) provide an overview of all available persistence data since marketing authorisation for serogroups A, C, W and Y, and

b) put the results generated in the studies described in the current report in perspective, based upon the provided overview of all available persistence data.

MAH responses to Request for supplementary information

A: The MAH is requested to provide an overview of all available persistence data since marketing authorisation for serogroups A, C, W and Y

Persistence of bactericidal antibodies after administration of 1 or more doses of MenACWY has been examined in 10 clinical studies, across age groups, during the clinical development of MenACWY. An overview of these 10 studies is provided in Table 1.

Table 1 Overview of MenACWY Persistence Studies

Study	Phase	Population	Number of subjects[a]	Assay(s) used	Persistence Assessments
Persistence After 1 dose of MenACWY					
V59_67[b]	2	Toddlers (12-15 mo)	100	hSBA, rSBA	6 mo after 1-dose primary vaccination
V59P6[c]	2	Adolescents (11-17 y)	524	hSBA, rSBA	12 mo after 1-dose primary vaccination
V59P6E1	2b	Adolescents (11-17 years at V59P6 enrolment)	153	hSBA	12 months and 5 years after 1 dose primary vaccination
V59_57[c]	3b	Children (2-10 y)	715	hSBA	12 mo after 1-dose primary vaccination
V59P13E1[c]	3	Adolescents and adults (11-18 y at V59P13 enrolment)	389	hSBA, rSBA	21 mo, 3 y, 5 y after 1-dose primary vaccination
Persistence After 1 or 2 doses of MenACWY					
V59P22E1	3b	Children (22-45 mo)	205	hSBA	13-33 mo after 1- or 2-dose primary vaccinaiton
V59P20E1[c]	4	Children (7-15 y)	465	hSBA	5 y after 1- and 2-dose primary vaccination
V59P22[c]	3	Infants (6-8 mo)	662	hSBA	7 mo after 2-dose primary vaccination
Persistence after 2 or more doses of MenACWY					
V59P14[c]	3	Infants (2 mo)	479	hSBA	6 mo after 3-dose infant series
V59P14E1[c]	3b	Children (40 and 60 mo)	433	hSBA, rSBA	40 and 60 mo after 4-dose infant series and after 2-dose toddler series

Abbreviations: mo = months. y = years. hSBA = serum bactericidal assay using human complement. rSBA = serum bactericidal assay using rabbit complement. a Total number of subjects enrolled into the study. b Included in the analyses by Bona et al. 2016 paper. c Included in the analyses by Baxter et al. 2016 paper.

Persistence data from studies V59P6, V59P13E1, V59_57, V59P20E1, V59P22, V59P14, and V59P14E1
An overview of antibody persistence after Menveo vaccination across age groups is presented by Baxter et al. [Baxter 2016] including data from studies V59P6, V59P13E1, V59_57, V59P20E1, V59P22, V59P14, and V59P14E1. Persisting antibody titres were assessed using the serum bactericidal assay with human (all studies) and rabbit (V59P6, V59P13E1, and V59P14E1 only) complement (hSBA and rSBA, respectively; Table 1). In summary, primary vaccination with MenACWY (one or more doses, depending on age) induced a robust immune response across age groups, which was maintained to a considerable degree for up to 5 years. In adolescents and children, a single dose of MenACWY (or 2 doses in children ≤ 5 years) induced high antibody titres immediately post-vaccination (percentages of subjects with hSBA titres ≥ 8 at 1 month post-vaccination ranging from 69% to 96% across serogroups, age groups, and studies), with an age- and serogroup-specific decline up to 1 year (range: 11% to 95%), followed by relatively stable levels up to 5 years post-vaccination (range: 14% to 82%). In infants and toddlers, MenACWY was administered as a multi-dose regimen and results in moderate to high antibody persistence across serogroups (percentages of subjects with hSBA titres ≥ 8 at 6 or 7 months after vaccination ranging from 12% to 75% across serogroups and age groups, and from 6% to 85% across serogroups at 40 and 60 months of age).

Antibody persistence after priming in infants and toddlers also appeared to be impacted by maturity of the immune system at time of priming, as evidenced by better persistence after a 2-dose primary series in the second year of life than after a 4-dose primary series given to infants. Across age groups, the degree of persistence of antibodies was serogroup-specific, with generally high antibody titres up to 5 years for serogroups W and Y, while persistence of antibodies is moderate against serogroup C, and lowest against serogroup A, as measured using hSBA. Interestingly, this trend was not seen when assessed using a different assay method using rabbit complement, (in adolescents, percentages of subjects with rSBA titres ≥ 8 at 21 months and 3 years after a single vaccination were still 96% to 99%, compared with 37% to 40% of subjects hSBA titres ≥ 8 at the same timepoints), while antibody titres against the other serogroups were relatively comparable between the 2 assay methods. These observations suggest that the decline of antibodies against serogroup A over time seen with hSBA may be an assay-specific finding and may underestimate the true protection against meningococcal disease following MenACWY vaccination.

Results as presented by Baxter et al are presented in figures 1 and 2. (HUMAN VACCINES & IMMUNOTHERAPEUTICS 2016, VOL. 12, NO. 5, 1300–1310)

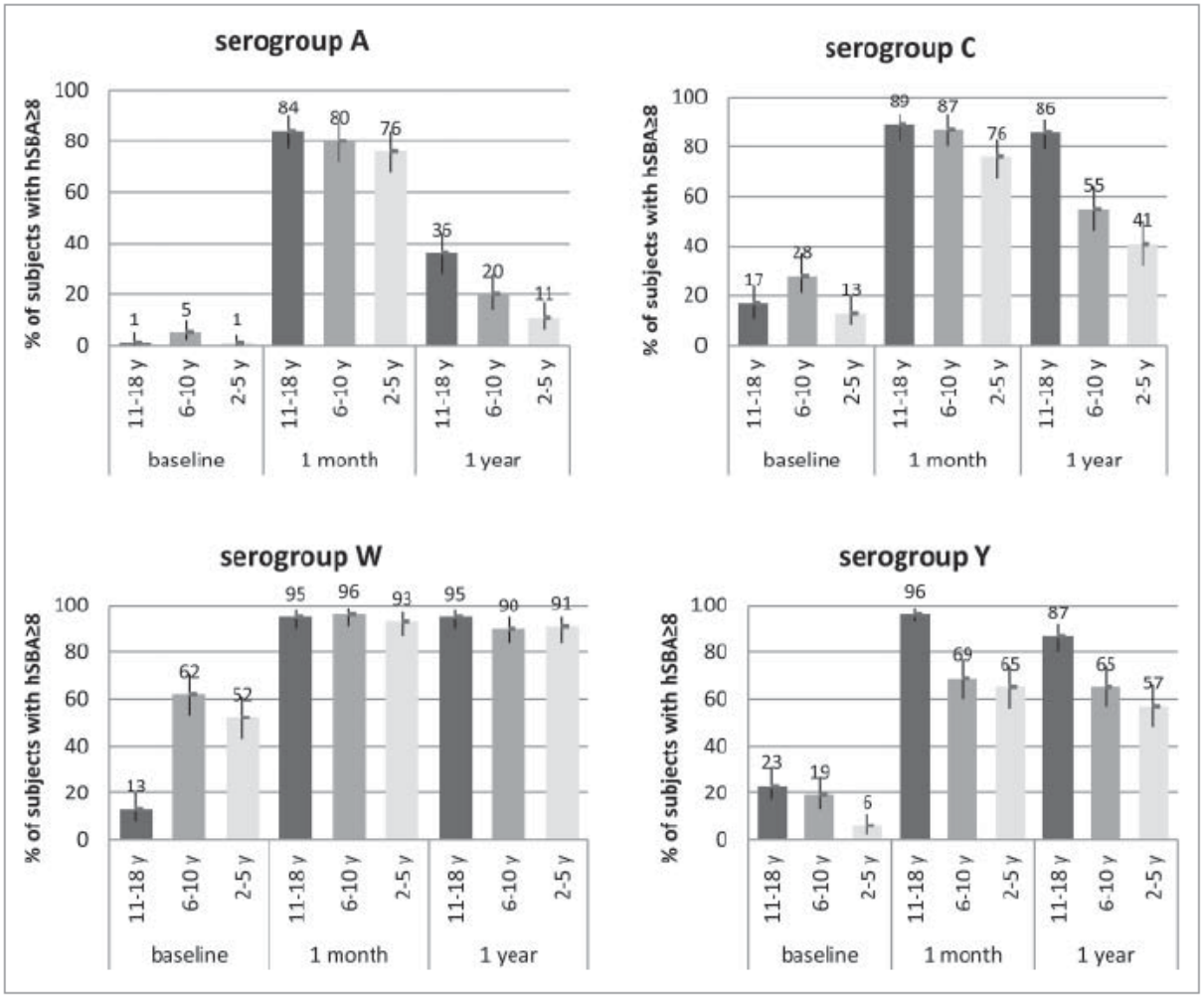


Figure 1. Percentages of subjects with SBA titers 8 and 95% CIs (error bars) at baseline (pre-vaccination), and 1 month and 1 y after 1 dose of MenACWY-CRM given to adolescents (11–18 y at time of vaccination; Study 1) and children (2–5 and 6–10 y at time of vaccination; Study 2), by serogroup.

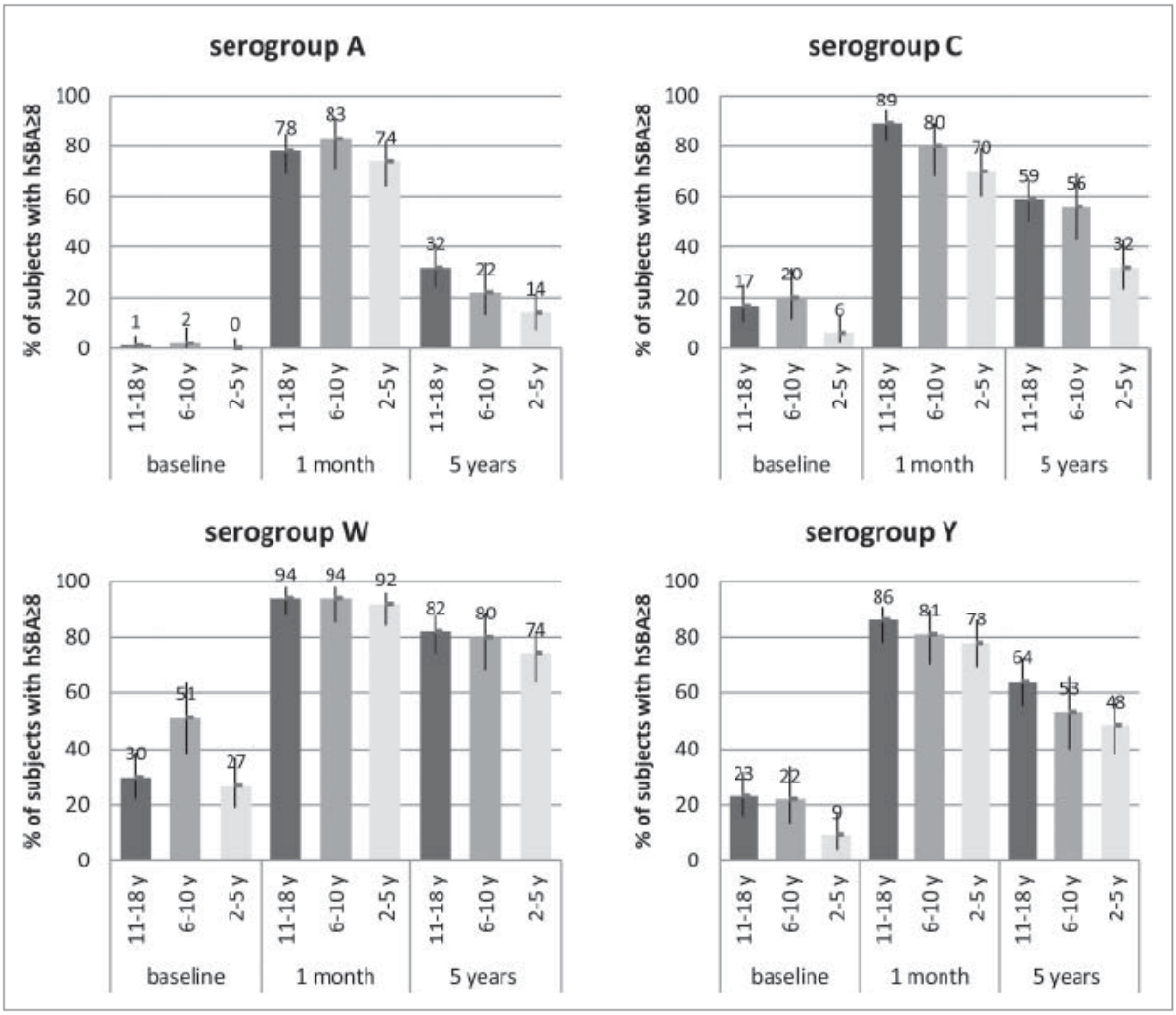


Figure 2. Percentages of subjects with SBA titers 8 and 95% CIs (error bars) at baseline (pre-vaccination), 1 month, and 5 y after 1 dose of MenACWY-CRM given to adolescents (11–18 y of age at the time of vaccination; Study 3) and children (2–5 and 6–10 y at the time of vaccination; Study 4), by serogroup.

Persistence data from study V59P6E1

Study V59P6E1 [Jacobson 2013] assessed antibody persistence at approximately 5 years after a single primary vaccination with MenACWY at 11 to 17 years of age. Antibody persistence was assessed using both hSBA and rSBA (Table 1). Primary vaccination with MenACWY provided a broad and persistent immune response in adolescents. Five years after primary vaccination with MenACWY, the percentages of subjects with hSBA titres ≥ 8 ranged from 72% to 76% for serogroups C, W, and Y, while for serogroup A the percentage was 30%. In line with what was described by GSK Vaccines Baxter et al. (see above), the same trend for serogroup A was not seen when assessed using rSBA (percentages of subjects with rSBA titres ≥ 8 ranging from 78% to 98% across serogroups).

Persistence data from study V59P22E1

Study V59P22E1 assessed antibody persistence at approximately 13-33 months after primary vaccination with 2 doses (at 6-8 and 12 months of age; Group 1) or 1 dose (at 12 months of age; Group 2) of MenACWY, or with 1 dose (at 12 months of age; Group 3) of the monovalent conjugate MenC vaccine. Persistence was summarized by time period since the last vaccination in the parent

study, V59P22 (time intervals of ≤ 23 months, 24 to 31 months, and ≥ 32 months; Table 2). Percentages of subjects with hSBA titres ≥ 8 directed against serogroups C, W, and Y were higher than those for serogroup A in all the study groups (excluding A, W and Y serogroups in group 3 as these represent background activity; Table 2). These results suggest that antibodies to serogroups C, W, and Y are able to persist long-term, with 14% to 55% of subjects having hSBA titres ≥ 8 at 24 to 31 months after one or two doses of MenACWY. These data are in line with previously observed trends in antibody persistence; however, the results should be interpreted with caution as numbers of subjects enrolled in each group for the persistence assessment was very low.

Table 2 Percentage (95% CI) of Subjects With hSBA titres ≥ 8 by Time Since the Last Dose of Primary Vaccination - Per Protocol Persistence Population (Study V59P22E1)

Time since last dose	Serogroup	Group 1 After 2 doses Men ACWY[a]	Group 2 After 1 dose Men ACWY[b]	Control Group After 1 dose MenC[c]
≤ 23 Months	MenA	N=25	N=17	N=19
		16% (5%-36%)	6% (0%-29%)	0% (0%-18%)
	MenC	N=25	N=16	N=18
		36% (18%-57%)	38% (15%-65%)	44% (22%-69%)
	MenW	N=25	N=17	N=19
		48% (28%-69%)	76% (50%-93%)	21% (6%-46%)
	MenY	N=25	N=17	N=19
		40% (21%-61%)	53% (28%-77%)	5% (0%-26%)
24-31 Months	MenA	N=26	N=22	N=24
		12% (2%-30%)	9% (1%-29%)	0% (0%-14%)
	MenC	N=26	N=22	N=24
		19% (7%-39%)	14% (3%-35%)	29% (13%-51%)
	MenW	N=26	N=22	N=24
		54% (33%-73%)	55% (32%-76%)	4% (0%-21%)
	MenY	N=26	N=22	N=24
		38% (20%-59%)	27% (11%-50%)	29% (13%-51%)
≥ 32 Months	MenA	N=1	N=2	N=0
		0% (0%-98%)	0% (0%-84%)	
	MenC	N=1	N=2	N=0
		0% (0%-98%)	50% (1%-99%)	
	MenW	N=1	N=2	N=0
		0% (0%-98%)	50% (1%-99%)	
	MenY	N=1	N=2	N=0
		100% (3%-100%)	50% (1%-99%)	

Source: V59P22E1 CSR Table 11.4.1-1. a At 6-8 and at 12 months of age, in study V59P22. b At 12 months of age, in study V59P22. c At 12 months of age, in study V59P22.

Persistence data from study V59_67

Study V59_67 [Bona 2016] assessed antibody persistence in toddlers 12-15 months of age at 6 months following 1 dose of MenACWY in terms of hSBA and rSBA titers against serogroups A, C, W, and Y (Table 1).

At 6 months following vaccination (Day 180), the proportion of subjects with hSBA titers ≥ 8 against serogroup A declined compared to 1 month post-vaccination (Day 29) while the proportion of subjects with rSBA titers ≥ 8 or ≥128 against serogroup A remained relatively constant between Day 29 and Day 180. Against serogroup C, the proportion of subjects with hSBA titers ≥ 8 remained constant, while rSBA titers decreased slightly over the 5 month period. However, the proportion of subjects with hSBA titers ≥ 8 against serogroups W and Y at 6 months after vaccination increased above those measured at 1 month following vaccination. A similar increase has previously been described by Vesikari et al, who showed an increase in hSBA titers against serogroups W and Y between 1 and 12 months after a single dose of Nimenrix in toddlers [Vesikari 2012].

Assessor's comments

The overview provided by the company does not provide many new insights. Currently, the SmPC includes persistence data up to 5 years after vaccination in adolescents, children aged 2-10 years. From these data, it can be deducted that persistence is poorer in younger children. The data in the SmPC stem from studies V59P13E1 and V59P20E1.

Follow up in study V59P22E1 is poor and the data does not add to what is already described. The findings of study V59P6E1 are in line with data already described. The discrepancies between the hSBA and rSBA have been discussed in earlier assessments. Study V59_67 falls outside the indication.

B: The MAH is requested to put the results generated in the studies described in the current report in perspective, based upon the provided overview of all available persistence data.

In the study V102_03E1, antibody persistence after a single dose of MenACWY-CRM was assessed in a control arm at 24 and 36 months after vaccination in healthy adolescents. While trends in antibody persistence against serogroups A and C were in line with previous results, antibody titres against serogroups W and Y appeared to be lower than could be expected from previously generated persistence data (Table 3).

However, these findings should be interpreted with caution as the number of subjects analysed for persistence in study V102_03E1 was very low. *The group analysed at 24 months after vaccination consisted of 59 subjects, and the group analysed at 36 months after vaccination consisted of only 19 subjects*. Interpretation of results obtained using such small sample sizes is extremely difficult.

Furthermore, the serum samples from the V102_03E1 study (and the parent V102_03 study) were analysed using a different assay (high-throughput [HT]-SBA), than samples from studies included in the Menveo development program (manual hSBA). Results obtained using different assays, which have different sensitivity aspects, cannot be directly compared. This was also shown in multiple previous studies in the Menveo development program (i.e., V59P6, V59P6E1, V59P13E1, V59P14, and V59_67) in which the use of 2 different assays (hSBA and rSBA) resulted in differences in percentages of subjects with titres ≥ 1:8 and GMTs (see Part A for more details).

In summary, the V102_03E1 study does show considerable persistence of bactericidal antibodies up to 36 months after a single vaccination, across serogroups and the Company believes that, overall, the results from this study are in line with the substantial body of data already available on persistence of antibodies after MenACWY vaccination.

Table 3 Antibody Persistence of hSBA Titres in Adolescents at 12-36 Months After a Single Dose of MenACWY

Endpoint		% subjects with hSBA titers ≥ 8			hSBA GMTs		
Assay		Manual hSBA		HT-hSBA	Manual hSBA		HT-hSBA
Study		V59P6/P6E1[a]	V59P13E1	V102_03E1	V59P6	V59P13E1	V102_03E1
Age at vaccination		11-18 years	11-18 years	10-25 years	11-18 years	11-18 years	10-25 years
A	Baseline	1% (0%-5%) N=140	3% (1%-5%) N=239	4% (0.44%-12.5%) N=55	2.08 (1.98-2.18) N=140	2.15 (2.05-2.26) N=239	1.48 (1.19-1.84) N=55
	1 month	81% (74%-87%) N=140	75% (69%-80%) N=239	77% (63.6%-87.0%) N=56	33 (25-44) N=140	30 (24-37) N=239	37 (21-65) N=56
	12 months	29% (22%-38%) N=140	-	-	4.24 (3.35-5.38) N=140	-	-
	21 months	-	36% (30%-42%) N=275	-	-	5.29 (4.63-6.05) N=275	-
	24 months	-	-	31% (19.5%-44.5%) N=58	-	-	4.14 (2.75-6.23) N=58
	36 months	-	28% (23%-33%) N=291	35% (14.2%-61.7%) N=17	-	5.04 (4.17-6.09) N=291	3.54 (1.4-8.92) N=17
	5 years	30% (18%-45%) N=50	32% (24%-41%) N=128	-	5.38 (3.29-8.78) N=50	4.34 (3.41-5.53) N=128	-
C	Baseline	18% (12%-25%) N=140	20% (15%-25%) N=278	29% (17.6%-42.9%) N=55	3.26 (2.77-3.83) N=140	3.48 (3.1-3.92) N=278	4.11 (2.88-5.87) N=55
	1 month	84% (77%-90%) N=140	85% (81%-89%) N=278	83% (70.6%-91.4%) N=58	59 (39-89) N=140	73 (56-96) N=278	58 (32-106) N=58
	12 months	77% (69%-84%) N=140	-	-	28 (19-41) N=140	-	-
	21 months	-	62% (56%-68%) N=275	-	-	10 (9.02-12) N=275	-
	24 months	-	-	57% (43.2%-69.8%) N=58	-	-	10 (6.36-17) N=58
	36 months	-	64% (58%-69%) N=292	65% (38.3%-85.8%) N=17	-	18 (14-24) N=292	24 (8.98-66) N=17
	5 years	76% (62%-87%) N=50	59% (50%-67%) N=128	-	21 (12-37) N=50	14 (9.41-20) N=128	-

Endpoint		% subjects with hSBA titers ≥ 8			hSBA GMTs		
Assay		Manual hSBA		HT-hSBA	Manual hSBA		HT-hSBA
Study		V59P6/P6E1[a]	V59P13E1	V102_03E1	V59P6	V59P13E1	V102_03E1
Age at vaccination		11-18 years	11-18 years	10-25 years	11-18 years	11-18 years	10-25 years
W	Baseline	13% (8%-20%) N=138	38% (32%-45%) N=238	60% (44.3%-73.6%) N=47	2.86 (2.39-3.42) N=138	6.25 (5.13-7.63) N=238	8.55 (4.97-15) N=47
	1 month	91% (84%-95%) N=138	96% (93%-98%) N=239	91% (79.2%-97.6%) N=46	48 (31-52) N=138	88 (73-106) N=238	65 (39-108) N=46
	12 months	93% (88%-97%) N=138	-	-	40 (31-52) N=138	-	-
	21 months	-	84% (79%-88%) N=273	-	-	18 (15-20) N=273	-
	24 months	-	-	68% (54.0%-79.7%) N=56	-	-	17 (9.65-29) N=56
	36 months	-	82% (77%-86%) N=287	65% (38.3%-85.8%) N=17	-	34 (26-43) N=287	16 (5.27-49) N=17
	5 years	72% (58%-84%) N=50	82% (74%-88%) N=128	-	30 (18-52)	32 (23-45) N=128	-
Y	Baseline	24% (17%-32%) N=139	31% (25%-37%) N=239	7% (2.1%-17.9%) N=54	3.66 (3.04-4.41) N=139	4.42 (3.79-5.16) N=239	1.48 (1.11-1.96) N=54
	1 month	95% (90%-98%) N=139	86% (81%-90%) N=239	88% (74.8%-95.3%) N=48	92 (68-124) N=139	48 (39-60) N=239	62 (35-108) N=48
	12 months	82% (75%-88%) N=139	-	-	30 (22-41) N=139	-	-
	21 months	-	67% (61%-72%) N=275	-	-	12 (10-14) N=275	-
	24 months	-	-	46% (32.7%-59.2%) N=59	-	-	6.49 (3.72-11) N=59
	36 months	-	65% (60%-71%) N=291	47% (23%-72.2%) N=17	-	16 (13-21) N=291	9.56 (2.44-37) N=17
	5 years	76% (62%-87%) N=50	64% (55%-72%) N=128	-	30 (18-49) N=50	12 (8.49-16) N=128	-

Source: CSR V59P6, CSR V59P6E1, CSR V59P13E1, and CSR V102_03E1. Abbreviations: hSBA = serum bactericidal assay using human complement. HT = high-throughput. a Data for timepoints Baseline, 1 month, and 12 months comes from study V59P6, data for timepoint 5 years from study V59P6E1

Assessor's comments

Trends in antibody persistence for serogroups W and Y appear lower than previously generated persistence data. The MAH points out two possible reasons; one is the small numbers in V102_03E1 (the confidence intervals provide some measure of uncertainty, and these overlap between studies). A second is the use of a different assay in V102_03E1; a high-throughput [HT]-SBA was used here. It is agreed with the MAH that results obtained using different assays, which have different sensitivity aspects, cannot be directly compared.

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