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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

Procedures:

- EMEA/H/C/001095/P46/041
- EMEA/H/C/001095/P46/042

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 March 2019, the MAH submitted 2 completed paediatric studies 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 meningitidis* groups A, C, W135 and Y.

In the parent study V102_16 Menveo was used as a comparator vaccine.

2. Scientific discussion

2.1. Information on the development programme

The MAH stated that the phase 2, open-label, controlled, multi-centre study (V102_16) and the extension (V102_16E1) to assess the effectiveness, immunogenicity and safety of the MenABCWY vaccine compared to a single dose of MenACWY, is a stand-alone study.

2.2. Information on the pharmaceutical formulation used in the study

MenABCWY is a combination vaccine containing MenACWY conjugated to a carrier protein cross reactive material (CRM_{197}) combined with recombinant MenB with outer member vesicle (OMV) from the New Zealand (NZ) strain. Novartis MenABCWY vaccine is prepared immediately before injection by extemporaneous mixing of a fully lyophilized formulation of MenACWY with 1 dose of liquid rMenB+OMV vaccine for a total injection volume of 0.5 ml.

Novartis MenACWY conjugate vaccine was obtained by extemporaneous mixing a lyophilized MenA-CRM197 conjugate component with a liquid MenCWY-CRM197 conjugate component. After reconstitution, the total volume of injection was 0.5 ml. The placebo consisted a saline solution (NaCl 0.9%; lot number: IF12361035), the total injection volume was 0.5 ml.

Vaccines were to be administered IM, preferably in the deltoid area of nondominant arm.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted final reports for:

- A Phase 2b, Randomized, Controlled, Observer-Blind, Multicenter Study Assessing the Effectiveness, Immunogenicity and Safety of Novartis Meningococcal ABCWY Vaccine Administered to Healthy Adolescents in the U.S. (Protocol V102_16)

and the extension study V102_16E1

- A Phase 2b, controlled, observer-Blind, multi-center study assessing the effectiveness, immunogenicity and safety of the 3rd dose of Novartis meningococcal ABCWY vaccine administered to healthy adolescents in the US.

2.3.2. Clinical studies

Studies V102_16 & V102_16E1

Description

The V102_16 study evaluated the effectiveness of 2 doses of Meningococcal Serogroups A, B, C, W, and Y (MenABCWY) vaccine in adolescents by measuring the bactericidal serum activity against a large panel of epidemiologically relevant invasive disease strains of Neisseria meningitidis (N meningitidis) serogroup B (110 strains overall) using an endogenous complement human serum bactericidal assay (enc-hSBA), when compared to a single dose of Meningococcal Serogroups A, C, W, and Y (MenACWY) vaccine. The analysis of MenABCWY vaccine effectiveness was performed at 1 month and 4 months after completion of the 2-dose vaccination series to assess short term persistence of bactericidal antibodies.

In the extension of study V102_16 immunogenicity data were collected after a third vaccination with meningococcal ABCWY vaccine 6 months after the first vaccination (i.e. subjects were vaccinated at 0, 2, 6 month). Subjects were followed for about 44 months after the last vaccination. Again safety and efficacy was compared to a single dose of meningococcal serogroups A, C, W, and Y vaccine (Menveo).

Methods

Objectives

Assessor's comment

Note that only the objectives which relate to measuring the response against MenACWY of both study V102_16 and study V102_16E1 are mentioned. The response against the serogroups B strains is not mentioned as this is of no relevance for Menveo .

Secondary objectives (relevant for MenACWY)

Secondary Immunogenicity Objectives:

To assess the immunogenicity of MenABCWY vaccine against *N meningitidis* serogroups A, C, W and Y as measured by HT-hSBA GMTs, the percentages of subjects with HT-hSBA titers ≥ LLQ and the percentages of subjects with 2-, 3- and 4-fold hSBA titer rise at 1 and 4 months after the 2-dose vaccination series, when compared to a single dose of MenACWY (study V102_16).

• To assess the immunogenicity of MenABCWY vaccine against N meningitidis serogroups A, C, W and Y as measured by hSBA GMTs, the percentages of subjects with hSBA titers ≥ LLQ and the percentages of subjects with 2-, 3- and 4-fold rise in hSBA titer at 1 and 4 months after the 3-dose vaccination series, when compared to a single dose of MenACWY (study V102_16E1).

Assessor's comment

In the present procedure the focus will be on Menveo. Therefore, results for the objectives described in the CSR in which the response against serogroup B is measured will not be discussed in this report.

Only the objectives which concerns the response to or persistence after receiving MenACWY for serogroups A, C, W and Y will be discussed.

Note that a high throughput assay was used with different cut offs (LLOQ/LOD) as compared to previous assays employed in the clinicial development of Menveo. Direct comparisons of immune responses between the present study and older studies should be avoided or at least interpreted with caution.

Study design

Study V102_16: This was a phase 2b, randomized (1:1), controlled, observer-blind, multicentre study in healthy adolescents aged 10 through 18 years with 2 study groups.

Table 1 Schematic Diagram of the Study Design.

Group	No. of Subjects Planned	No. of Subjects Enrolled	Day 1	Month 2	Month 3	Month 4	Month 6
MenABCWY	150	154	Blood draw MenABCWY	MenABCWY	Blood draw	Safety Phone Call	Blood draw Study termination
MenACWY	150	151	Blood draw Placebo	MenACWY	Blood draw	Safety Phone Call	Blood draw Study termination

Abbreviations: MenABCWY, meningococcal (groups A, C, W, and Y) oligosaccharide diphtheria CRM-197 conjugate combined with meningococcal (group B) multicomponent recombinant vaccine; MenACWY, meningococcal (groups A, C, W, and Y) oligosaccharide diphtheria CRM-197 conjugate vaccine.

V102_16E1: Subjects who received either 2 doses of MenABCWY or one dose of placebo followed by MenACWY vaccine in the parent V102_16 study and completed study V102_16 were asked to participate in the extension study, maintaining the same group (MenABCWY or MenACWY) and testing assignment (starting strain for enc-hSBA testing) as in the parent V102_16 study. The same methodology for assessments was to be used in this extension study.

Table 2 Schematic diagram of the extension (V102_16E1) study design

Group	V102_16 Visits	V102_16E1 Expected No. Subjects (N)	Month 6[a]	Month 7	Month 8	Month 10
MenABCWY	Day 1 (BD, MenABCWY) Month 2 (MenABCWY) Month 3 (BD) Month 4 (SPC) Month 6 (BD)	120	MenABCWY	BD	SPC	BD Study termination
MenACWY	Day 1 (BD, Placebo) Month 2 (MenACWY) Month 3 (BD) Month 4 (SPC) Month 6 (BD)	120	Placebo	BD	SPC	BD Study termination

Abbreviations: BD, blood draw, SPC safety phone call.
a For subjects who were to be enrolled in the extension study, visit Month 6 of the parent study was the first study visit of the extension study. All consecutive study visits were numbered accordingly. In the event of a transient clinical circumstance which may warrant delay of extension study vaccination, the first day of the extension study could be postponed, but was to occur within a maximum of 14 days from Visit Month 6 of the parent study.

Study population /Sample size

V120_16

The study included healthy male and female adolescents who, at the time of enrolment into V102_16 trial, were 10 through 18 years of age. Subjects were in good health as determined by the outcome of medical history, physical examination and clinical judgment of the investigator. Subjects with a history of any meningococcal vaccine administration, current or previous, confirmed or suspected disease caused by N meningitidis or household contact with and/or intimate exposure to an individual with any laboratory confirmed N meningitidis infection within 60 days of enrolment, were excluded.

MenABCWY group: Approximately 150 subjects were planned to receive MenABCWY vaccine at visit day 1 and visit month 2;

MenACWY group: Approximately 150 subjects were planned to receive 1 dose of placebo at visit day 1 and 1 dose of MenACWY vaccine at visit month 2.

V120_16E1: All subjects who completed parent study and received the protocol-specified study vaccines were to be invited to participate in the extension study (V102_16E1).

Treatments

In study V102_16 subjects in the MenABCWY group received 2 doses of MenABCWY vaccine at day 1 and month 2 whereas subjects in the MenACWY group received 1 dose of placebo at day 1 and 1 dose of MenACWY vaccine at month 2. In the extension (V102_16E1) (i.e. six months after the first injection in study V102_16) subjects received either a third vaccination with MenABCWY (MenABCWY group) or a placebo (MenACWY group).

Assessor's comments

Healthy subjects aged 10 to 18 years old either received MenABCWY vaccine at visit day 1, visit month 2 and (in V102_16E1) after 6 months or dose of placebo at visit day 1, 1 dose of MenACWY vaccine at visit month 2 and a placebo again at the start of study V102_16E1 (6 months after the first placebo vaccination). Subjects were naïve for meningococcal vaccine and did not experience caused by N meningitides.

Outcomes/endpoints

Assessor's comment:

Note that below only endpoints relevant for evaluating the response to MenACWY are listed.

Secondary Immunogenicity Endpoints study V102_16:

- HT-hSBA GMTs against N meningitidis serogroups A, C, W and Y at baseline, 1 and 4 months after the 2-dose vaccination series.
- Percentages of subjects with HT-hSBA titers ≥ LLQ against N meningitidis serogroups A, C, W and Y at baseline, 1 and 4 months after the 2-dose vaccination series.
- Percentages of subjects with 2-, 3-, and 4-fold rise in HT-hSBA titer against N meningitidis serogroups A, C, W and Y at 1 and 4 months after the 2-dose vaccination series.

Secondary Immunogenicity Endpoints V102_16E1:

- hSBA GMTs against N meningitidis serogroups A, C, W and Y at 1 and 4 months after the 3-dose vaccination series.

- Percentages of subjects with hSBA titers ≥ LLQ against N meningitidis serogroups A, C, W and Y at 1 and 4 months after the 3-dose vaccination series.
- Percentages of subjects with 2-, 3-, and 4-fold rise in hSBA titer against N meningitidis serogroups A, C, W and Y at 1 and 4 months after the 3-dose vaccination series.

Secondary Safety Endpoints

Safety of the study vaccines were to be assessed in all subjects in terms of the frequency and percentage of reported AEs including:

- Any unsolicited and solicited AEs reported within 30 min after each vaccination;
- Solicited local (i.e., pain, erythema and induration) and systemic (ie, loss of appetite, headache, fatigue, myalgia, arthralgia, nausea, fever (body temperature ≥ 38° C [100.4°F]). AEs reported from day 1 (6 h) through day 7 after each vaccination;
- All unsolicited AEs reported from day 1 to day 30 after each vaccination;
- Medically attended AEs reported during the entire study period;
- AEs leading to premature withdrawal from the study during the entire study period;
- SAEs reported during the entire study period.

Statistical Methods

Considering that the acceptable volume of blood sample in adolescents aged 10 through 18 years is 20 ml, approximately 33 (range 25-40) endemic US N meningitidis serogroup B strains from the strain panel and the 4 serogroup B test strains (one test strain per antigen, fHbp, NHBA, NadA and Por A P1.4) were to be tested per subject using enc-hSBA. In addition, 8 test strains (4 serogroup B test strains and 1 each for serogroups A, C, W and Y) could be tested using HT-hSBA in each subject.

Assuming 150 enrolled subjects per group and a dropout rate of 20%, approximately 120 subjects were to be evaluated for the vaccine effectiveness (VE) analysis.

Considering the total number of endemic US N meningitidis serogroup B invasive strains in the selected panel (n = 110) and the expected number of strains tested in each subject (n = 33, range 25-40), each strain was to be tested in approximately 36 (range 27-44) subjects.

For each strain, VE was to be calculated as VE = 1− [percentage of subjects without bactericidal serum activity at 1:4 dilution using enc-hSBA in the MenABCWY group/percentage of subjects without bactericidal serum activity at 1:4 dilution in the MenACWY group] x 100.

For the overall panel of the US *N meningitidis* serogroup B invasive isolates (the primary objective of the study), the VE and associated 95% confidence interval (CI) were to be computed as the average for VE of the 110 US N meningitidis serogroup B strains tested in this study.

If the lower limit of the 95% CI for VE against the panel of the endemic US N meningitidis serogroup B strains between the MenABCWY group and the MenACWY group is above 10% the null hypothesis was to be rejected and effectiveness declared.

Statistical method for the primary endpoint was the generalized linear model using individual strain Bernoulli measure (killed/not killed) as outcome measure with treatment group and strain as independent variables.

Results

Recruitment/ Number analysed Study V102-16 and V102_16E1 combined

In the parent study V102_16, a total of 305 subjects were enrolled, 154 of which were randomized to MenABCWY-group, and 151 subjects were enrolled to the MenACWY-group. In the MenABCWY-group 137 subjects completed protocol in the MenACWY-group there were 139 patients competing the protocol.

In the extension study V102_16E1, a total of 189 subjects were enrolled, 95 of which were randomized to MenABCWY-group, and 94 subjects were enrolled to the MenACWY-group. In each group 90 patients completed the protocol.

Centres (n=8) were located in the US.

Table 3 Overview of Datasets Analysed –As Randomized – All Enrolled Set

	Number (percentage) of Subjects		
Analysis Set	**MenABCWY**	**MenACWY**	**Total**
Study V102_16 and V102_16E1			
	N = 154	**N = 151**	**N = 305**
All Enrolled Set	154 (100%)	151 (100%)	305 (100%)
All Exposed	152 (100%)	149 (100%)	301 (99%)
FAS Effectiveness			
Baseline	148 (96%)	146 (97%)	294 (96%)
Month 3	139 (90%)	135 (89%)	274 (90%)
4 Months After 2nd Vaccination (Month 6)	95 (100%)	94 (100 %)	189 (100%)
1 Month After 3rd Vaccination (Month 7)	93 (98%)	93 (99%)	186 (98%)
4 Months After 3rd Vaccination (Month 10)	90 (95%)	90 (96%)	180 (95%)
FAS Immunogenicity			
Baseline	152 (99%)	147 (97%)	299 (98%)
Month 3	139 (90%)	134 (89%)	273 (90%)
4 Months After 2nd Vaccination (Month 6)	94 (99%)	93 (99%)	187 (99%)
1 Month After 3rd Vaccination (Month 7)	92 (97%)	91 (97%)	183 (97%)
4 Months After 3rd Vaccination (Month 10)	89 (94%)	91 (97%)	180 (95%)
PPS Effectiveness			
Baseline	148 (96%)	144 (95%)	292 (96%)
Month 3	127 (82%)	119 (79%)	246 (81%)
4 Months After 2nd Vaccination (Month 6)	93 (98%)	94 (100%)	187 (99%)
1 Month After 3rd Vaccination (Month 7)	68 (72%)	67 (71%)	135 (71%)
4 Months After 3rd Vaccination (Month 10)	67 (71%)	72 (77%)	139 (74%)
PPS Immunogenicity			
Baseline	152 (99%)	145 (96%)	297 (97%)
Month 3	127 (82%)	119 (79%)	246 (81%)
4 Months After 2nd Vaccination (Month 6)	92 (97%)	93 (99%)	185 (98%)
1 Month After 3rd Vaccination (Month 7)	68 (72%)	66 (70%)	134 (71%)
4 Months After 3rd Vaccination (Month 10)	66 (69%)	73 (78%)	139 (74%)

Assessor's comments:

In total 305 healthy adolescent subjects (10 to 18 years of age) were enrolled. Previous immunization with any meningococcal vaccine was exclusion criteria, therefore, patients included are naïve for N meningitides vaccination.

Efficacy data V102_16 and V102_16E1 combined

Assessor's comments

As indicated earlier only results directly relevant for evaluating the response to MenACWY will be discussed. Subjects who only received placebo/MenACWY did not develop protective hSBA titres against the panel of MenB strains tested against.

Immunogenicity

HT-hSBA GMTs against N meningitidis serogroups A, C, W and Y

The results of the Geometric Mean HT-hSBA Titers against N meningitidis serogroups A, C, W and Y are summarised in Table 4 through to Table 7. No information on GMT could be found for study V102_16E1.

Table 4 Geometric Mean HT-hSBA Titers, Geometric Mean Ratios over Baseline and Vaccine Group Ratios by Serogroup A at 1 Month After Second Dose MenABCWy (single dose MenACWY) FAS Immunogenicity (Month 3)

Day 1	**MenABCWY**	**MenACWY**
Adjusted GMT	1.08	1.12
95% Conf Int	(0.99 - 1.18)	(1.03 - 1.23)
Median	1.0	1.0
Min, Max	1.0 - 32.5	1.0 - 136.8
n	134	129
Month 3		
Adjusted GMT	77.02	22.08
95% Conf Int	(59 - 101)	(17 - 30)
Median	80.6	43.6
Min, Max	1.0 - 589.2	1.0 - 1194.6
n	137	115

Table 5 Geometric Mean HT-hSBA Titers, Geometric Mean Ratios over Baseline and Vaccine Group Ratios by Serogroup C at 1 Month After Second Dose MenABCWY (single dose MenACWY) FAS Immunogenicity (Month 3)

Day 1	MenABCWY	MenACWY
Adjusted GMT	2.80	3.63
95% Conf Int	(2.19 - 3.56)	(2.84 - 4.64)
Median	1.0	3.4
Min, Max	1.0 - 4310.7	1.0 - 436.8
n	136	131
Month 3		
Adjusted GMT	235.88	38.61
95% Conf Int	(171 - 325)	(28 - 54)
Median	220.2	32.8
Min, Max	6.7 - 3865.8	1.0 - 3559.8
n	134	125

Table 6 Geometric Mean HT-hSBA Titers, Geometric Mean Ratios over Baseline and Vaccine Group Ratios by Serogroup W at 1 Month After Second Dose MenABCWy (single dose MenACWY) FAS Immunogenicity (Month 3)

Day 1	MenABCWY	MenACWY
Adjusted GMT	3.47	4.13
95% Conf Int	(2.50 - 4.80)	(2.98 - 5.72)
Median	1.0	1.0
Min, Max	1.0 - 440.6	1.0 - 340.3
n	123	120
Month 3		
Adjusted GMT	157.72	37.51
95% Conf Int	(120 - 207)	(28 - 49)
Median	163.2	41.9
Min, Max	2.0 - 3686.3	1.0 - 7242.4
n	119	115

Table 7 Geometric Mean HT-hSBA Titers, Geometric Mean Ratios over Baseline and Vaccine Group Ratios by Serogroup Y at 1 Month After Second Dose MenABCWy (single dose MenACWY) FAS Immunogenicity (Month 3)

Day 1		
Adjusted GMT	1.64	1.64
95% Conf Int	(1.31 - 2.05)	(1.30 - 2.06)
Median	1.0	1.0
Min, Max	1.0 - 210.9	1.0 - 438.0
n	128	123
Month 3		
Adjusted GMT	155.43	27.76
95% Conf Int	(110 - 220)	(19 - 40)
Median	168.7	57.8
Min, Max	1.0 - 1387.1	1.0 - 1660.2
n	107	94

Assessor's comment

Results of the Geometric Mean HT-hSBA Titers after the 3rd dose MenABCWY were not reported, only after the second dose. As this information is less relevant for the Menveo control arm this information is not requested in this art 46 procedure.

At baseline both treatment arms are comparable with respect to Geometric Mean HT-hSBA Titers as can be concluded form the vaccine comparison of the Geometric Mean HT-hSBA Titers ratios that vary from 0.77 to 1.0 for the various serogroups.

The Geometric Mean HT-hSBA Titers one month after the Menveo vaccination are also largely comparable with those mentioned in the initial EPAR for patient with baseline hSBA titre ≥1:4. This confirms the known immunologic effects of Menveo.

Percentages of subjects with HT-hSBA titers ≥ LLQ against N meningitidis serogroups A, C, W and Y

At baseline, the percentages of subjects with HT-hSBA titers ≥ LLQ against N meningitidis serogroups were: A (2% and 1%), C (32% and 43%); W (12% and 16%), and Y (10% and 11%), in MenABCWY and MenACWY vaccine groups, respectively

In the MenABCWY group, at 1 month after the second dose (2-dose MenABCWY vaccination series), there was increase in the percentages of subjects with HT-hSBA titers ≥ LLQ (90% to 100%) against all 4 N meningitidis serogroups A, C, W, and Y. At 4 months after the second dose, the percentages of subjects with persisting HT-hSBA titers ≥ LLQ were between 48% to 98% against all 4 N meningitidis serogroups A, C, W, and Y. Overall, the percentage of subjects with HT-hSBA titers ≥ LLQ at 4 months after the second dose were lower than the percentages of subjects at 1 month after the second dose, but were higher than the baseline (2% to 32%;Table 8).

In the MenACWY group, at 1 month after a single dose of MenACWY vaccine, there was increase in the percentages of subjects with HT-hSBA titers ≥ LLQ (range: 52%-82% across serogroups) against all 4 N meningitidis serogroups A, C, W, and Y. At 4 months after a single dose of MenACWY vaccine, the percentages of subjects with persisting HThSBA titers ≥ LLQ were between 32% to 78% against serogroups A, C, W, and Y (Table 8).

Table 8 Number (%) of Subjects With HT-hSBA Titers ≥ LLQ Against Serogroups A, C, W, and Y and Vaccine Group Differences at Baseline, 3, 6, 7 and 10 months after the fist administration

Serogroup		**Number (%) of Subjects (95% CI)**		**Vaccine Group Differences**
LLQ		**MenABCWY**	**MenACWY**	**MenABCWY-MenACWY**
Serogroup A LLQ = 22.7	Baseline (Day 1)	2 (2%) (0.19%-5.5%) n = 128	1 (1%) (0.02%-4.2%) n = 129	1% (-2.9%-4.8%)
	1 month after 2nd dose (Month 3)	121 (93%) (87.3%-96.8%) n = 130	70 (63%) (52.9%-71.5%) n = 112	31% (20.7%-40.6%)
	4 months after 2nd dose (Month 6)	60 (48%) (39.3%-57.5%) n = 124	42 (32%) (24.4%-41.1%) n = 130	16% (4.0%-27.7%)
	1 month after 3-dose series (Month 7)	89 (98%) (92.3%-99.73%) n = 91	21 (24%) (15.6%-34.5%) n = 87	74% (63.0%-81.9%)
	4 months after 3-dose series (Month 10)	69 (81%) (71.2%-88.8%) n = 85	16 (18%) (10.8%-27.8%) n = 88	63% (50.1%-73.2%)
Serogroup C LLQ = 5.2	Baseline (Day 1)	41 (32%) (23.7%-40.3%) n = 130	56 (43%) (34.2%-51.7%) n = 131	-11% (-22.7%-0.5%)
	1 month after 2nd dose (Month 3)	127 (100%) (97.1%-100.0%) n = 127	99 (82%) (73.8%-88.2%) n = 121	18% (12.3%-26.0%)
	4 months after 2nd dose (Month 6)	131 (98%) (94.7%-99.82%) n = 133	104 (78%) (70.2%-84.9%) n = 133	20% (13.5%-28.3%)
	1 month after 3-dose series (Month 7)	85 (100%) (95.8%-100.0%) n = 85	63 (73%) (62.6%-82.2%) n = 86	27% (18.5%-37.0%)
	4 months after 3-dose series (Month 10)	86 (100%) (95.8%-100.0%) n = 86	61 (69%) (57.8%-78.0%) n = 89	31% (22.7%-41.7%)
Serogroup W LLQ = 39.6	Baseline (Day 1)	14 (12%) (6.8%-19.4%) n = 116	19 (16%) (9.9%-23.8%) n = 119	-4% (-13.0%-5.2%)
	1 month after 2nd dose (Month 3)	101 (90%) (83.1%-95.0%) n = 112	58 (52%) (42.6%-61.8%) n = 111	38% (26.8%-48.4%)
	4 months after 2nd dose (Month 6)	101 (77%) (69.0%-84.0%) n = 131	75 (58%) (48.7%-66.3%) n = 130	19% (8.1%-30.3%)

	1 month after 3-dose series (Month 7)	82 (99%) (93.5%-99.97%) n = 83	53 (60%) (49.2%-70.5%) n = 88	39% (28.4%-49.2%)
	4 months after 3-dose series (Month 10)	76 (89%) (80.9%-95.0%) n = 85	42 (51%) (39.4%-61.8%) n = 83	39% (25.8%-50.9%)
Serogroup Y LLQ = 14.7	Baseline (Day 1)	12 (10%) (5.2%-16.6%) n = 122	13 (11%) (5.8%-17.4%) n = 123	-1% (-8.7%-7.2%)
	1 month after 2nd dose (Month 3)	98 (96%) (90.3%-98.9%) n = 102	64 (70%) (59.8%-79.5%) n = 91	26% (16.0%-36.3%)
	4 months after 2nd dose (Month 6)	112 (85%) (77.6%-90.5%) n = 132	83 (63%) (54.0%-71.1%) n = 132	22% (11.5%-32.1%)
	1 month after 3-dose series (Month 7)	91 (100%) (96.0%-100.0%) n = 91	50 (57%) (45.8%-67.3%) n = 88	43% (33.3%-53.6%)
	4 months after 3-dose series (Month 10)	74 (86%) (76.9%-92.6%) n = 86	48 (53%) (42.0%-63.3%) n = 91	33% (20.2%-45.4%)

Abbreviations: CI, confidence interval; FAS, full analysis set; HT-hSBA, high throughput human serum bactericidal assay; LLQ, lower limit of quantification.
a For subjects who were enrolled in the extension study, Visit Month 6 of the parent study V102_16 was the first study visit of the extension study V102_16E1. All consecutive study visits were numbered accordingly.
Note: Subjects in the MenABCWY group had received 2 doses of MenABCWY vaccine at day 1 and month 2 in the parent study V102_16, and received a single dose of MenABCWY vaccine at month 6 (4 months after the second dose) in the extention study V102_16E1.
Subjects in the MenACWY group had received 1 dose of placebo at day 1 and 1 dose of MenACWY vaccine at month 2 in the parent study V102_16, and received a single dose of placebo at month 6 in the extention study V102_16E1.

Assessor's comment

The percentages of subjects in the MenACWY group with HT-hSBA titers ≥ LLQ against serogroups A, C, W, and Y were 1%, 43%, 16%, and 11%, respectively at baseline. The percentages increased at 1 month after the second dose to 63%, 82%, 52%, and 70%, respectively, and were 32%, 78%, 58%, and 63%, respectively at 4 months after the second dose, 1 month after 3-dose series (Month 7) 24%, 73%, 60%, 57%. At the end of the study 4 months after 3-dose series (Month 10) the percentages of subjects in the MenABCWY group with HT-hSBA titers ≥ LLQ against serogroups A, C, W, and Y were 18%, 69%, 51% and 53%, respectively.

Given the used high throughput assay the LLQ of all serogroups (A, C, W, and Y) is well above the commonly used 1:4 titer. As all HT-hSBA titers are above the 1:4 titer protection against serogroups A, C, W, and Y might be assumed for most patients. Results are largely in line with the current knowledge about Menveo.

Percentages of subjects with 2-, 3-, and 4-fold rise in hSBA titer against N meningitidis serogroups A, C, W and Y

2-fold rise

In the MenABCWY group, at 1 month after the second dose (2-dose MenABCWY vaccination series), the percentages of subjects with at least 2-fold rise in HT-hSBA titers against 4 N meningitidis serogroups were: A (81%), C (98%), W (74%), and Y (92%). At 4 months after the second dose, 23%, 94%, 54%, and 72% subjects, respectively had at least 2-fold rise in HT-hSBA titers (Table 9 to Table 12).

In the MenACWY group (one dose of MenACWY), at 1 month after the second dose, the percentages of subjects with at least 2-fold rise in HT-hSBA titers against 4 N meningitidis serogroups were: A (48%),

C (66%), W (25%), and Y (59%). At 4 months after the second dose, 21%, 55%, 30%, and 47% subjects, respectively had at least 2-fold rise in HT-hSBA titers (Table 9to Table 12).

In the MenABCWY group, at 1 month after the 3-dose series, the percentages of subjects with at least 2-fold rise in HT-hSBA titers against 4 N meningitidis serogroups were: A (88%), C (87%), W (83%), and Y (57%). At 4 months after the 3-dose series, 32%, 56%, 24%, and 26% subjects, respectively had at least 2-fold rise in HT-hSBA. In the MenACWY group (one dose of MenACWY), at 1 month after the 3-dose series (5 months after the MenACWY dose), the percentages of subjects with at least 2-fold rise in HT-hSBA titers against 4 N meningitidis serogroups were: A (2%), C (2%), W (5%), and Y (2%). At 4 months after the 3-dose series (8 months after the MenACWY dose), 1%,8%, 1%, and 3% subjects, respectively had at least 2-fold rise in HT-hSBA.

3-fold rise

In the MenABCWY group (2-dose MenABCWY vaccination series), at 1 month after the second dose, the percentages of subjects with at least 3-fold rise in HT-hSBA titers against 4 N meningitidis serogroups were: A (61%), C (98%), W (56%), and Y (85%). At 4 months after the second dose, 13%, 88%, 32%, and 61% subjects, respectively had at least 3-fold rise in HT-hSBA titers (Table 9to Table 12).

In the MenACWY group (one dose of MenACWY), at 1 month after the second dose, the percentages of subjects with at least 3-fold rise in HT-hSBA titers against 4 N meningitidis serogroups were: A (36%), C (58%), W (19%), and Y (50%). At 4 months after the second dose, 14%, 48%, 22%, and 40% subjects, respectively had at least 3-fold rise in HT-hSBA titers (Table 9to Table 12).

In the MenABCWY group, at 1 month after the 3-dose series, the percentages of subjects with at least 3-fold rise in HT-hSBA titers against 4 N meningitidis serogroups were: A (69%), C (60%), W (67%), and Y (39%). At 4 months after the 3-dose series, 16%, 29%, 13%, and 15% subjects, respectively had at least 3-fold rise in HT-hSBA titers. In the MenACWY group (one dose of MenACWY), at 1 month after the 3-dose series (5 months after the MenACWY dose), the percentages of subjects with at least 3-fold rise in HT-hSBA titers against 4 N meningitidis serogroups were: A (0%), C (1%), W (0%), and Y (0%). At 4 months after the 3-dose series (8 months after the MenACWY dose), 1%, 5%, 0%, and 2% subjects, respectively had at least 3-fold rise in HT-hSBA titers

4-fold rise

In the MenABCWY group, at 1 month after the second dose, the percentages of subjects with at least 4-fold rise in HT-hSBA titers against 4 N meningitidis serogroups were: A (45%), C (95%), W (50%), and Y (81%). At 4 months after the second dose, 8%, 86%, 27%, and 49% subjects, respectively had at least 4-fold rise in HT-hSBA titers (Table 9to Table 12).

In the MenACWY group, at 1 month after the second dose, the percentages of subjects with at least 4-fold rise in HT-hSBA titers against 4 N meningitidis serogroups were: A (26%), C (54%), W (15%), and Y (47%). At 4 months after the second dose, 11%, 43%, 17%, and 35% subjects, respectively had at least 4-fold rise in HT-hSBA titers (Table 9to Table 12).

In the MenABCWY group, at 1 month after the 3-dose series, the percentages of subjects with at least 4-fold rise in HT-hSBA titers against 4 N meningitidis serogroups were: A (53%), C (49%), W (49%), and Y (28%). At 4 months after the 3-dose series, 6%, 21%, 8%, and 6% subjects, respectively had at least 4-fold rise in HT-hSBA titers. In the MenACWY group (one dose of MenACWY), at 1 month after the 3-dose series (5 months after the MenACWY dose), the percentages of subjects with at least 4-fold rise in HT-hSBA titers against 4 N meningitidis serogroups were: A (0%), C (1%), W (0%), and Y (0%). At 4 months after the 3-dose series (8 months after the MenACWY dose), 1%, 2%, 0%, and 1% subjects, respectively had at least 4-fold rise in HT-hSBA titers.

Table 9 Number (%) of Subjects With At Least 2-, 3- and 4-Fold Increase[a] in HT-hSBA Titers Against Serogroup A and Vaccine Group Difference at Month 3, 6, 7, and 10 - FAS Immunogenicity.

	Number (%) of Subjects (95% CI)		**Vaccine Group Differences**
	MenABCWY	**MenACWY**	**MenABCWY - MenACWY**
	1 month after 2nd dose (Month 3)		
	N = 132	**N = 110**	
2-Fold rise	107 (81%) (73.3%-87.4%)	53 (48%) (38.6%-57.9%)	33% (21.1%-44.0%)
3-Fold rise	80 (61%) (51.7%-69.0%)	40 (36%) (27.4%-46.1%)	24% (11.7%-36.0%)
4-Fold rise	59 (45%) (36.0%-53.6%)	29 (26%) (18.4%-35.6%)	18% (6.2%-29.8%)
	4 months after 2nd dose (Month 6)		
	N = 119	**N = 126**	
2-Fold rise	27 (23%) (15.5%-31.3%)	26 (21%) (13.9%-28.8%)	2% (-8.3%-12.5%)
3-Fold rise	16 (13%) (7.9%-20.9%)	18 (14%) (8.7%-21.6%)	-1% (-9.7%-8.1%)
4-Fold rise	9 (8%) (3.5%-13.9%)	14 (11%) (6.2%-17.9%)	-4% (-11.2%-4.0%)
	1 month after 3-dose series (Month 7)		
	N = 83	**N = 85**	
2-Fold rise	73 (88%) (79.0%-94.1%)	2 (2%) (0.29%-8.2%)	86% (76.0%-91.6%)
3-Fold rise	57 (69%) (57.6%-78.4%)	0 (0%) (0%-4.2%)	69% (58.0%-77.7%)
4-Fold rise	44 (53%) (41.7%-64.1%)	0 (0%) (0%-4.2%)	53% (42.4%-63.4%)
	4 months after 3-dose series (Month 10)		
	N = 77	**N = 86**	
2-Fold rise	25 (32%) (22.2%-44.1%)	1 (1%) (0.03%-6.3%)	31% (21.3%-42.6%)
3-Fold rise	12 (16%) (8.3%-25.6%)	1 (1%) (0.03%-6.3%)	14% (6.9%-24.3%)
4-Fold rise	5 (6%) (2.1%-14.5%)	1 (1%) (0.03%-6.3%)	5% (-0.6%-13.3%)

Abbreviations: CI, confidence interval; FAS, full analysis set; HT-hSBA, high throughput human serum bactericidal assay.

a. The n-fold increase in titers is defined as: a) for subjects with prevaccination hSBA titers <LLQ, a postvaccination hSBA ≥n LLQ; b) for subjects with a prevaccination hSBA titers ≥LLQ, an increase of at least n times of the prevaccination hSBA.

Note: Subjects in the MenABCWY group had received 2 doses of MenABCWY vaccine at day 1 and month 2 in the parent study V102_16, and received a single dose of MenABCWY vaccine at month 6 (4 months after the second dose) in the current study V102_16E1.

Subjects in the MenACWY group had received 1 dose of placebo at day 1 and 1 dose of MenACWY vaccine at month 2 in the parent study V102_16, and received a single dose of placebo at month 6 in the current study V102_16E1.

Table 10 Number (%) of Subjects With At Least 2-, 3- and 4-Fold Increase[a] in HT-hSBA Titers Against Serogroup C and Vaccine Group Difference at Month 3, 6, 7, and 10 - FAS Immunogenicity.

	Number (%) of Subjects (95% CI)		**Vaccine Group Differences**
	MenABCWY	**MenACWY**	**MenABCWY - MenACWY**
	1 month after 2nd dose (Month 3)		
	N = 131	**N = 123**	
2-Fold rise	129 (98%) (94.6%-99.81%)	81 (66%) (56.8%-74.2%)	33% (24.4%-41.6%)
3-Fold rise	129 (98%) (94.6%-99.81%)	71 (58%) (48.5%-66.6%)	41% (32.0%-49.8%)
4-Fold rise	124 (95%) (89.3%-97.8%)	66 (54%) (44.4%-62.7%)	41% (31.3%-50.5%)
	4 months after 2nd dose (Month 6)		
	N = 130	**N = 130**	
2-Fold rise	122 (94%) (88.2%-97.3%)	71 (55%) (45.7%-63.4%)	39% (29.6%-48.6%)
3-Fold rise	115 (88%) (81.7%-93.4%)	62 (48%) (38.9%-56.6%)	41% (30.2%-50.6%)
4-Fold rise	112 (86%) (79.0%-91.6%)	56 (43%) (34.4%-52.1%)	43% (32.2%-52.9%)
	1 month after 3-dose series (Month 7)		
	N = 84	**N = 84**	
2-Fold rise	73 (87%)	2 (2%)	85%
	(77.8%-93.3%)	(0.29%-8.3%)	(74.8%-90.8%)
3-Fold rise	50 (60%)	1 (1%)	58%
	(48.3%-70.1%)	(0.03%-6.5%)	(47.2%-68.4%)
4-Fold rise	41 (49%)	1 (1%)	48%
	(37.7%-60.0%)	(0.03%-6.5%)	(36.7%-58.3%)
	4 months after 3-dose series (Month 10)		
	N = 85	**N = 87**	
2-Fold rise	48 (56%)	7 (8%)	48%
	(45.3%-67.2%)	(3.3%-15.9%)	(35.8%-59.7%)
3-Fold rise	25 (29%)	4 (5%)	25%
	(20.0%-40.3%)	(1.3%-11.4%)	(14.4%-35.9%)
4-Fold rise	18 (21%)	2 (2%)	19%
	(13.1%-31.4%)	(0.28%-8.1%)	(10.2%-29.1%)

a. The n-fold increase in titers is defined as: a) for subjects with prevaccination hSBA titers <LLQ, a postvaccination hSBA ≥n LLQ; b) for subjects with a prevaccination hSBA titers ≥LLQ, an increase of at least n times of the prevaccination hSBA.

Note: Subjects in the MenABCWY group had received 2 doses of MenABCWY vaccine at day 1 and month 2 in the parent study V102_16, and received a single dose of MenABCWY vaccine at month 6 (4 months after the second dose) in the current study V102_16E1.

Subjects in the MenACWY group had received 1 dose of placebo at day 1 and 1 dose of MenACWY vaccine at month 2 in the parent study V102_16, and received a single dose of placebo at month 6 in the current study V102_16E1

Table 11 Number (%) of Subjects With At Least 2-, 3- and 4-Fold Increase[a] in HT-hSBA Titers Against Serogroup W and Vaccine Group Difference Month 3, 6, 7, and 10 - FAS Immunogenicity.

	Number (%) of Subjects (95% CI)		**Vaccine Group Differences**
	MenABCWY	**MenACWY**	**MenABCWY - MenACWY**
	1 month after 2nd dose (Month 3)		
	N = 107	**N = 103**	
2-Fold rise	79 (74%) (64.5%-81.9%)	26 (25%) (17.2%-34.8%)	49% (35.9%-59.5%)
3-Fold rise	60 (56%) (46.2%-65.7%)	20 (19%) (12.3%-28.4%)	37% (24.0%-48.1%)
4-Fold rise	53 (50%) (39.7%-59.4%)	15 (15%) (8.4%-22.9%)	35% (22.9%-46.2%)
	4 months after 2nd dose (Month 6)		
	N = 114	**N = 116**	
2-Fold rise	61 (54%) (43.9%-62.9%)	35 (30%) (22.0%-39.4%)	23% (10.6%-35.3%)
3-Fold rise	37 (32%) (24.0%-41.9%)	25 (22%) (14.5%-30.2%)	11% (-0.6%-22.2%)
4-Fold rise	31 (27%) (19.3%-36.3%)	20 (17%) (10.9%-25.4%)	10% (-0.8%-20.7%)
	1 month after 3-dose series (Month 7)		
	N = 81	**N = 84**	
2-Fold rise	67 (83%) (72.7%-90.2%)	4 (5%) (1.3%-11.8%)	78% (66.9%-85.9%)
3-Fold rise	54 (67%) (55.3%-76.8%)	0 (0%) (0%-4.3%)	67% (55.8%-76.0%)
4-Fold rise	40 (49%) (38.1%-60.7%)	0 (0%) (0%-4.3%)	49% (38.7%-60.1%)
	4 months after 3-dose series (Month 10)		
	N = 83	**N = 79**	
2-Fold rise	20 (24%) (15.4%-34.7%)	1 (1%) (0.03%-6.9%)	23% (14.0%-33.3%)
3-Fold rise	11 (13%) (6.8%-22.5%)	0 (0%) (0%-4.6%)	13% (7.6%-22.2%)
4-Fold rise	7 (8%) (3.5%-16.6%)	0 (0%) (0%-4.6%)	8% (3.6%-16.4%)

a. The n-fold increase in titers is defined as: a) for subjects with prevaccination hSBA titers <LLQ, a postvaccination hSBA ≥n LLQ; b) for subjects with a prevaccination hSBA titers ≥LLQ, an increase of at least n times of the prevaccination hSBA.

Note: Subjects in the MenABCWY group had received 2 doses of MenABCWY vaccine at day 1 and month 2 in the parent study V102_16, and received a single dose of MenABCWY vaccine at month 6 (4 months after the second dose) in the current study V102_16E1.

Subjects in the MenACWY group had received 1 dose of placebo at day 1 and 1 dose of MenACWY vaccine at month 2 in the parent study V102_16, and received a single dose of placebo at month 6 in the current study V102_16E1.

Table 12 Number (%) of Subjects With At Least 2-, 3- and 4-Fold Increase[a] in HT-hSBA Titers Against Serogroup Y and Vaccine Group Difference at Month 3, 6, 7, and 10 - FAS Immunogenicity.

	Number (%) of Subjects (95% CI)		**Vaccine Group Differences**
	MenABCWY	**MenACWY**	**MenABCWY - MenACWY**
	1 month after 2nd dose (Month 3)		
	N = 99	**N = 86**	
2-Fold rise	91 (92%) (84.7%-96.5%)	51 (59%) (48.2%-69.8%)	33% (20.9%-44.2%)
3-Fold rise	84 (85%) (76.2%-91.3%)	43 (50%) (39.0%-61.0%)	35% (21.8%-47.1%)
4-Fold rise	80 (81%) (71.7%-88.0%)	40 (47%) (35.7%-57.6%)	34% (20.8%-46.8%)
	4 months after 2nd dose (Month 6)		
	N = 122	**N = 121**	
2-Fold rise	88 (72%) (63.3%-79.9%)	57 (47%) (38.0%-56.4%)	25% (12.8%-36.5%)
3-Fold rise	74 (61%) (51.4%-69.4%)	49 (40%) (31.7%-49.8%)	20% (7.6%-32.1%)
4-Fold rise	60 (49%) (40.0%-58.4%)	42 (35%) (26.3%-43.9%)	14% (2.0%-26.5%)
	1 month after 3-dose series (Month 7)		
	N = 89	**N = 85**	
2-Fold rise	51 (57%)	2 (2%)	55%
	(46.4%-67.7%)	(0.29%-8.2%)	(43.8%-65.1%)
3-Fold rise	35 (39%)	0 (0%)	39%
	(29.1%-50.3%)	(0%-4.2%)	(29.8%-49.7%)
4-Fold rise	25 (28%)	0 (0%)	28%
	(19.1%-38.6%)	(0%-4.2%)	(19.8%-38.2%)
	4 months after 3-dose series (Month 10)		
	N = 84	**N = 88**	
2-Fold rise	22 (26%)	3 (3%)	23%
	(17.2%-36.9%)	(0.7%-9.6%)	(13.0%-33.6%)
3-Fold rise	13 (15%)	2 (2%)	13%
	(8.5%-25.0%)	(0.28%-8.0%)	(5.3%-22.8%)
4-Fold rise	5 (6%)	1 (1%)	5%
	(2.0%-13.4%)	(0.03%-6.2%)	(-0.9%-12.2%)

a. The n-fold increase in titers is defined as: a) for subjects with prevaccination hSBA titers <LLQ, a postvaccination hSBA ≥n LLQ; b) for subjects with a prevaccination hSBA titers ≥LLQ, an increase of at least n times of the prevaccination hSBA.
Note: Subjects in the MenABCWY group had received 2 doses of MenABCWY vaccine at day 1 and month 2 in the parent study V102_16, and received a single dose of MenABCWY vaccine at month 6 (4 months after the second dose) in the current study V102_16E1.
Subjects in the MenACWY group had received 1 dose of placebo at day 1 and 1 dose of MenACWY vaccine at month 2 in the parent study V102_16, and received a single dose of placebo at month 6 in the current study V102_16E1

Assessor's comment

The percentages of subjects with at least 4-fold rise in HT-hSBA titers, against serogroups A, C, W, and Y, at 1 month after the second dose (2-dose MenABCWY vaccination series), were numerically higher in the MenABCWY group (A [45%], C [95%], W [50%], and Y [81%]), compared to those in the MenACWY group (A [26%], C [54%], W [15%], and Y [47%]), after a single dose of MenACWY vaccine.

The percentages of subjects with at least 4-fold rise in HT-hSBA titers, at 1 month after the 3-dose series, against serogroups A, C, W, and Y, were numerically higher in the MenABCWY group (A [53%],

C [49%], W [49%], and Y [28%]), compared to those in the MenACWY group (0%-1%, across serogroups), who received a single dose of MenACWY.

At 4 months after the 3-dose series, the percentages in the MenABCWY group (A [6%], C [21%], W [8%], and Y [6%]) were numerically higher compared to those in the MenACWY group (0%-2%, across serogroups), who received a single dose of MenACWY.

Given the three dose vaccination with MenABCWY it is not surprising that a higher immune response over time is observed s compared to Menveo. The pattern reported for the Menveo group is in line with the known immune response reported in other studies (see EPAR).

Safety data

In total 152 subjects in the MenABCWY group and 149 subjects in the MenACWY group were exposed to the study vaccinations.

Solicited AEs

After first vaccination

- Between 6 hours through day 7 after first vaccination, at least one solicited AE was reported in 84% of subjects in the MenABCWY group and in 48% of subjects in the MenACWY group
- After first vaccination, 83% vs. 20% of subjects in respective groups had at least one local AE (erythema or induration or pain) and 35% vs. 38% of subjects in respective groups had at least one systemic AE (nausea or arthralgia or headache or fatigue, myalgia or fever or chills or loss of appetite.
- After first vaccination, the most frequently reported solicited local AE was pain (82% vs. 19%) in both the vaccine groups followed by erythema (11% vs. 1%). The percentage of subjects reporting local AEs were higher in the MenABCWY group than in the MenACWY group.
- Most of the observed solicited local AEs after first vaccination were mild to moderate in severity in both vaccine groups. None of the subjects in the MenACWY group experienced severe local AEs. Whereas, severe pain and erythema was observed in 3% and 1% of subjects, respectively in the MenABCWY group.
- After first vaccination, the most frequently reported solicited systemic AE was headache (18% vs. 25% in the MenABCWY vs. MenACWY groups) and fatigue (18% vs. 19%, respectively) followed by myalgia (9% vs. 6%, respectively).
- Most of the solicited systemic AEs after first vaccination were mild in severity in both the vaccine groups. Less than or equal to 2% of subjects had severe systemic AEs across the 2 vaccine groups. After first vaccination, 3 (2%) subjects in the MenABCWY group had fever (temperature $\geq$ 38°C).
- In the MenABCWY group, a higher proportion of subjects (37% vs. 4%) took analgesics or antipyretic medication to treat pain or fever compared to the MenACWY group.

After Second Vaccination:

- After the second vaccination, the percentage of subjects with at least one solicited AE were 62% vs. 44% (local AEs: 62% vs. 36%; Systemic AEs: 28% vs. 23%) in the MenABCWY vs. MenACWY groups respectively. The MenABCWY group had relatively high percentage of subjects experiencing solicited local and systemic AEs.

- After the second vaccination, the most frequently reported solicited local AE was pain (62% in the MenABCWY and 36% in the MenACWY group) followed by erythema (8% vs. 3%, in respective groups) and induration (9% vs. 6% respectively).
- The majority of observed solicited local AEs after second vaccination were mild to moderate in severity in both the vaccine groups. Severe pain and erythema was reported in 4% and 2% of subjects in the MenABCWY group, while severe erythema and induration was reported in 1% of subjects in the MenACWY group.
- The most frequently reported solicited systemic AE after second vaccination was fatigue (17% vs. 12%) and headache (16% of subjects) in the MenABCWY vs. the MenACWY groups, respectively followed by loss of appetite (13% vs. 2% in respective groups).
- The majority of the solicited systemic AEs after second vaccination were mild in severity in both vaccine groups. In the MenABCWY group, 1% of subjects experienced severe chills, headache, fatigue, nausea and loss of appetite. Only severe fatigue was observed in 2 subjects in the MenACWY group.
- Seven subjects (5%) in the MenABCWY group experienced fever (temperature ≥ 38°C).
- For the treatment of pain and/or fever, 18% of subjects in MenABCWY group and 3% of subjects in the MenACWY group used analgesics or antipyretic medication.

After third Vaccination:

- Between 6 hours through day 7 after vaccination, at least one solicited AE was reported by 69% of subjects in the MenABCWY group and by 29% of subjects in the MenACWY group. Solicited local AEs were reported by 67% and 17% of subjects in the respective groups, and solicited systemic AEs by 30% and 17% of subjects.
- The most frequently reported solicited local AE was pain at the injection site in both study groups: 67% of subjects in the MenABCWY group and 17% of subjects in the MenACWY group. Erythema and induration were both reported by 7% of subjects in the the MenABCWY group; no subjects in the MenACWY group reported these solicited local AEs. One subject (in the MenABCWY group) reported a severe solicited local AE (pain).
- The most frequently reported solicited systemic AEs were fatigue (16% in the MenABCWY group vs. 13% in the MenACWY group) and headache (15% vs. 10%), followed by myalgia (15% vs. 4%). One subject (MenACWY) reported fever (temperature ≥38°C).
- Most of the solicited systemic AEs were mild in severity in both study groups. There were few reports of severe solicited systemic AEs: one case each of severe myalgia, arthralgia, and fatigue in the MenABCWY groups, none in the MenACWY group.
- With regards to other indicators of solicited AEs, a higher proportion of subjects in the MenABCWY group (14%) took analgesics or antipyretic medication to treat pain or fever compared to the MenACWY group (4%).

Number (%) of Subjects With Solicited AEs		
After the first vaccination		
	MenABCWY	**MenACWY**
Any	123 (84%)	70 (48%)
Local	122 (83%)	29 (20%)
Systemic	52 (35%)	55 (38%)
After the second vaccination		

Any	**83 (62%)**	**60 (44%)**
Local	83 (62%)	50 (36%)
Systemic	37 (28%)	32 (23%)
After the third vaccination		
Any	62 (69%)	25 (29%)
Local	60 (67%)	15 (17%)
Systemic	27 (30%)	15 (17%)

Unsolicited AEs

- In total, unsolicited AEs after any vaccination were observed in 33% of subjects in the MenABCWY group and 37% of subjects in the MenACWY group. Out of these, 5% and 2% of subjects in respective groups reported at least possibly or probably related unsolicited AEs as per the investigator.
- Only one SAE was reported in one subject in the MenACWY group and the SAE was not considered to be possibly or probably related to study vaccine according to the investigator.
- Medically attended AEs were reported in 25% of subjects in the MenABCWY group and 30% of subjects in the MenACWY group.
- There were no deaths reported in this study and 2 subjects, one in each vaccine group were prematurely withdrawn from the study due to unsolicited AEs.
- After administration of first dose of study vaccine, 2 subjects in the MenACWY group had bronchitis and tonsillitis which lead to dose interruption of study vaccination. One subject in the MenACWY group was hospitalized due to pharyngitis.

After First Vaccination

- After the first vaccination, 16% of subjects in the MenABCWY group and 20% of subjects in the MenACWY group experienced any unsolicited AE. According to the investigator, 3% of subjects in the MenABCWY group and 1% of subjects in the MenACWY group had possibly or probably related unsolicited AEs after first vaccination.
- By system organ class (SOC), 6% of subjects in the MenABCWY and 5% of subjects in the MenACWY group were affected with either infections or infestations.
- By preferred term (PT), otitis externa and injection site pain were the most frequent unsolicited AEs experienced by 2% of subjects in the MenABCWY group after first vaccination. Similarly cough and ligament sprain were the most frequent unsolicited AEs experienced by 3% of subjects in the MenACWY group.

After second vaccination

- After the second vaccination, 28% of subjects in the MenABCWY group and 26% of subjects in the MenACWY group reported any unsolicited AEs. Among these, 3% of subjects in the MenABCWY group and 1% of subjects in the MenACWY group had at least possibly or probably related unsolicited AEs as per the investigator judgement.
- By SOC, the subjects in both the vaccine groups were most frequently affected by infections or infestations (13% of subjects in the MenABCWY and 11% of subjects in MenACWY).

- By preferred term, nasopharyngitis was the most frequently reported unsolicited AE after second vaccination in the MenABCWY group (4% of subjects), while headache and influenza were frequent in the MenACWY group (3% of subjects).

After third vaccination

- Overall, 26% of subjects in the MenABCWY group and 27% of subjects in the MenACWY group reported any unsolicited AE from day 1 through study termination. At least possibly related unsolicited AEs were reported by 4% in the MenABCWY group, while no subjects in the MenACWY reported such AEs; medically attended AEs were reported by 15% and 22% of subjects in the respective study groups.
- There were no AEs leading to withdrawal, SAEs, or deaths reported in this study.

Assessor's comment

After study vaccination, the most frequently reported solicited local AE was pain in both the vaccine groups, whereas the most frequently reported systemic AE was fatigue in the MenABCWY group and headache in the MenACWY group. The most frequently reported solicited local AE after the third vaccination was pain in both study groups, while the most frequently reported solicited systemic AE was fatigue in both study groups. The majority of the local and systemic AEs were mild to moderate in intensity.

Unsolicited AEs after any vaccination were reported in 33% of subjects in the MenABCWY group and 37% of subjects in the MenACWY group. Overall, any unsolicited AE was reported by 26% of subjects in the MenABCWY group and by 27% of subjects in the MenACWY group during the entire study period after third vaccination.

Only one SAE was reported after the second vaccination in one subject in the MenACWY group and the SAE was considered not related to study vaccination as per the investigator.

There were no AEs leading to withdrawal, SAEs, or deaths reported in the extension study.

2.3.3. Discussion on clinical aspects

This report contains the clinical study reports of V102_16 and V102_16E1. These studies were conducted as part of the development program of the investigational meningococcal combination vaccine MenABCWY, intended to protect against the five most common *Neisseria meningitidis* serogroups (A, B, C, W and Y). Menveo was given as a comparator vaccine in one control arm in the parent study V102_16. The persistence of the immune response was followed in study V102_16E1.

The study enrolled vaccine naïve subjects aged 10 to 18 years who did not report any disease caused by *N meningitidis* previously.

As the efficacy results are reported for serogroup B invasive disease isolates only no relevant conclusions on the efficacy of Menveo can be made. Therefore, the present P46 AR, only the safety analysis of the Menveo arm after vaccination is directly relevant to Menveo.

In the combined study (V102_16 and V102_16E1) a total 152 subjects in the MenABCWY group and 149 subjects in the MenACWY group were exposed to the study vaccinations.

No relevant differences can be observed comparing the results of the Geometric Mean HT-hSBA titers at baseline with those mentioned in the initial EPAR for patient with baseline hSBA titre ≥1:4. The Geometric Mean HT-hSBA Titers one month after the Menveo vaccination are also comparable with those mentioned in the initial EPAR for patient with baseline hSBA titre ≥1:4.

Given the used high throughput assay the LLQ of all serogroups (A, C, W, and Y) is well above the commonly used 1:4 titer. As all HT-hSBA titers are above the 1:4 titer protection against serogroups A, C, W, and Y might be assumed for most patients. This is in line with the current knowledge about Menveo.

One (1) month after vaccination in the MenACWY group the percentages of subjects with 4-fold rise in HT-hSBA titers was 26% for serogroup A, 54% for C, 15% for W, and 47% for Y. At month 10 in the MenACWY group the percentages of subjects with 4-fold rise in HT-hSBA titers against the 4 N meningitidis serogroups was 0%-1. This is in line with the known immunologic response over time where the HT-hSBA titers wane of after about 6 months.

After study vaccination, the most frequently reported solicited local AE was pain in both the vaccine groups, whereas the most frequently reported systemic AE was fatigue in the MenABCWY group and headache in the MenACWY group. The most frequently reported solicited local AE after the third vaccination was pain in both study groups, while the most frequently reported solicited systemic AE was fatigue in both study groups. The majority of the local and systemic AEs were mild to moderate in intensity.

Unsolicited AEs after any vaccination were reported in 33% of subjects in the MenABCWY group and 37% of subjects in the MenACWY group. Overall, any unsolicited AE was reported by 26% of subjects in the MenABCWY group and by 27% of subjects in the MenACWY group during the entire study period after third vaccination.

Only one SAE was reported after the second vaccination in one subject in the MenACWY group and the SAE was considered not related to study vaccination as per the investigator.

There were no AEs leading to withdrawal, SAEs, or deaths reported in the extension study.

Reported AEs for Menveo were included in the SmPC with comparable frequencies. Therefore no further action is necessary.

3. Overall conclusion and recommendation

Immunogenicity data presented for Menveo are largely in line with the known immunogenicity of Menveo, with the caveat that a HT assay was employed in this study. Regarding Menveo safety analysis did not reveal unlisted or unexpected adverse events. There were no AEs leading to withdrawal, SAEs, or deaths reported in the Menveo arm. Therefore, the results from the study are considered in line with the known clinical characteristics of Menveo.

The B/R remains positive. No changes to the SmPC are considered necessary.

☒ PAM fulfilled