Amsterdam, 31 March 2022
EMA/233264/2022
Committee for Medicinal Products for Human Use (CHMP)

Type II variation assessment report

Procedure No. EMEA/H/C/002226/II/0115

Invented name: Nimenrix

Common name: meningococcal group A, C, W135 and Y conjugate vaccine

Marketing authorisation holder (MAH): Pfizer Europe MA EEIG

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Status of this report and steps taken for the assessment				
Current step	**Description**	**Planned date**	**Actual Date**	**Need for discussion**
☐	Start of procedure	31 Jan 2022	31 Jan 2022	☐
☐	CHMP Rapporteur Assessment Report	07 Mar 2022	07 Mar 2022	☐
☐	CHMP members comments	21 Mar 2022	21 Mar 2022	☐
☐	Updated CHMP Rapporteur Assessment Report	24 Mar 2022	24 Mar 2022	☐
☐	Start of written procedure	29 Mar 2022	29 Mar 2022	☐
☒	Opinion	31 Mar 2022	31 Mar 2022	☐

Table of contents

1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Pfizer Europe MA EEIG submitted to the European Medicines Agency on 21 January 2022 an application for a variation.

The following changes were proposed:

Variation requested		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I and II

Update of section 5.1 of the SmPC, as requested by the CHMP following the conclusion of procedure P46/055, in order to include long-term antibody persistence data from study MenACWY-TT-104: a phase III, randomised, open, controlled, multicentre, primary vaccination study to evaluate the immunogenicity and persistence of 1 and 2 doses of meningococcal conjugate vaccine MenACWY-TT in toddlers (after 1 month and up to 5 years) and to demonstrate non-inferiority of co-administration of MenACWY-TT and 13-valent pneumococcal conjugate vaccine prevenar 13 versus separate administration of the 2 vaccines. The Annex II has been updated accordingly.

The requested variation proposed amendments to the Summary of Product Characteristics and Annex II.

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

The proposed change in the submitted application for a variation is an update of the SmPC section 5.1 of Nimenrix to include long-term antibody persistence data from study MenACWY-TT-104 for the toddler age group, as these data are currently missing from the SmPC. Study MenACWY-TT-104 is a Phase 3, open-label, randomized, controlled, multicentre study designed to evaluate the immunogenicity after 1 month and the persistence of the response up to 5 years following 1 and 2 doses (given 2 months apart) of MenACWY-TT in toddlers aged 12 to 14 months and to demonstrate noninferiority of coadministration of MenACWY-TT and Prevenar 13 (PCV13), versus separate administration of the 2 vaccines. The long-term antibody persistence data from study MenACWY-TT-104 have previously been assessed in a P46 procedure (EMEA/H/C/002226/P46/055).

The MAH also considers this submission to fulfil the obligation to evaluate long term immunogenicity (5 years) and therefore proposes to delete this obligation from Annex II.D in the Nimenrix Product Information.

Long-term antibody persistence data after 1 or 2 doses of MenACWY-TT were evaluated in terms of the percentage of subjects at Year 5 with serum bactericidal assay using rabbit complement (rSBA) titres ≥1:8 and ≥1:128 for each of the 4 meningococcal groups, percentage of subjects at Year 5 with serum bactericidal assay using human complement (hSBA) titres $\geq$1:4 and $\geq$1:8, and geometric mean titres (GMTs).

At 5 years after the last vaccination (first or second dose), the percentages of subjects achieving rSBA titres ≥1:8 in the ACWY1d and ACWY2d groups were 58.6% and 65.8%, respectively, for rSBA-MenA; 20.5% and 28.4%, respectively, for rSBA-MenC; 44.4% and 50.4%, respectively, for rSBA-MenW-135; and 47.4% and 58.1%, respectively, for rSBA-MenY. rSBA-MenW-135 titres in the ACWY2d group were slightly elevated compared to the ACWY1d group.

At 5 years after the last vaccination (first or second dose), the percentages of participants achieving hSBA titres ≥1:8 in the ACWY1d and ACWY2d groups were 27.9% and 17.9%, respectively, for hSBA-

MenA; 60.7% and 67.8%, respectively, for hSBA-MenC; 58.9% and 63.6%, respectively, for hSBA-MenW-135; and 61.5% and 54.2%, respectively, for hSBA-MenY.

GMTs 5 years after the last vaccination for participants in the ACWY1d and ACWY2d groups were 4.4 and 3.1, respectively, for hSBA-MenA; 18.1 and 29.4, respectively, for hSBA-MenC; 20.8 and 19.5, respectively, for hSBA-MenW-135; and 24.3 and 16.8, respectively, for hSBA-MenY. Compared to prevaccination levels, GMTs for each group were higher at 5 years after vaccination. See also Table 2 and Table 3 in Section 6.2 of this assessment report.

The inclusion of data in Table 5 in the section 5.1. of Nimenrix SmPC is welcomed, as there is currently no long-term antibody persistence data for toddlers in the SmPC. These data should also be reflected in the text, as at present the text only mentions the rSBA and hSBA data one month following dose 1 or 2. Regarding the hSBA data, Nimenrix elicited higher hSBA titres, in terms of the percentage of subjects with hSBA titre ≥8, against group W-135 and Y after two doses compared to one, one month post-dose. However, data from Year 3 and 5 reveals only a small difference in long-term immunogenicity, reflected as percentages of subjects with hSBA titres $\geq$ 8 against group W-135 and Y after two doses compared to one. Antibody persistence against group A stands out with a more pronounced decline compared to group C, W-135 and Y.

The CHMP proposes to add the following text under the sub headline "Long-term immunogenicity in toddlers" (new text in italic): *One month post dose one or two* Nimenrix elicited hSBA titres against groups W-135 and Y that were higher in terms of the percentage of subjects with hSBA titre ≥8 when two doses were given compared with one (see section 4.4). Nimenrix elicited hSBA titres against groups A and C that were similar in terms of the percentage of subjects with hSBA titre ≥8 when two doses were given compared with one. *At Year 5 only a small difference in antibody persistence between one and two doses was observed, in terms of percentages of subjects with hSBA titres > 8 against all groups. There was antibody persistence observed at Year 5 against groups C, W-135 and Y, with percentages of subjects with hSBA titres > 8 against group C being 60.7% and 67.8% after one and two doses, respectively, 58.9% and 63.6% against group W-135 and 61.5% and 54.2% against group Y. For group A, 27.9% and 17.9% of subjects receiving one or two doses, respectively, had hSBA titres > 8.*

An updated SmPC text with minor revisions was received from the marketing authorisation holder (MAH): "*Antibody persistence was observed at Year 5 against groups C, W-135 and Y. After one and two doses the percentages of subjects with hSBA titres ≥8 for group C were 60.7% and 67.8%, group W-135 were 58.9% and 63.6% and group Y were 61.5% and 54.2%, respectively*" (see also section 5.1 in the Nimenrix SmPC). The minor revisions are considered approvable.

The obligation to evaluate long-term immunogenicity (5 years) is considered fulfilled and can be deleted from Annex II.D in the Nimenrix Product Information.

Comments were received from MS1, which have been taken into account. An endorsing comment was received from MS2.

The benefit-risk balance of Nimenrix, remains positive.

3. Recommendations

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

Variation requested		Type	Annexes affected
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I and II

Update of section 5.1 of the SmPC, as requested by the CHMP following the conclusion of procedure P46/055, in order to include long-term antibody persistence data from study MenACWY-TT-104: a phase III, randomised, open, controlled, multicentre, primary vaccination study to evaluate the immunogenicity and persistence of 1 and 2 doses of meningococcal conjugate vaccine MenACWY-TT in toddlers (after 1 month and up to 5 years) and to demonstrate non-inferiority of co-administration of MenACWY-TT and 13-valent pneumococcal conjugate vaccine prevenar 13 versus separate administration of the 2 vaccines. The Annex II has been updated accordingly.

☒is recommended for approval.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and II are recommended.

The following obligation has been fulfilled, and therefore it is recommended that it be deleted from the Annex II to the Opinion:

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
Study to evaluate immediate and longer term antibody titres elicited by one or two doses of Nimenrix administered in children aged 12-23 months. The safety and antibody persistence data up to year 5 and the data on co-administration of MenACWY-TT with Prevenar 13 will be provided in sequential study reports at 1, 3 and 5 years after vaccination.	1 year CSR Q1 2017 3 year CSR Q1 2019 5 year CSR Q1 2021

4. EPAR changes

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

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'EMEA/H/C/002226/II/0115' and 'EMEA/H/C/002226/P46/055'.

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

5. Introduction

Nimenrix was first licensed to GlaxoSmithKline (GSK) for use in the European Union on 20 April 2012 (EMEA/H/C/00226) as a single dose vaccine for the active immunization of individuals from the age of 12 months and above, against invasive meningococcal disease caused by Neisseria meningitidis group A (MenA), group C (MenC), group W-135 (MenW-135), and group Y (MenY). In October 2015, the vaccine was acquired by Pfizer, the present marketing authorization holder (MAH). The expanded indication to include individuals from 6 weeks of age was approved on 12 December 2016.

Currently there is no long-term antibody persistence data in the toddler age group in the Nimenrix SmPC. The proposed change, an update of section 5.1 of the SmPC, was requested by the CHMP following the conclusion of the EMEA/H/C/002226/P46/055 procedure, to include long-term antibody persistence data from study MenACWY-TT-104. Study MenACWY-TT-104 was designed to evaluate the immunogenicity after 1 month and the persistence of the response up to 5 years following 1 and 2 doses of MenACWY-TT administered to toddlers aged 12 to 14 months. This study was also conducted to demonstrate that coadministration of MenACWY-TT with a booster dose of 13-valent pneumococcal conjugate vaccine (Prevenar 13) does not adversely impact the immunogenicity of either of the vaccines.

6. Clinical Efficacy aspects

The clinical trial data, of which this variation application is based on, has been reviewed in the EMEA/H/C/002226/P46/055 procedure and no new data or information is provided in this submission. The data presented below is a short review of the data presented in the P46 procedure. For further details please refer to the EMEA/H/C/002226/P46/055 procedure.

Results relating to the immunogenicity endpoints for the primary time-point (up to one month after each vaccination) were previously reported in the Main Clinical Study Report (MenACWY-TT-104 CSR, dated 28 July 2015). Immunogenicity endpoints that assessed the antibody persistence 1 year and 3 years after vaccination were previously reported in the Year 1 Clinical Study Report (MenACWY-TT-104 Year 1 CSR, dated 15 March 2017) and the Year 3 Clinical Study Report (MenACWY-TT-104 Year 3 CSR, dated 19 December 2019).

6.1. Methods – analysis of data submitted

Design of the study:

MenACWY-TT-104 (C0921003) was a Phase 3, open-label, randomized, controlled, multicenter study designed to evaluate the immunogenicity after 1 month and the persistence of the response up to 5 years following 1 and 2 doses (given 2 months apart) of MenACWY-TT in toddlers aged 12 to 14 months and to demonstrate noninferiority of coadministration of MenACWY-TT and Prevenar 13 (PCV13), versus separate administration of the 2 vaccines. Participants were randomized to 4 parallel groups of approximately 200 participants each to receive:

- ACWY1d group: 1 dose of MenACWY-TT at Month 0;
- ACWY2d group: 2 doses of MenACWY-TT at Month 0 and Month 2;
- Co-ad group: 1 dose of MenACWY-TT and 1 dose of PCV13 at Month 0;
- PCV13 group: 1 dose of PCV13 at Month 0 and 1 dose of MenACWY-TT at Month 2.

The planned duration of the study was 62 months for each participant. For the Year 5 time point, the participants in the Co-ad and the ACWY1d groups were to be 72 to 74 months of age and the participants in the ACWY2d and PCV13 groups were to be 74 to 76 months of age. Samples were collected at one month post dose one or two, as well as at Year 1, Year 3 and Year 5.

Immunogenicity Objectives and Endpoints:

The primary immunogenicity objective of the study for Year 5 was to evaluate the long-term persistence of the immune response induced by 1 or 2 doses of MenACWY-TT in terms of the percentage of participants at Year 5 with serum bactericidal assay using rabbit complement (rSBA) titres ≥1:8 and ≥1:28 for each of the 4 meningococcal groups, and geometric mean titres (GMTs) in the ACWY1d and ACWY2d groups.

A secondary immunogenicity objective was to evaluate the long-term persistence of the immune response induced by 1 dose of MenACWY-TT in the Co-ad and PCV13 groups in terms of the percentage of participants at Year 5 with rSBA titres ≥1:8 and ≥1:28 for each of the 4 meningococcal groups, and GMTs.

Another secondary immunogenicity objective was to evaluate the long-term persistence of the immune response induced by 1 or 2 doses of MenACWY-TT in terms of the percentage of participants at Year 5 with serum bactericidal assay using human complement (hSBA) titres ≥1:4 and ≥1:8, and GMTs in a subset of participants in the ACWY1d and ACWY2d groups.

Statistical methods

The numbers and percentages of subjects for immunogenicity and safety endpoints were tabulated with exact 95% CIs by vaccine group. The GMT calculations were performed by taking the anti-log of the mean of the log titre transformations. Antibody titres below the cut-off of the assay were given a value of half the cut-off for the purpose of GMT calculation.

6.2. Results

Study population:

Of the 802 participants randomized in the study, 619 participants completed the study through Year 5. The proportion of randomized participants completing through Year 5 was similar across the 4 vaccine groups. For the according-to-protocol (ATP) cohort for persistence at Year 5, the mean age was 73.4 months and 54.3% of the participants were male. Participant characteristics in all vaccine groups were similar with respect to age, months since last vaccination, sex, ethnicity, geographic ancestry, and the number of previous PCV13 doses received. Study population is presented in Table 1.

Table 1. Study population. Persistence phase at Year 5 (Total Cohort Year 5)

Vaccine Group	ACWY1d	ACWY2d	Co-ad	PCV13	Total
Planned, N	200	200	200	200	800
Randomized, N (total vaccinated cohort)	203	197	201	201	802
N (total cohort Year 5)	156	146	160	157	619
Completed Year 5, N (%)	156 (100.0)	146 (100.0)	160 (100.0)	157 (100.0)	619 (100.0)
Females:males	72:84	65:81	77:83	75:82	289:330
Mean age, months (SD)	72.5 (1.5)	74.4 (1.4)	72.5 (1.4)	74.5 (1.4)	73.5 (1.7)
Median age, months (minimum, maximum)	72.0 (69, 76)	74.0 (72, 78)	72.5 (70, 75)	74.0 (71, 78)	74.0 (69, 78)
Geographic ancestry					
African heritage/African American, n (%)	27 (17.3)	27 (18.5)	26 (16.3)	22 (14.0)	102 (16.5)
American Indian or Alaskan Native, n (%)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.2)
Asian - East Asian heritage, n (%)	0 (0.0)	0 (0.0)	2 (1.3)	2 (1.3)	4 (0.6)
Asian - Japanese heritage, n (%)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.2)
Asian - South East Asian heritage, n (%)	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.6)	2 (0.3)
Native Hawaiian or Other Pacific Islander, n (%)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.6)	2 (0.3)
White - Arabic/North African heritage, n (%)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.6)	2 (0.3)
White - Caucasian/European heritage, n (%)	108 (69.2)	101 (69.2)	112 (70.0)	115 (73.2)	436 (70.4)
Other, n (%)	21 (13.5)	16 (11.0)	17 (10.6)	15 (9.6)	69 (11.1)
Ethnicity					
American Hispanic or Latino, n (%)	4 (2.6)	5 (3.4)	5 (3.1)	4 (2.5)	18 (2.9)
Not American Hispanic or Latino, n (%)	152 (97.4)	141 (96.6)	155 (96.9)	153 (97.5)	601 (97.1)

Note: Age is calculated using visit date at Year 5.

Note: "Completed Year 5" includes subjects who returned for the Year 5 visit.

Note: For the "Planned, N" row, the number of subjects is based on the target enrollment of approximately 800 subjects (200 per study group).

Note: For the "Randomized, N (total vaccinated cohort)" row, the number of subjects is the number of randomized subjects who received at least 1 study vaccination.

ACWY1d = subjects who received 1 dose of MenACWY-TT at Month 0.

ACWY2d = subjects who received 2 doses of MenACWY-TT at Month 0 and Month 2.

Co-ad = subjects who received 1 dose of MenACWY-TT and 1 dose of Prevenar 13 at Month 0.

PCV13 = subjects who received 1 dose of Prevenar 13 at Month 0 and 1 dose of MenACWY-TT at Month 2.

Immunogenicity results:

The number and percentage of participants with rSBA titres greater than or equal to the cut-off values (1:8 and 1:128) and GMTs up to Year 5 for the adapted ATP cohort (ATP cohort at each time point) are presented in Table 2.

After vaccination, immune responses declined over time but were higher 5 years after vaccination compared to pre-vaccination levels. Comparable antibody persistence at Year 5 was observed for participants receiving 1 dose of MenACWY-TT (ACWY1d group) and participants receiving 2 doses of MenACWY-TT (ACWY2d group), although the GMTs were elevated in the ACWY2d group compared to the ACWY1d group. The percentage of participants with rSBA titres ≥1:8 in the Co-ad and PCV13 groups at Year 5 were similar to those observed for participants in the ACWY1d and ACWY2d groups

Table 2. Number and Percentage of Subjects With rSBA-MenA, rSBA-MenC, rSBA-MenW-135, and rSBA-MenY Titres Equal to or Above the Cut-off Values (1:8 and 1:128) and GMTs (Adapted ATP Cohort)

				≥1:8				≥1:128				GMT		
					95% CI				95% CI				95% CI	
Antibody	Vaccine Group	Visit	N	n	%	LL	UL	n	%	LL	UL	Value	LL	UL
rSBA-MenA	ACWY1d	PRE	175	5	2.9	0.9	6.5	2	1.1	0.1	4.1	4.3	4.0	4.6
		PI (M1)	180	176	97.8	94.4	99.4	170	94.4	90.0	97.3	1437.0	1118.3	1846.6
		Y1	167	106	63.5	55.7	70.8	75	44.9	37.2	52.8	62.7	42.6	92.2
		Y3	147	69	46.9	38.7	55.3	50	34.0	26.4	42.3	29.7	19.8	44.5
		Y5	133	78	58.6	49.8	67.1	58	43.6	35.0	52.5	46.8	30.7	71.5
	ACWY2d	PRE	153	7	4.6	1.9	9.2	5	3.3	1.1	7.5	4.7	4.1	5.4
		PI (M1)	158	153	96.8	92.8	99.0	151	95.6	91.1	98.2	1275.2	970.5	1675.4
		PII (M3)	150	147	98.0	94.3	99.6	142	94.7	89.8	97.7	1176.3	921.8	1501.0
		Y1	143	101	70.6	62.4	77.9	72	50.3	41.9	58.8	76.6	50.7	115.7
		Y3	121	66	54.5	45.2	63.6	38	31.4	23.3	40.5	28.5	18.7	43.6
		Y5	117	77	65.8	56.5	74.3	62	53.0	43.5	62.3	69.9	44.7	109.3
	Co-ad	PRE	169	4	2.4	0.6	5.9	2	1.2	0.1	4.2	4.2	4.0	4.5
		PI (M1)	178	169	94.9	90.6	97.7	167	93.8	89.2	96.9	1146.4	867.9	1514.3
		Y1	173	115	66.5	58.9	73.5	74	42.8	35.3	50.5	59.5	40.7	87.2
		Y3	151	77	51.0	42.7	59.2	59	39.1	31.2	47.3	38.6	25.4	58.8
		Y5	142	65	45.8	37.4	54.3	27	19.0	12.9	26.4	15.4	11.1	21.3
	PCV13	PRE	171	5	2.9	1.0	6.7	2	1.2	0.1	4.2	4.3	4.0	4.6
		PII (M3)	169	163	96.4	92.4	98.7	162	95.9	91.7	98.3	1957.7	1513.4	2532.3
		Y1	169	119	70.4	62.9	77.2	95	56.2	48.4	63.8	119.4	79.5	179.3
		Y3	132	71	53.8	44.9	62.5	53	40.2	31.7	49.0	42.3	27.2	65.6
		Y5	129	61	47.3	38.4	56.3	47	36.4	28.1	45.4	28.3	18.5	43.2
rSBA-MenC	ACWY1d	PRE	175	5	2.9	0.9	6.5	2	1.1	0.1	4.1	4.4	4.0	4.8
		PI (M1)	179	170	95.0	90.7	97.7	153	85.5	79.4	90.3	452.3	345.6	591.9
		Y1	167	82	49.1	41.3	56.9	35	21.0	15.1	27.9	16.2	12.4	21.1
		Y3	147	52	35.4	27.7	43.7	14	9.5	5.3	15.5	9.8	7.6	12.7
		Y5	132	27	20.5	13.9	28.3	8	6.1	2.7	11.6	6.6	5.3	8.2
	ACWY2d	PRE	153	1	0.7	0.0	3.6	1	0.7	0.0	3.6	4.2	3.8	4.5
		PI (M1)	157	150	95.5	91.0	98.2	134	85.4	78.8	90.5	369.3	280.9	485.5
		PII (M3)	150	148	98.7	95.3	99.8	145	96.7	92.4	98.9	639.1	521.8	782.9
		Y1	143	79	55.2	46.7	63.6	39	27.3	20.2	35.3	21.2	15.6	28.9
		Y3	121	41	33.9	25.5	43.0	19	15.7	9.7	23.4	11.5	8.4	15.8

				≥1:8				≥1:128				GMT		
					95% CI				95% CI				95% CI	
Antibody	Vaccine Group	Visit	N	n	%	LL	UL	n	%	LL	UL	Value	LL	UL
		Y5	116	33	28.4	20.5	37.6	12	10.3	5.5	17.4	8.5	6.4	11.2
	Co-ad	PRE	170	2	1.2	0.1	4.2	1	0.6	0.0	3.2	4.1	3.9	4.4
		PI (M1)	176	169	96.0	92.0	98.4	155	88.1	82.3	92.5	337.3	263.8	431.1
		Y1	171	73	42.7	35.2	50.5	27	15.8	10.7	22.1	12.6	10.0	16.0
		Y3	151	43	28.5	21.4	36.4	22	14.6	9.4	21.2	9.1	7.1	11.6
		Y5	142	34	23.9	17.2	31.8	17	12.0	7.1	18.5	7.9	6.2	10.0
	PCV13	PRE	171	0	0.0	0.0	2.1	0	0.0	0.0	2.1	4.0	NE	NE
		PII (M3)	169	161	95.3	90.9	97.9	145	85.8	79.6	90.7	376.4	284.7	497.6
		Y1	169	85	50.3	42.5	58.1	34	20.1	14.4	27.0	16.0	12.2	20.9
		Y3	132	42	31.8	24.0	40.5	14	10.6	5.9	17.2	9.3	7.1	12.1
		Y5	129	25	19.4	13.0	27.3	10	7.8	3.8	13.8	7.0	5.5	8.8
rSBA-MenW-135	ACWY1d	PRE	175	4	2.3	0.6	5.7	4	2.3	0.6	5.7	4.5	4.0	5.1
		PI (M1)	180	171	95.0	90.7	97.7	171	95.0	90.7	97.7	2120.2	1601.0	2807.8
		Y1	167	109	65.3	57.5	72.5	78	46.7	39.0	54.6	57.2	39.9	82.0
		Y3	147	87	59.2	50.8	67.2	63	42.9	34.7	51.3	42.5	29.2	61.8
		Y5	133	59	44.4	35.8	53.2	43	32.3	24.5	41.0	25.0	16.7	37.6
	ACWY2d	PRE	153	4	2.6	0.7	6.6	3	2.0	0.4	5.6	4.4	4.0	4.8
		PI (M1)	158	150	94.9	90.3	97.8	149	94.3	89.5	97.4	2030.1	1510.7	2728.2
		PII (M3)	150	150	100.0	97.6	100.0	149	99.3	96.3	100.0	3533.0	2914.5	4282.7
		Y1	143	111	77.6	69.9	84.2	86	60.1	51.6	68.2	123.1	82.7	183.4
		Y3	121	88	72.7	63.9	80.4	64	52.9	43.6	62.0	92.9	59.9	143.9
		Y5	117	59	50.4	41.0	59.8	46	39.3	30.4	48.8	37.1	23.3	59.0
	Co-ad	PRE	169	2	1.2	0.1	4.2	2	1.2	0.1	4.2	4.2	3.9	4.5
		PI (M1)	177	165	93.2	88.5	96.4	164	92.7	87.8	96.0	1550.9	1137.4	2114.7
		Y1	171	103	60.2	52.5	67.6	73	42.7	35.2	50.5	52.0	35.5	76.4
		Y3	151	80	53.0	44.7	61.1	59	39.1	31.2	47.3	34.4	23.4	50.6
		Y5	142	61	43.0	34.7	51.5	48	33.8	26.1	42.2	26.2	17.6	39.0
	PCV13	PRE	171	2	1.2	0.1	4.2	2	1.2	0.1	4.2	4.2	3.9	4.6
		PII (M3)	169	163	96.4	92.4	98.7	163	96.4	92.4	98.7	3490.5	2643.3	4609.3
		Y1	169	123	72.8	65.4	79.3	98	58.0	50.2	65.5	109.5	75.0	160.0
		Y3	132	75	56.8	47.9	65.4	56	42.4	33.9	51.3	44.5	28.9	68.7

					≥1:8				≥1:128			GMT		
						95% CI				95% CI			95% CI	
Antibody	Vaccine Group	Visit	N	n	%	LL	UL	n	%	LL	UL	Value	LL	UL
rSBA-MenY	ACWY1d	Y5	129	58	45.0	36.2	54.0	46	35.7	27.4	44.6	31.7	20.2	49.6
		PRE	175	17	9.7	5.8	15.1	16	9.1	5.3	14.4	6.0	5.0	7.3
		PI (M1)	180	167	92.8	88.0	96.1	163	90.6	85.3	94.4	951.8	705.0	1284.9
		Y1	167	122	73.1	65.7	79.6	87	52.1	44.2	59.9	76.8	54.2	109.0
		Y3	147	91	61.9	53.5	69.8	72	49.0	40.7	57.3	58.0	39.1	86.0
		Y5	133	63	47.4	38.7	56.2	53	39.8	31.5	48.7	36.5	23.6	56.2
	ACWY2d	PRE	153	8	5.2	2.3	10.0	8	5.2	2.3	10.0	5.2	4.3	6.1
		PI (M1)	157	147	93.6	88.6	96.9	144	91.7	86.3	95.5	933.3	692.3	1258.3
		PII (M3)	150	149	99.3	96.3	100.0	149	99.3	96.3	100.0	1133.6	944.5	1360.5
		Y1	143	114	79.7	72.2	86.0	87	60.8	52.3	68.9	112.3	77.5	162.8
		Y3	121	83	68.6	59.5	76.7	65	53.7	44.4	62.8	75.1	48.7	115.9
		Y5	117	68	58.1	48.6	67.2	61	52.1	42.7	61.5	55.8	35.7	87.5
	Co-ad	PRE	169	10	5.9	2.9	10.6	9	5.3	2.5	9.9	5.1	4.4	6.0
		PI (M1)	177	159	89.8	84.4	93.9	158	89.3	83.7	93.4	778.5	566.2	1070.4
		Y1	173	116	67.1	59.5	74.0	93	53.8	46.0	61.4	70.7	49.0	102.1
		Y3	151	95	62.9	54.7	70.6	80	53.0	44.7	61.1	67.6	45.6	100.3
		Y5	142	75	52.8	44.3	61.2	60	42.3	34.0	50.8	43.3	28.3	66.2
	PCV13	PRE	171	12	7.0	3.7	11.9	10	5.8	2.8	10.5	5.2	4.5	6.1
		PII (M3)	169	164	97.0	93.2	99.0	164	97.0	93.2	99.0	1481.2	1158.4	1893.9
		Y1	169	136	80.5	73.7	86.2	117	69.2	61.7	76.1	169.2	119.2	240.1
		Y3	132	97	73.5	65.1	80.8	79	59.8	51.0	68.3	106.0	70.2	160.0
		Y5	129	72	55.8	46.8	64.5	62	48.1	39.2	57.0	53.9	34.5	84.2

Abbreviations: 95% CI = 95% confidence interval; ATP = according-to-protocol; GMT = geometric mean antibody titer calculated for all subjects; LL = lower limit; NE = not estimable; rSBA-MenA, rSBA-MenC, rSBA-MenW-135, and rSBA-MenY = serum bactericidal assay using rabbit complement to measure activity against *Neisseria meningitidis* group A, group C, group W-135, and group Y; UL = upper limit.
N = number of subjects with available data.
n = Number of subjects with titer within the specified range.
% = Percentage of subjects with titer within the specified range.
ACWY1d = subjects who received 1 dose of MenACWY-TT at Month 0.
ACWY2d = subjects who received 2 doses of MenACWY-TT at Month 0 and Month 2.

Table 3 presents the number and percentage of participants with hSBA titres equal to or above the cut-off values (1:4 and 1:8) and GMTs for the adapted ATP cohort.

At 5 years after the last vaccination (first or second dose), the percentages of participants achieving hSBA titres ≥1:8 in the ACWY1d and ACWY2d groups were 27.9% and 17.9%, respectively, for hSBA-MenA; 60.7% and 67.8%, respectively, for hSBA-MenC; 58.9% and 63.6%, respectively, for hSBA-MenW-135; and 61.5% and 54.2%, respectively, for hSBA-MenY.

GMTs 5 years after the last vaccination for participants in the ACWY1d and ACWY2d groups were 4.4 and 3.1, respectively, for hSBA-MenA; 18.1 and 29.4, respectively, for hSBA-MenC; 20.8 and 19.5, respectively, for hSBA-MenW-135; and 24.3 and 16.8, respectively, for hSBA-MenY. Compared to prevaccination levels, GMTs for each group were higher at 5 years after vaccination.

Table 3. Number and Percentage of Subjects With hSBA-MenA, hSBA-MenC, hSBA-MenW-135, and hSBA-MenY Titres Equal to or Above the Cut-off Values (1:4 and 1:8) and GMTs (Adapted ATP Cohort)

				≥1:4				≥1:8				GMT		
					95% CI				95% CI			95% CI		
Antibody	Vaccine Group	Visit	N	n	%	LL	UL	n	%	LL	UL	Value	LL	UL
hSBA-MenA	ACWY1d	PRE	78	6	7.7	2.9	16.0	6	7.7	2.9	16.0	2.4	2.1	2.8
		PI (M1)	74	71	95.9	88.6	99.2	71	95.9	88.6	99.2	118.0	86.8	160.5
		Y1	70	26	37.1	25.9	49.5	25	35.7	24.6	48.1	6.1	4.1	8.9
		Y3	55	20	36.4	23.8	50.4	20	36.4	23.8	50.4	5.8	3.8	8.9
		Y5	61	17	27.9	17.1	40.8	17	27.9	17.1	40.8	4.4	3.1	6.2
	ACWY2d	PRE	62	6	9.7	3.6	19.9	6	9.7	3.6	19.9	2.6	2.1	3.2
		PI (M1)	66	64	97.0	89.5	99.6	64	97.0	89.5	99.6	132.9	98.1	180.1
		PII (M3)	66	64	97.0	89.5	99.6	64	97.0	89.5	99.6	170.5	126.2	230.2
		Y1	62	22	35.5	23.7	48.7	22	35.5	23.7	48.7	6.4	4.2	10.0
		Y3	50	18	36.0	22.9	50.8	18	36.0	22.9	50.8	5.4	3.6	8.0
		Y5	56	10	17.9	8.9	30.4	10	17.9	8.9	30.4	3.1	2.4	4.0
hSBA-MenC	ACWY1d	PRE	82	3	3.7	0.8	10.3	3	3.7	0.8	10.3	2.2	2.0	2.4
		PI (M1)	78	77	98.7	93.1	100.0	77	98.7	93.1	100.0	151.9	104.8	220.4
		Y1	71	58	81.7	70.7	89.9	57	80.3	69.1	88.8	35.2	22.5	55.2
		Y3	61	40	65.6	52.3	77.3	40	65.6	52.3	77.3	23.6	13.9	40.2
		Y5	61	37	60.7	47.3	72.9	37	60.7	47.3	72.9	18.1	10.9	30.0
	ACWY2d	PRE	66	0	0.0	0.0	5.4	0	0.0	0.0	5.4	2.0	NE	NE
		PI (M1)	70	68	97.1	90.1	99.7	67	95.7	88.0	99.1	160.8	109.8	235.5
		PII (M3)	69	69	100.0	94.8	100.0	69	100.0	94.8	100.0	1753.3	1278.7	2404.2
		Y1	63	59	93.7	84.5	98.2	57	90.5	80.4	96.4	73.4	47.5	113.4
		Y3	56	38	67.9	54.0	79.7	38	67.9	54.0	79.7	27.0	15.6	46.8
		Y5	59	40	67.8	54.4	79.4	40	67.8	54.4	79.4	29.4	16.3	52.9

				≥1:4				≥1:8				GMT		
					95% CI				95% CI			95% CI		
Antibody	Vaccine Group	Visit	N	n	%	LL	UL	n	%	LL	UL	Value	LL	UL
hSBA-MenW-135	ACWY1d	PRE	73	1	1.4	0.0	7.4	1	1.4	0.0	7.4	2.2	1.8	2.6
		PI (M1)	72	45	62.5	50.3	73.6	45	62.5	50.3	73.6	27.5	16.1	46.8
		Y1	72	69	95.8	88.3	99.1	69	95.8	88.3	99.1	209.0	149.9	291.4
		Y3	67	48	71.6	59.3	82.0	48	71.6	59.3	82.0	30.5	18.7	49.6
		Y5	56	33	58.9	45.0	71.9	33	58.9	45.0	71.9	20.8	11.6	37.1
	ACWY2d	PRE	62	0	0.0	0.0	5.8	0	0.0	0.0	5.8	2.0	NE	NE
		PI (M1)	61	42	68.9	55.7	80.1	42	68.9	55.7	80.1	26.2	16.0	43.0
		PII (M3)	70	68	97.1	90.1	99.7	68	97.1	90.1	99.7	756.8	550.1	1041.3
		Y1	65	64	98.5	91.7	100.0	64	98.5	91.7	100.0	232.6	168.3	321.4
		Y3	54	47	87.0	75.1	94.6	47	87.0	75.1	94.6	55.5	35.3	87.1
		Y5	44	28	63.6	47.8	77.6	28	63.6	47.8	77.6	19.5	10.7	35.2
hSBA-MenY	ACWY1d	PRE	65	4	6.2	1.7	15.0	4	6.2	1.7	15.0	2.5	2.0	3.1
		PI (M1)	71	48	67.6	55.5	78.2	48	67.6	55.5	78.2	41.2	23.7	71.5
		Y1	62	57	91.9	82.2	97.3	57	91.9	82.2	97.3	144.4	97.2	214.5
		Y3	64	34	53.1	40.2	65.7	34	53.1	40.2	65.7	17.3	10.1	29.6
		Y5	65	40	61.5	48.6	73.3	40	61.5	48.6	73.3	24.3	14.3	41.1
	ACWY2d	PRE	60	5	8.3	2.8	18.4	5	8.3	2.8	18.4	2.5	2.1	3.0
		PI (M1)	56	36	64.3	50.4	76.6	36	64.3	50.4	76.6	31.9	17.6	57.9
		PII (M3)	64	61	95.3	86.9	99.0	61	95.3	86.9	99.0	513.0	339.4	775.4
		Y1	58	51	87.9	76.7	95.0	51	87.9	76.7	95.0	143.9	88.5	233.8
		Y3	52	32	61.5	47.0	74.7	32	61.5	47.0	74.7	24.1	13.3	43.8
		Y5	48	26	54.2	39.2	68.6	26	54.2	39.2	68.6	16.8	9.0	31.3

Abbreviations: 95% CI = 95% confidence interval; ATP = according-to-protocol; GMT = geometric mean antibody titer calculated for all subjects; hSBA-MenA, hSBA-MenC, hSBA-MenW-135, and hSBA-MenY = serum bactericidal assay using human complement to measure activity against *Neisseria meningitidis* group A, group C, group W-135, and group Y; LL = lower limit; NE = not estimable; UL = upper limit.
N = number of subjects with available data.
n = Number of subjects with titer within the specified range.
% = Percentage of subjects with titer within the specified range.
ACWY1d = subjects who received 1 dose of MenACWY-TT at Month 0.
ACWY2d = subjects who received 2 doses of MenACWY-TT at Month 0 and Month 2.
PRE = at Month 0, before first vaccine dose.
PI (M1) = at Month 1, 1 month after vaccine dose at Month 0.
PII (M3) = at Month 3, 1 month after vaccine dose at Month 2.
Y1 = one (1) year after last primary vaccine dose.
Y3 = three (3) years after last primary vaccine dose.
Y5 = five (5) years after last primary vaccine dose.
Program ID: Study MenACWY-TT-104 (C0921003)/CP IMM_FREQ.SAS. Date of Reporting Dataset Creation: 27MAY2021. Runtime ID: 03JUN2021 01:27. File ID: 28_IMM_H_ATP.HTM.

6.3. Discussion

As there are currently no description of the long-term antibody persistence in the Nimenrix SmPC, the inclusion of Table 5 in the SmPC (see section 5.1 in Nimenrix SmPC) is welcomed. Nimenrix elicited hSBA titres against groups W-135 and Y that were higher in terms of the percentage of subjects with hSBA titre ≥8 when two doses were given compared with one, as also stated in the SmPC. This is correct when looking at the data one month following one or two doses (administered two months apart). However, looking at the hSBA data from Year 5, the difference in long-term antibody persistence against groups W-135 and Y after one or two doses is small (see Table 3). Nimenrix elicited hSBA titres against groups A and C that were similar in terms of the percentage of subjects with hSBA titre ≥8 when two doses were given compared with one, as also stated in the SmPC. The hSBA titres against groups A and C after one or two doses is similar also at Year 5 (see Table 3). The hSBA data, hence, indicates that the long-term antibody persistence is similar, regardless of one or two doses, for all groups.

There is a more pronounced decline in the hSBA titres against group A, compared to groups C, W-135 and Y. The decline is especially clear from one month post dose one or two to Year 1, while the drop is less pronounced at Years 3 and 5.

The long-term antibody persistence should be mentioned the text in section 5.1 in the SmPC. The Rapporteur proposes to add the following text under the sub headline "Long-term immunogenicity in toddlers" (new text in italic): *One month post dose one or two* Nimenrix elicited hSBA titres against groups W-135 and Y that were higher in terms of the percentage of subjects with hSBA titre ≥8 when two doses were given compared with one (see section 4.4). Nimenrix elicited hSBA titres against groups A and C that were similar in terms of the percentage of subjects with hSBA titre ≥8 when two doses were given compared with one. *At Year 5 only a small difference in antibody persistence between one and two doses was observed, in terms of percentages of subjects with hSBA titres > 8 against all groups. There was antibody persistence observed at Year 5 against groups C, W-135 and Y, with percentages of subjects with hSBA titres > 8 against group C being 60.7% and 67.8% after one and two doses, respectively, 58.9% and 63.6% against group W-135 and 61.5% and 54.2% against group Y. For group A, 27.9% and 17.9% of subjects receiving one or two doses, respectively, had hSBA titres > 8* (see also section 5.1 in the SmPC).

An updated SmPC text with minor revisions has been received from the MAH (see section 2 of this assessment report). This text is considered approvable.

The obligation to evaluate long-term immunogenicity (5 years) is considered fulfilled and can be deleted from Annex II.D in the Nimenrix Product Information.

7. Clinical Safety aspects

7.1. Methods – analysis of data submitted

Not applicable.

7.2. Results

No new safety data has been provided with this variation.

7.3. Discussion

Not applicable.

8. PRAC advice

Not applicable.

9. Changes to the Product Information

As a result of this variation, section 5.1 of the SmPC are being updated to include long-term antibody persistence data from study MenACWY-TT-104 and to demonstrate non-inferiority of co-administration of MenACWY-TT and 13-valent pneumococcal conjugate vaccine prevenar 13 versus separate administration of the two vaccines, following the conclusion of EMEA/H/C/002226/P46/055 procedure.

Changes are made to the Opinion Annex II conditions as detailed in the recommendations section above.

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

10. Assessment of the responses to the request for supplementary information

10.1. Major objections

Not applicable.

10.2. Other concerns

Question

The variation is considered approvable given that the MAH agrees to the proposed changes in the Nimenrix SmPC.

Summary of the MAH's response

The MAH accepted the recommendation to include additional text in the SmPC with minor revisions. An updated SmPC text with the minor revisions was received from the MAH "*Antibody persistence was observed at Year 5 against groups C, W-135 and Y. After one and two doses the percentages of*

subjects with hSBA titres ≥8 for group C were 60.7% and 67.8%, group W-135 were 58.9% and 63.6% and group Y were 61.5% and 54.2%, respectively".

Assessment of the MAH's response

The text is considered approvable.

Conclusion

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☐No need to update overall conclusion and impact on benefit-risk balance

11. Attachments

Product Information (changes highlighted) as adopted by the CHMP on 31 March 2022.

12. Appendix

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006 - EMEA/H/C/002226/P46/055

12. Appendix

Amsterdam, 11 November 2021
EMA/233264/2022
Human Medicines Division

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

Nimenrix

meningococcal group a, c, w135 and y conjugate vaccine

Procedure no: EMEA/H/C/002226/P46/055

Note

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

Table of contents

1. Introduction

On 30 March 2021, the marketing authorization holder (MAH) submitted a completed paediatric study for MenACWY-TT-104 (C0921003), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

These data are also submitted as part of the post-authorisation measure: ANX 013.4. The previous assessment report was circulated with rSBA 5-year data only. This current report includes 5-year data for hSBA.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study MenACWY-TT-104 is a stand-alone study.

2.2. Information on the pharmaceutical formulation used in the study

Nimenrix was first licensed to GlaxoSmithKline (GSK) for use in the European Union on 20 April 2012 (EMEA/H/C/00226) as a single dose vaccine for the active immunization of individuals from the age of 12 months and above, against invasive meningococcal disease caused by Neisseria meningitidis groups A, C, W-135, and Y. In October 2015, the vaccine was acquired by Pfizer, the present MAH. The expanded indication to include individuals from 6 weeks of age was approved on 12 December 2016.

2.3. Clinical aspects

2.3.1. Introduction

This report covers the following post-authorisation commitments undertaken by the MAH:

Post-Authorisation Measure (PAM ANX 013.4) covers submission of the 5-year antibody persistence data from study MenACWY-TT-104 (C0921003) as detailed in Annex II of the PI:

Description	Due date
Study to evaluate immediate and longer term antibody titres elicited by one or two doses of Nimenrix administered in children aged 12-23 months. The safety and antibody persistence data up to year 5 and the data on co-administration of MenACWY-TT with Prevenar 13 will be provided in sequential study reports at 1, 3 and 5 years after vaccination.	1 year CSR Q1 2017 3 year CSR Q1 2019 5 year CSR Q1 2021

The initial CSR included the safety and immunogenicity results up to one month after vaccination with one or two doses of Nimenrix (MenACWY-TT) in toddlers. The current submission provides the CSR for the data at 5 years and also including a summary of all time points up to 5 years.

2.3.2. Clinical study

MenACWY-TT-104 (C0921003); formerly GlaxoSmithKline Study 116892

Title: Final report (Year 5 report): A Phase III, Randomised, Open, Controlled, Multicentre, Primary Vaccination Study to Evaluate the Immunogenicity and Persistence of 1 and 2 Doses of Meningococcal Conjugate Vaccine MenACWY-TT in Toddlers (After 1 Month and up to 5 Years) and to Demonstrate Non-Inferiority of Co-Administration of MenACWY-TT and 13- Valent Pneumococcal Conjugate Vaccine Prevenar 13 (Registered) Versus Separate Administration of the 2 Vaccines.

Description

Context of the Study

Study MenACWY-TT-104 (C0921003) was designed to evaluate the immunogenicity after 1 month and the persistence of the response up to 5 years following 1 and 2 doses of MenACWY-TT administered to toddlers aged 12 to 14 months. This study was also conducted to demonstrate that co-administration of MenACWY-TT with a booster dose of 13-valent pneumococcal conjugate vaccine (Prevenar 13) does not adversely impact the immunogenicity of either vaccines.

Results relating to the immunogenicity endpoints for the primary time-point (up to one month after each vaccination) were previously reported in the Main Clinical Study Report (MenACWY-TT-104 CSR, dated 28 July 2015). Immunogenicity endpoints that assessed the antibody persistence 1 year and 3 years after vaccination were previously reported in the Year 1 Clinical Study Report (MenACWY-TT-104 Year 1 CSR, dated 15 March 2017) and the Year 3 Clinical Study Report (MenACWY-TT-104 Year 3 CSR, dated 19 December 2019).

Only those objectives relating to the immunogenicity endpoints at 5 years after vaccination and safety results for Year 3 through Year 5 are described here, but to provide context, immunogenicity data for all 4 time-points (1 month, 1 year, 3 years and 5 years after vaccination) will be presented.

Methods

Study design

MenACWY-TT-104 (C0921003) was a Phase 3, open-label, randomized, controlled, multicenter study designed to evaluate the immunogenicity after 1 month and the persistence of the response up to 5 years following 1 and 2 doses (given 2 months apart) of MenACWY-TT in toddlers aged 12 to 14 months and to demonstrate non-inferiority of co-administration of MenACWY-TT and Prevenar 13 (PCV13), versus separate administration of the 2 vaccines. Subjects were randomized to 4 parallel groups of approximately 200 subjects each to receive:

- ACWY1d group: 1 dose of MenACWY-TT at Month 0;
- ACWY2d group: 2 doses of MenACWY-TT at Month 0 and Month 2;
- Co-ad group: 1 dose of MenACWY-TT and 1 dose of PCV13 at Month 0;
- PCV13 group: 1 dose of PCV13 at Month 0 and 1 dose of MenACWY-TT at Month 2

The planned duration of the study was 62 months for each subject. For the Year 5 time-point, the subjects in the Co-ad and the ACWY1d groups were to be 72 to 74 months of age and the subjects in the ACWY2d and PCV13 groups were to be 74 to 76 months of age.

Treatments

Nimenrix (MenACWY-TT) and Prevenar 13 (PCV13).

Objectives/endpoints

Immunogenicity Objectives and Endpoints

The primary immunogenicity objective of the study for Year 5 was to evaluate the long-term persistence of the immune response induced by 1 or 2 doses of MenACWY-TT in terms of the percentage of subjects at Year 5 with serum bactericidal assay using rabbit complement (rSBA) titers ≥1:8 and ≥1:128 for each of the 4 meningococcal groups, and geometric mean titers (GMTs) in the ACWY1d and ACWY2d groups.

The first secondary immunogenicity objective relating to the hSBA immunogenicity endpoint at five years after vaccination was to evaluate the long-term persistence of the immune response induced by one or two doses of MenACWY-TT in terms of percentage of participants at Year 5 with serum bactericidal assay using human complement (hSBA) titers ≥1:4 and ≥1:8, and geometric means titers (GMTs) in a subset of participants in the ACWY1d and ACWY2d groups.

The second secondary immunogenicity objective was to evaluate the long-term persistence of the immune response induced by 1 dose of MenACWY-TT in Co-ad and PCV13 groups in terms of the percentage of subjects at Year 5 with rSBA titres ≥1:8 and ≥1:28 for each of the 4 meningococcal groups, and GMTs.

Safety Objectives and Endpoints

The secondary safety objective for Year 5 was to evaluate the occurrence of serious adverse events (SAEs) related to study vaccine administration and any events (AE/SAE) related to lack of vaccine efficacy (i.e. meningococcal disease) from 3 years to 5 years after the last vaccination.

Statistical Methods

The numbers and percentages of subjects for immunogenicity and safety endpoints were tabulated with exact 95% CIs by vaccine group. The GMT calculations were performed by taking the anti-log of the mean of the log titer transformations. Antibody titers below the cutoff of the assay were given a value of half the cutoff for the purpose of GMT calculation.

Results

Recruitment/Number analysed

Study population

A summary of the study population at 5 years after the last vaccination is presented in Table 1. Of the 802 subjects randomized in the study, 619 subjects completed the study through Year 5. The proportion of randomized subjects completing through Year 5 was similar across the 4 vaccine groups. For the according-to-protocol (ATP) cohort for persistence at Year 5, the mean age was 73.4 months and 54.3% of the subjects were male. Subject characteristics in all vaccine groups were similar with respect to age, months since last vaccination, sex, ethnicity, geographic ancestry, and the number of previous PCV13 doses received.

Table 1. Study population. Persistence phase at Year 5 (Total Cohort Year 5)

Vaccine Group	ACWY1d	ACWY2d	Co-ad	PCV13	Tota
Planned, N	200	200	200	200	800
Randomized, N (total vaccinated cohort)	203	197	201	201	802
N (total cohort Year 5)	156	146	160	157	619
Completed Year 5, N (%)	156 (100.0)	146	160	157 (100.0)	619 (100.0)
Females:males	72:84	65:81	77:83	75:8	289:330
Mean age, months (SD)	72.5 (1.5)	74.4 (1.4)	72.5 (1.4)	74.5 (1.4)	73.5 (1.7)
Median age, months (minimum, maximum)	72.0 (69, 76)	74.0 (72,	72.5 (70,	74.0 (71, 78)	74.0 (69, 78)
Geographic ancestry					
African heritage/African American, n (%)	27 (17.3)	27 (18.5)	26 (16.3)	22 (14.0)	102 (16.5)
American Indian or Alaskan Native, n (%)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.2)
Asian - East Asian heritage, n (%)	0 (0.0)	0 (0.0)	2 (1.3)	2 (1.3)	4 (0.6)
Asian - Japanese heritage, n (%)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.2)
Asian - South East Asian heritage, n (%)	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.6)	2 (0.3)
Native Hawaiian or Other Pacific Islander, n (%)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.6)	2 (0.3)
White - Arabic/North African heritage, n (%)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.6)	2 (0.3)
White - Caucasian/European heritage, n (%)	108 (69.2)	101 (69.2)	112 (70.0)	115 (73.2)	436 (70.4)
Other, n (%)	21 (13.5)	16 (11.0)	17 (10.6)	15 (9.6)	69 (11.1)
Ethnicity					
American Hispanic or Latino, n (%)	4 (2.6)	5 (3.4)	5 (3.1)	4 (2.5)	18 (2.9)
Not American Hispanic or Latino, n (%)	152 (97.4)	141 (96.6)	155 (96.9)	153 (97.5)	601 (97.1)

Note: Age is calculated using visit date at Year 5.
Note: "Completed Year 5" includes subjects who returned for the Year 5 visit.
Note: For the "Planned, N" row, the number of subjects is based on the target enrollment of approximately 800 subjects (200 per study group).
Note: For the "Randomized, N (total vaccinated cohort)" row, the number of subjects is the number of randomized subjects who received at least 1 study vaccination.
ACWY1d = subjects who received 1 dose of MenACWY-TT at Month 0.
ACWY2d = subjects who received 2 doses of MenACWY-TT at Month 0 and Month 2.
Co-ad = subjects who received 1 dose of MenACWY-TT and 1 dose of Prevenar 13 at Month 0.
PCV13 = subjects who received 1 dose of Prevenar 13 at Month 0 and 1 dose of MenACWY-TT at Month 2.
N = number of subjects in each vaccine group. These values are used as the denominators for the percentage calculations. n = Number of subjects within each category.
% = Percentage of subjects within each category.

Table 2. Disposition of Subject

Vaccine Group	ACWY1d		ACWY2d		Co-ad		PCV13		Total	
	n	%	n	%	n	%	n	%	n	%
Enrolled	203	N/A	198	N/A	20	N/A	201	N/A	803	N/A
Total vaccinated cohort	203	100.0	197	99.5	20	100.0	201	100.0	802	99.9
Number of subjects who returned at Year 5	156	76.8	146	73.7	16	79.6	157	78.1	619	77.1
Number of subjects withdrawn from Month 0 to Year 5	47	23.2	52	26.3	41	20.4	44	21.9	184	22.9
Reason for withdrawal										
Serious adverse event	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Nonserious adverse event	1	0.5	0	0.0	0	0.0	0	0.0	1	0.1
Protocol violation	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Consent withdrawal (not due to an adverse event)	22	10.8	25	12.6	15	7.5	17	8.5	79	9.8
Migrated/moved from study area	5	2.5	7	3.5	3	1.5	6	3.0	21	2.6
Lost to follow-up	18	8.9	17	8.6	17	8.5	17	8.5	69	8.6
Subject died	0	0.0	0	0.0	1	0.5	1	0.5	2	0.2
Sponsor study termination	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
No longer meets eligibility criteria	0	0.0	0	0.0	1	0.5	0	0.0	1	0.1
Other reason	1	0.5	3	1.5	4	2.0	3	1.5	11	1.4

Abbreviation: N/A = not applicable.

Note: Subject 104-205082-204 was randomized to ACWY2d but was withdrawn from study due to consent withdrawal. This subject is included in this table but does not belong to total vaccinated cohort.
ACWY1d = subjects who received 1 dose of MenACWY-TT at Month 0.
ACWY2d = subjects who received 2 doses of MenACWY-TT at Month 0 and Month 2.
Co-ad = subjects who received 1 dose of MenACWY-TT and 1 dose of Prevenar 13 at Month 0.
PCV13 = subjects who received 1 dose of Prevenar 13 at Month 0 and 1 dose of MenACWY-TT at Month 2. n = Number of subjects in each group with the specified characteristic.
% = Percentage of subjects in each group with the specified characteristic.

Efficacy results

rSBA results

The primary objective of the Year 5 analysis was to evaluate the long-term persistence of the immune response in subjects who received 1 or 2 doses of MenACWY-TT with respect to rSBA-MenA, rSBA-MenC, rSBA-MenW-135, and rSBA-MenY titers in the ACWY1d and ACWY2d groups.

Table 3 presents the number and percentage of participants with rSBA titers greater than or equal to the cutoff values (1:8 and 1:128) and GMTs for the adapted ATP cohort. Number and percentages of participants with rSBA titers ≥1:8 in the ACWY1d and ACWY2d groups were low before vaccination and were increased at 1 month and 1 year after the last vaccination (see MenACWY-TT-104 [C0921003] Year 1 CSR for a full discussion of these results).

At 5 years after the last vaccination (first or second dose), the percentages of subjects achieving rSBA titers ≥1:8 in the ACWY1d and ACWY2d groups were 58.6% and 65.8%, respectively, for rSBA-MenA; 20.5% and 28.4%, respectively, for rSBA-MenC; 44.4% and 50.4%, respectively, for rSBA-MenW-135; and 47.4% and 58.1%, respectively, for rSBA-MenY. rSBA-MenW-135 titers in the ACWY2d group were slightly elevated compared to the ACWY1d group.

Table 3. Number and Percentages of Subject With rSBA-MenA, rSBA-MenC, rSBA-MenW-135, and rSBA-MenY Titers Equal to or Above the Cutoff Values (1:8 and 1:128) and GMTs (Adapted ATP Cohort)

			≥1:8					≥1:128				GMT		
					95% CI				95% CI			95% CI		
Antibody	Vaccine Group	Visit	N	n	%	LL	UL	n	%	LL	UL	Value	LL	UL
rSBA-MenA	ACWY1d	PRE	175	5	2.9	0.9	6.5	2	1.1	0.1	4.1	4.3	4.0	4.6
		PI (M1)	180	176	97.8	94.4	99.4	170	94.4	90.0	97.3	1437.0	1118.3	1846.6
		Y1	167	106	63.5	55.7	70.8	75	44.9	37.2	52.8	62.7	42.6	92.2
		Y3	147	69	46.9	38.7	55.3	50	34.0	26.4	42.3	29.7	19.8	44.5
		Y5	133	78	58.6	49.8	67.1	58	43.6	35.0	52.5	46.8	30.7	71.5
	ACWY2d	PRE	153	7	4.6	1.9	9.2	5	3.3	1.1	7.5	4.7	4.1	5.4
		PI (M1)	158	153	96.8	92.8	99.0	151	95.6	91.1	98.2	1275.2	970.5	1675.4
		PII (M3)	150	147	98.0	94.3	99.6	142	94.7	89.8	97.7	1176.3	921.8	1501.0
		Y1	143	101	70.6	62.4	77.9	72	50.3	41.9	58.8	76.6	50.7	115.7
		Y3	121	66	54.5	45.2	63.6	38	31.4	23.3	40.5	28.5	18.7	43.6
		Y5	117	77	65.8	56.5	74.3	62	53.0	43.5	62.3	69.9	44.7	109.3
	Co-ad	PRE	169	4	2.4	0.6	5.9	2	1.2	0.1	4.2	4.2	4.0	4.5
		PI (M1)	178	169	94.9	90.6	97.7	167	93.8	89.2	96.9	1146.4	867.9	1514.3
		Y1	173	115	66.5	58.9	73.5	74	42.8	35.3	50.5	59.5	40.7	87.2
		Y3	151	77	51.0	42.7	59.2	59	39.1	31.2	47.3	38.6	25.4	58.8
		Y5	142	65	45.8	37.4	54.3	27	19.0	12.9	26.4	15.4	11.1	21.3
	PCV13	PRE	171	5	2.9	1.0	6.7	2	1.2	0.1	4.2	4.3	4.0	4.6
		PII (M3)	169	163	96.4	92.4	98.7	162	95.9	91.7	98.3	1957.7	1513.4	2532.3
		Y1	169	119	70.4	62.9	77.2	95	56.2	48.4	63.8	119.4	79.5	179.3
		Y3	132	71	53.8	44.9	62.5	53	40.2	31.7	49.0	42.3	27.2	65.6
		Y5	129	61	47.3	38.4	56.3	47	36.4	28.1	45.4	28.3	18.5	43.2
rSBA-MenC	ACWY1d	PRE	175	5	2.9	0.9	6.5	2	1.1	0.1	4.1	4.4	4.0	4.8
		PI (M1)	179	170	95.0	90.7	97.7	153	85.5	79.4	90.3	452.3	345.6	591.9
		Y1	167	82	49.1	41.3	56.9	35	21.0	15.1	27.9	16.2	12.4	21.1
		Y3	147	52	35.4	27.7	43.7	14	9.5	5.3	15.5	9.8	7.6	12.7
		Y5	132	27	20.5	13.9	28.3	8	6.1	2.7	11.6	6.6	5.3	8.2
	ACWY2d	PRE	153	1	0.7	0.0	3.6	1	0.7	0.0	3.6	4.2	3.8	4.5
		PI (M1)	157	150	95.5	91.0	98.2	134	85.4	78.8	90.5	369.3	280.9	485.5
		PII (M3)	150	148	98.7	95.3	99.8	145	96.7	92.4	98.9	639.1	521.8	782.9
		Y1	143	79	55.2	46.7	63.6	39	27.3	20.2	35.3	21.2	15.6	28.9

			≥1:8	≥1:128	GMT

Antibody	Vaccine Group	Visit	N	n	%	95% CI LL	95% CI UL	n	%	95% CI LL	95% CI UL	Value	95% CI LL	95% CI UL
		Y3	121	41	33.9	25.5	43.0	19	15.7	9.7	23.4	11.5	8.4	15.8
		Y5	116	33	28.4	20.5	37.6	12	10.3	5.5	17.4	8.5	6.4	11.2
	Co-ad	PRE	170	2	1.2	0.1	4.2	1	0.6	0.0	3.2	4.1	3.9	4.4
		PI (M1)	176	169	96.0	92.0	98.4	155	88.1	82.3	92.5	337.3	263.8	431.1
		Y1	171	73	42.7	35.2	50.5	27	15.8	10.7	22.1	12.6	10.0	16.0
		Y3	151	43	28.5	21.4	36.4	22	14.6	9.4	21.2	9.1	7.1	11.6
		Y5	142	34	23.9	17.2	31.8	17	12.0	7.1	18.5	7.9	6.2	10.0
	PCV13	PRE	171	0	0.0	0.0	2.1	0	0.0	0.0	2.1	4.0	NE	NE
		PII (M3)	169	161	95.3	90.9	97.9	145	85.8	79.6	90.7	376.4	284.7	497.6
		Y1	169	85	50.3	42.5	58.1	34	20.1	14.4	27.0	16.0	12.2	20.9
		Y3	132	42	31.8	24.0	40.5	14	10.6	5.9	17.2	9.3	7.1	12.1
		Y5	129	25	19.4	13.0	27.3	10	7.8	3.8	13.8	7.0	5.5	8.8
rSBA-MenW-135	ACWY1d	PRE	175	4	2.3	0.6	5.7	4	2.3	0.6	5.7	4.5	4.0	5.1
		PI (M1)	180	171	95.0	90.7	97.7	171	95.0	90.7	97.7	2120.2	1601.0	2807.8
		Y1	167	109	65.3	57.5	72.5	78	46.7	39.0	54.6	57.2	39.9	82.0
		Y3	147	87	59.2	50.8	67.2	63	42.9	34.7	51.3	42.5	29.2	61.8
		Y5	133	59	44.4	35.8	53.2	43	32.3	24.5	41.0	25.0	16.7	37.6
	ACWY2d	PRE	153	4	2.6	0.7	6.6	3	2.0	0.4	5.6	4.4	4.0	4.8
		PI (M1)	158	150	94.9	90.3	97.8	149	94.3	89.5	97.4	2030.1	1510.7	2728.2
		PII (M3)	150	150	100.0	97.6	100.0	149	99.3	96.3	100.0	3533.0	2914.5	4282.7
		Y1	143	111	77.6	69.9	84.2	86	60.1	51.6	68.2	123.1	82.7	183.4
		Y3	121	88	72.7	63.9	80.4	64	52.9	43.6	62.0	92.9	59.9	143.9
		Y5	117	59	50.4	41.0	59.8	46	39.3	30.4	48.8	37.1	23.3	59.0
	Co-ad	PRE	169	2	1.2	0.1	4.2	2	1.2	0.1	4.2	4.2	3.9	4.5
		PI (M1)	177	165	93.2	88.5	96.4	164	92.7	87.8	96.0	1550.9	1137.4	2114.7
		Y1	171	103	60.2	52.5	67.6	73	42.7	35.2	50.5	52.0	35.5	76.4
		Y3	151	80	53.0	44.7	61.1	59	39.1	31.2	47.3	34.4	23.4	50.6
		Y5	142	61	43.0	34.7	51.5	48	33.8	26.1	42.2	26.2	17.6	39.0
	PCV13	PRE	171	2	1.2	0.1	4.2	2	1.2	0.1	4.2	4.2	3.9	4.6
		PII (M3)	169	163	96.4	92.4	98.7	163	96.4	92.4	98.7	3490.5	2643.3	4609.3
		Y1	169	123	72.8	65.4	79.3	98	58.0	50.2	65.5	109.5	75.0	160.0
		Y3	132	75	56.8	47.9	65.4	56	42.4	33.9	51.3	44.5	28.9	68.7
				≥1:8				≥1:128				GMT		

Antibody	Vaccine Group	Visit	N	n	%	95% CI LL	95% CI UL	n	%	95% CI LL	95% CI UL	Value	95% CI LL	95% CI UL
		Y5	129	58	45.0	36.2	54.0	46	35.7	27.4	44.6	31.7	20.2	49.6
rSBA-MenY	ACWY1d	PRE	175	17	9.7	5.8	15.1	16	9.1	5.3	14.4	6.0	5.0	7.3
		PI (M1)	180	167	92.8	88.0	96.1	163	90.6	85.3	94.4	951.8	705.0	1284.9
		Y1	167	122	73.1	65.7	79.6	87	52.1	44.2	59.9	76.8	54.2	109.0
		Y3	147	91	61.9	53.5	69.8	72	49.0	40.7	57.3	58.0	39.1	86.0
		Y5	133	63	47.4	38.7	56.2	53	39.8	31.5	48.7	36.5	23.6	56.2
	ACWY2d	PRE	153	8	5.2	2.3	10.0	8	5.2	2.3	10.0	5.2	4.3	6.1
		PI (M1)	157	147	93.6	88.6	96.9	144	91.7	86.3	95.5	933.3	692.3	1258.3
		PII (M3)	150	149	99.3	96.3	100.0	149	99.3	96.3	100.0	1133.6	944.5	1360.5
		Y1	143	114	79.7	72.2	86.0	87	60.8	52.3	68.9	112.3	77.5	162.8
		Y3	121	83	68.6	59.5	76.7	65	53.7	44.4	62.8	75.1	48.7	115.9
		Y5	117	68	58.1	48.6	67.2	61	52.1	42.7	61.5	55.8	35.7	87.5
	Co-ad	PRE	169	10	5.9	2.9	10.6	9	5.3	2.5	9.9	5.1	4.4	6.0
		PI (M1)	177	159	89.8	84.4	93.9	158	89.3	83.7	93.4	778.5	566.2	1070.4
		Y1	173	116	67.1	59.5	74.0	93	53.8	46.0	61.4	70.7	49.0	102.1
		Y3	151	95	62.9	54.7	70.6	80	53.0	44.7	61.1	67.6	45.6	100.3
		Y5	142	75	52.8	44.3	61.2	60	42.3	34.0	50.8	43.3	28.3	66.2
	PCV13	PRE	171	12	7.0	3.7	11.9	10	5.8	2.8	10.5	5.2	4.5	6.1
		PII (M3)	169	164	97.0	93.2	99.0	164	97.0	93.2	99.0	1481.2	1158.4	1893.9
		Y1	169	136	80.5	73.7	86.2	117	69.2	61.7	76.1	169.2	119.2	240.1
		Y3	132	97	73.5	65.1	80.8	79	59.8	51.0	68.3	106.0	70.2	160.0
		Y5	129	72	55.8	46.8	64.5	62	48.1	39.2	57.0	53.9	34.5	84.2

Abbreviations: 95% CI = 95% confidence interval; ATP = according-to-protocol; GMT = geometric mean antibody titer calculated for all subjects; LL = lower limit; NE = not estimable; rSBA-MenA, rSBA-MenC, rSBA-MenW-135, and rSBA-MenY = serum bactericidal assay using rabbit complement to measure activity against *Neisseria meningitidis* group A, group C, group W-135, and group Y; UL = upper limit.

N = number of subjects with available data.
n = Number of subjects with titer within the specified range.
% = Percentage of subjects with titer within the specified range. ACWY1d = subjects who received 1 dose of MenACWY-TT at Month 0.
ACWY2d = subjects who received 2 doses of MenACWY-TT at Month 0 and Month 2.
Co-ad = subjects who received 1 dose of MenACWY-TT and 1 dose of Prevenar 13 at Month 0.
PCV13 = subjects who received 1 dose of Prevenar 13 at Month 0 and 1 dose of MenACWY-TT at Month 2.

hSBA results

The secondary objective relating to the hSBA immunogenicity endpoint at 5 years after vaccination was to evaluate the long-term persistance of the Year 5 analysis was to evaluate the long-term persistence of the immune response induced by one or two doses of MenACWY-TT in terms of percentage of participants at year 5 with serum bactericidal assay using human complement (hSBA) titers $\geq$1:4 and $\geq$1:8, and geometric mean titers (GMTs) in a subset of participants in the ACWY1d and ACWY2d groups.

Table 4 presents the number and percentage of participants with hSBA titers equal to or above the cutoff values (1:4 and 1:8) and GMTs for the adapted ATP cohort.

At 5 years after the last vaccination (first or second dose), the percentages of participants achieving hSBA titers ≥1:8 in the ACWY1d and ACWY2d groups were 27.9% and 17.9%, respectively, for hSBA-MenA; 60.7% and 67.8%, respectively, for hSBA-MenC; 58.9% and 63.6%, respectively, for hSBA-MenW-135; and 61.5% and 54.2%, respectively, for hSBA-MenY.

GMTs 5 years after the last vaccination for participants in the ACWY1d and ACWY2d groups were 4.4 and 3.1, respectively, for hSBA-MenA; 18.1 and 29.4, respectively, for hSBA-MenC; 20.8 and 19.5, respectively, for hSBA-MenW-135; and 24.3 and 16.8, respectively, for hSBA-MenY. Compared to prevaccination levels, GMTs for each group were higher at 5 years after vaccination.

Table 4. Number and Percentage of Subjects With hSBA-MenA, hSBA-MenC, hSBA-MenW-135, and hSBA-MenY Titers Equal to or Above the Cutoff Values (1:4 and 1:8) and GMTs (Adapted ATP Cohort)

				≥1:4				≥1:8				GMT		
					95% CI				95% CI				95% CI	
Antibody	Vaccine Group	Visit	N	n	%	LL	UL	n	%	LL	UL	Value	LL	UL
hSBA-MenA	ACWY1d	PRE	78	6	7.7	2.9	16.0	6	7.7	2.9	16.0	2.4	2.1	2.8
		PI (M1)	74	71	95.9	88.6	99.2	71	95.9	88.6	99.2	118.0	86.8	160.5
		Y1	70	26	37.1	25.9	49.5	25	35.7	24.6	48.1	6.1	4.1	8.9
		Y3	55	20	36.4	23.8	50.4	20	36.4	23.8	50.4	5.8	3.8	8.9
		Y5	61	17	27.9	17.1	40.8	17	27.9	17.1	40.8	4.4	3.1	6.2
	ACWY2d	PRE	62	6	9.7	3.6	19.9	6	9.7	3.6	19.9	2.6	2.1	3.2
		PI (M1)	66	64	97.0	89.5	99.6	64	97.0	89.5	99.6	132.9	98.1	180.1
		PII (M3)	66	64	97.0	89.5	99.6	64	97.0	89.5	99.6	170.5	126.2	230.2
		Y1	62	22	35.5	23.7	48.7	22	35.5	23.7	48.7	6.4	4.2	10.0
		Y3	50	18	36.0	22.9	50.8	18	36.0	22.9	50.8	5.4	3.6	8.0
		Y5	56	10	17.9	8.9	30.4	10	17.9	8.9	30.4	3.1	2.4	4.0
hSBA-MenC	ACWY1d	PRE	82	3	3.7	0.8	10.3	3	3.7	0.8	10.3	2.2	2.0	2.4
		PI (M1)	78	77	98.7	93.1	100.0	77	98.7	93.1	100.0	151.9	104.8	220.4
		Y1	71	58	81.7	70.7	89.9	57	80.3	69.1	88.8	35.2	22.5	55.2
		Y3	61	40	65.6	52.3	77.3	40	65.6	52.3	77.3	23.6	13.9	40.2
		Y5	61	37	60.7	47.3	72.9	37	60.7	47.3	72.9	18.1	10.9	30.0
	ACWY2d	PRE	66	0	0.0	0.0	5.4	0	0.0	0.0	5.4	2.0	NE	NE
		PI (M1)	70	68	97.1	90.1	99.7	67	95.7	88.0	99.1	160.8	109.8	235.5
		PII (M3)	69	69	100.0	94.8	100.0	69	100.0	94.8	100.0	1753.3	1278.7	2404.2
		Y1	63	59	93.7	84.5	98.2	57	90.5	80.4	96.4	73.4	47.5	113.4
		Y3	56	38	67.9	54.0	79.7	38	67.9	54.0	79.7	27.0	15.6	46.8
		Y5	59	40	67.8	54.4	79.4	40	67.8	54.4	79.4	29.4	16.3	52.9

					≥1:4				≥1:8			GMT		
						95% CI				95% CI			95% CI	
Antibody	Vaccine Group	Visit	N	n	%	LL	UL	n	%	LL	UL	Value	LL	UL
hSBA-MenW-135	ACWY1d	PRE	73	1	1.4	0.0	7.4	1	1.4	0.0	7.4	2.2	1.8	2.6
		PI (M1)	72	45	62.5	50.3	73.6	45	62.5	50.3	73.6	27.5	16.1	46.8
		Y1	72	69	95.8	88.3	99.1	69	95.8	88.3	99.1	209.0	149.9	291.4
		Y3	67	48	71.6	59.3	82.0	48	71.6	59.3	82.0	30.5	18.7	49.6
		Y5	56	33	58.9	45.0	71.9	33	58.9	45.0	71.9	20.8	11.6	37.1
	ACWY2d	PRE	62	0	0.0	0.0	5.8	0	0.0	0.0	5.8	2.0	NE	NE
		PI (M1)	61	42	68.9	55.7	80.1	42	68.9	55.7	80.1	26.2	16.0	43.0
		PII (M3)	70	68	97.1	90.1	99.7	68	97.1	90.1	99.7	756.8	550.1	1041.3
		Y1	65	64	98.5	91.7	100.0	64	98.5	91.7	100.0	232.6	168.3	321.4
		Y3	54	47	87.0	75.1	94.6	47	87.0	75.1	94.6	55.5	35.3	87.1
		Y5	44	28	63.6	47.8	77.6	28	63.6	47.8	77.6	19.5	10.7	35.2
hSBA-MenY	ACWY1d	PRE	65	4	6.2	1.7	15.0	4	6.2	1.7	15.0	2.5	2.0	3.1
		PI (M1)	71	48	67.6	55.5	78.2	48	67.6	55.5	78.2	41.2	23.7	71.5
		Y1	62	57	91.9	82.2	97.3	57	91.9	82.2	97.3	144.4	97.2	214.5
		Y3	64	34	53.1	40.2	65.7	34	53.1	40.2	65.7	17.3	10.1	29.6
		Y5	65	40	61.5	48.6	73.3	40	61.5	48.6	73.3	24.3	14.3	41.1
	ACWY2d	PRE	60	5	8.3	2.8	18.4	5	8.3	2.8	18.4	2.5	2.1	3.0
		PI (M1)	56	36	64.3	50.4	76.6	36	64.3	50.4	76.6	31.9	17.6	57.9
		PII (M3)	64	61	95.3	86.9	99.0	61	95.3	86.9	99.0	513.0	339.4	775.4
		Y1	58	51	87.9	76.7	95.0	51	87.9	76.7	95.0	143.9	88.5	233.8
		Y3	52	32	61.5	47.0	74.7	32	61.5	47.0	74.7	24.1	13.3	43.8
		Y5	48	26	54.2	39.2	68.6	26	54.2	39.2	68.6	16.8	9.0	31.3

Abbreviations: 95% CI = 95% confidence interval; ATP = according-to-protocol; GMT = geometric mean antibody titer calculated for all subjects; hSBA-MenA, hSBA-MenC, hSBA-MenW-135, and hSBA-MenY = serum bactericidal assay using human complement to measure activity against *Neisseria meningitidis* group A, group C, group W-135, and group Y; LL = lower limit; NE = not estimable; UL = upper limit.
N = number of subjects with available data.
n = Number of subjects with titer within the specified range.
% = Percentage of subjects with titer within the specified range.
ACWY1d = subjects who received 1 dose of MenACWY-TT at Month 0.
ACWY2d = subjects who received 2 doses of MenACWY-TT at Month 0 and Month 2.
PRE = at Month 0, before first vaccine dose.
PI (M1) = at Month 1, 1 month after vaccine dose at Month 0.
PII (M3) = at Month 3, 1 month after vaccine dose at Month 2.
Y1 = one (1) year after last primary vaccine dose.
Y3 = three (3) years after last primary vaccine dose.
Y5 = five (5) years after last primary vaccine dose.
Program ID: Study MenACWY-TT-104 (C0921003)/CP IMM_FREQ.SAS. Date of Reporting Dataset Creation: 27MAY2021. Runtime ID: 03JUN2021 01:27. File ID: 28_IMM_H_ATP.HTM.

Source: Table 3, Year 5 hSBA Immunogenicity Clinical Study Report for Study MenACWY-TT-104

Safety results

The following safety data from year 3 to year 5 were collected at the year 5 visit:

AEs/SAEs leading to withdrawal from the study, any adverse event (AE or SAE) related to lack of vaccine efficacy, any occurrence of meningococcal and pneumococcal disease, and SAEs that the investigator assessed were related to vaccine or study participation.

No participants were withdrawn from the study for safety-related reasons from Year 3 to Year 5. A total of 3 subjects reported a total of 4 AEs from Year 3 to Year 5, all of which were SAEs and were assessed by the investigator as not related to the study vaccine. One subject in the ACWY1d reported pneumococcal pneumonia; one subject in the PCV13 group reported aseptic meningitis; and one subject in the Co-ad group reported diabetes mellitus and pneumonia. For the event of pneumonia (verbatim term of bronchopneumonia) reported in the Co-ad group, the investigator determined there was a reasonable possibility that this event was related to pneumococcal 13-valent conjugate vaccine lack of efficacy, although results of both a nose swab and a throat culture for this subject were positive for *Streptococcus viridans*, not *Streptococcus pneumoniae*.

With respect to cumulative safety data, from Visit 1 to Year 5 there were 15, 18, 19, and 18 SAEs reported by 12, 11, 13, and 16 participants, in the ACWY1d, ACWY2d, Co-ad, and PCV13 vaccine groups, respectively. From Visit 1 to Year 5 there were a total of 2 fatal SAEs (1 event of asphyxia in the Co-ad vaccine group and 1 event of aspiration in the PCV13 vaccine group) and a total of 4 related SAEs. Three related SAEs were reported for 2 participants in the ACWY2d group (one participant experienced leukopenia and neutropenia, and one participant had pneumonia) and 1 related SAE was reported for 1 participant in the Co-ad group (pneumonia). From Visit 1 to Year 5 SAEs were most commonly reported in the MedDRA System Organ Class (SOC) of infections and infestations in all vaccine groups (3.0%, 4.6%, 5.0%, and 5.0% in the ACWY1d, ACWY2d, Co-ad, and PCV13 vaccine groups, respectively).

2.3.3. Discussion on clinical aspects

A graphical presentation of the data for rSBA and hSBA is shown below, from post-primary vaccination up to 5 years has been included for ease of review (for confidence intervals please see the tables).

Figure 1.

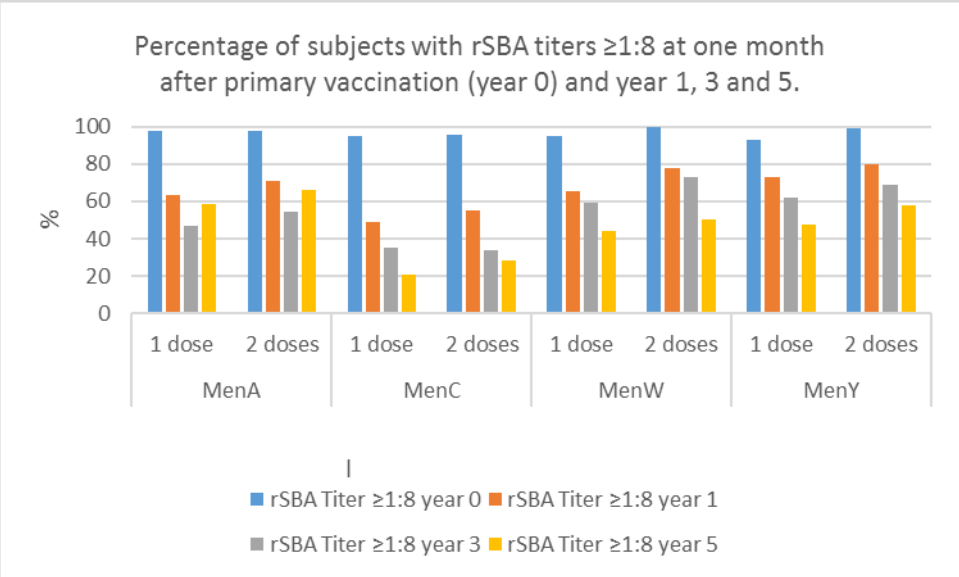


Figure 2.

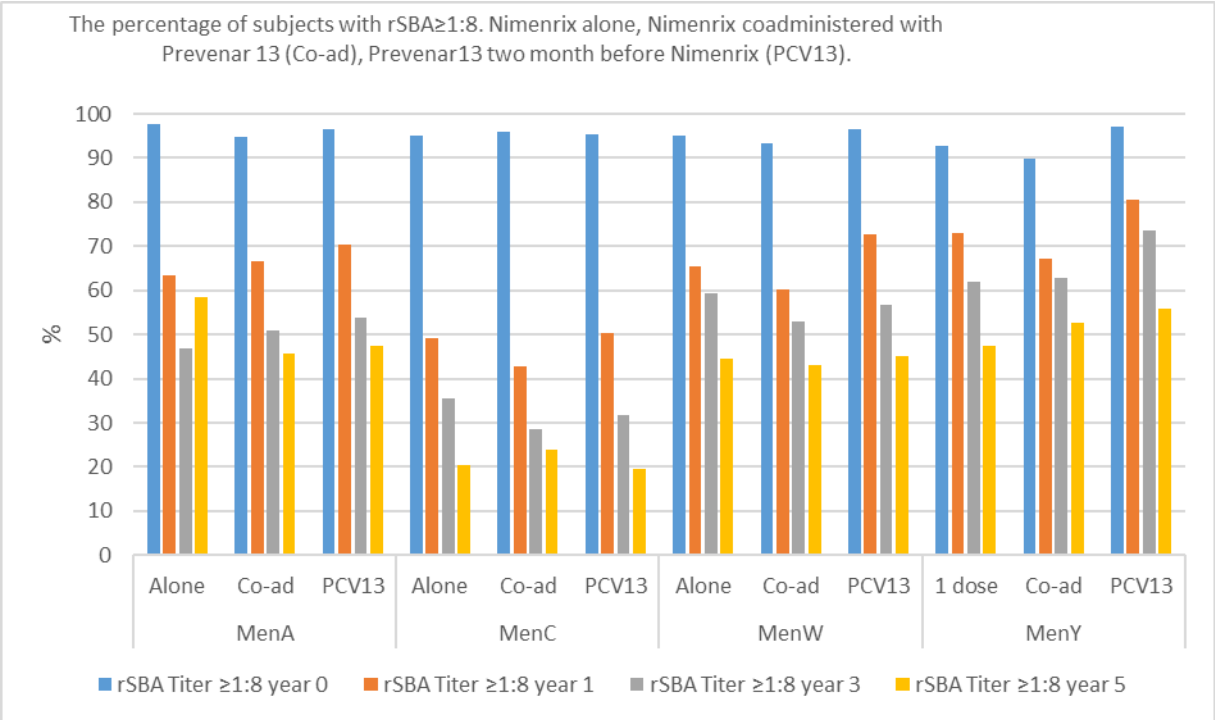
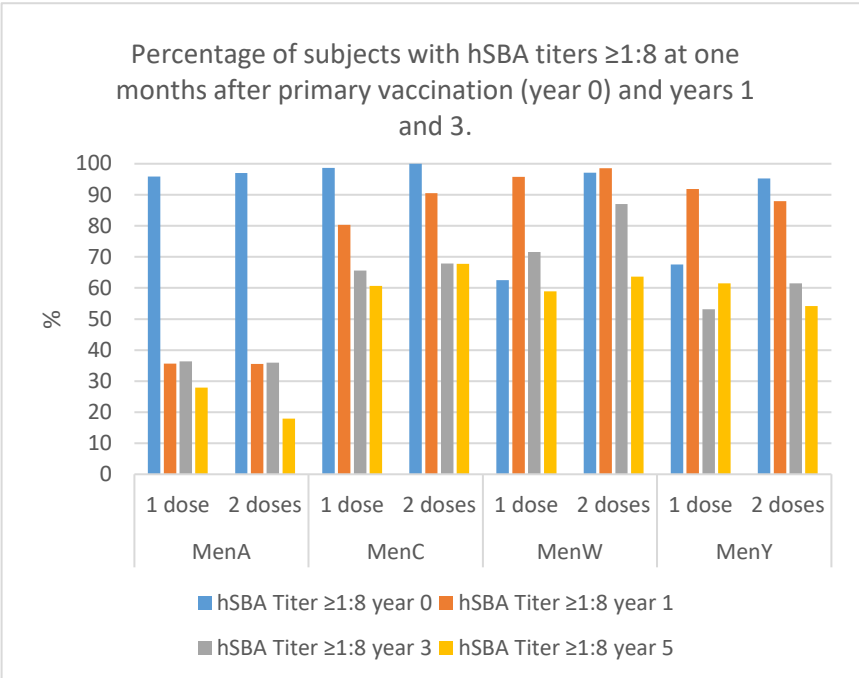


Figure 3.



The largest decrease in percentage of subjects with rSBA titer≥1:8 is generally seen between first vaccination and the 1 year time point. In the period 1-5 years a further but smaller drop is observed, except for MenA where the level is stable. The largest drop in response is seen with MenC where the percentage ends at around 20% with rSBA titer≥1:8 at 5 years, while for the other serogroups A, W and Y the percentage is around 50% at year 5. However, the hSBA results from primary vaccination up to year 5 show a much slower decrease in response to serogroup C with a percentage of subjects with hSBA titer≥1:8 between 60-70% at year 5. On the contrary, the decrease in response to MenA is more

pronounced in the hSBA data compared to the rSBA data, with a percentage of subjects with hSBA titers ≥1:8 between 17-30% at year 5, while for MenW and MenY the results are more similar between the assays. Of note, there is an increase in percentage of subjects with a hSBA titer ≥1:8 from post-primary vaccination to 1 year for MenW and MenY. This could potentially be explained by antibodies to subcapsular antigens acquired by asymptomatic carriage of strains with a similar subcapsular antigenic composition as the target strain used in the SBA assay.

Comparing one or two doses using both the rSBA and hSBA data there is a tendency of higher percentages of subjects with titers ≥1:8 after two doses, but the differences are numerically small.

Following review of the initial CSR for study 104 the following statements were added to section 4.4 of the SmPC based on the one-month post-dose data:

> *Immune responses in toddlers aged 12-14 months*
>
> Toddlers aged 12-14 months had similar rSBA titres to groups A, C, W-135 and Y at one month after one dose of Nimenrix or at one month after two doses of Nimenrix given two months apart.
>
> A single dose was associated with lower hSBA titres to groups W-135 and Y compared with two doses given two months apart. Similar responses to groups A and C were observed after one or two doses (see section 5.1). The clinical relevance of this observation is unknown. If a toddler is expected to be at particular risk of invasive meningococcal disease due to exposure to groups W-135 and/or Y, consideration may be given to administering a second dose of Nimenrix after an interval of 2 months. Regarding waning of antibody against group A or group C after a first dose of Nimenrix in children aged 12-23 months, see under Persistence of serum bactericidal antibody titres.
>
> Persistence of serum bactericidal antibody titres
>
> Following administration of Nimenrix there is a waning of serum bactericidal antibody titres against group A when using hSBA (see section 5.1). The clinical relevance of this observation is unknown. However, if an individual is expected to be at particular risk of exposure to group A and received a dose of Nimenrix more than approximately one year previously, consideration may be given to administering a booster dose.
>
> A decline in antibody titres over time has been observed for groups A, C, W-135 and Y. The clinical relevance of this observation is unknown. A booster dose might be considered in individuals vaccinated at toddler age remaining at high risk of exposure to meningococcal disease caused by groups A, C, W-135 or Y (see section 5.1).

Based on the complete set of data on rSBA and hSBA up to 5 years the description in section 4.4 of the SmPC is still relevant and could remain unchanged.

In addition to data for 1 or 2 doses of Nimenrix, there were two more groups that received a single dose of Nimenrix: One group received Prevenar 13 at the same time as Nimenrix (Coadministration, Co-ad), and one group that got Prevenar 13 two month before Nimenrix (PCV13). Figure 2 demonstrates the lack of any effect of co-administration of Prevenar 13 with Nimenrix or if Prevenar 13 is administered two months before Nimenrix. Within each serogroup and time point there are very little variation in the data comparing Nimenrix alone, co-administration with Prevenar 13, and Prevenar 13 two months before Nimenrix.

3. Member states comments

An endorsing comment was received from MS1.

4. Rapporteur's overall conclusion and recommendation

The greatest decrease in percentage of subjects with rSBA titer≥1:8 is generally seen between one month post primary series (one or two doses) and the 1 year time point. In the time period 1-5 years after the primary vaccination a further but smaller drop is observed, except for MenA where the level is stable.

The recommendation of 1 dose as a primary vaccination in toddlers is supported by the data and the lack of interference from co-administration with Prevenar 13 is still valid. Based on the complete set of data on rSBA and hSBA up to 5 years the description of the immune response in toddlers in SPC section 4.4 is still relevant and could remain unchanged.

No new safety concerns have been identified.

The SPC section 5.1 should be updated to include long term antibody persistence data based on the complete data set (rSBA and hSBA) from the study.

☒ **Not fulfilled:**

Data are expected in the context of a variation prior to any conclusion on product information amendments is made. The variation should contain an update to section 5.1 in the SmPC (as specified below), as well as an update of the Annex II.D in the PI, as the obligation to evaluate long term immunogenicity (5 years) is considered fulfilled and can be deleted. The MAH should commit to submit this variation application by 21 January 2022.

In the SmpC section 5.1 under "Immunogenicity in toddlers" Table 3 from Year 5 hSBA Immunogenicity Clinical Study Report for Study MenACWY-TT-104 (see table 3 below) should be inserted and the following wording is recommended with the subtitle Long term immunogenicity in toddlers:

"MenACWY-TT-104 (C0921003) was a Phase 3, open-label, randomized, controlled, multicenter study designed to evaluate the immunogenicity after 1 month and the persistence of the response up to 5 years following 1 and 2 doses (given 2 months apart) of MenACWY-TT in toddlers aged 12 to 14 months and to demonstrate non-inferiority of co-administration of MenACWY-TT and Prevenar 13 (PCV13), versus separate administration of the 2 vaccines.

The hSBA data (% responders >1:4, >1:8 and GMT) from primary vaccination up to year 5 showed a more pronounced decrease in response to MenA in the hSBA compared to the rSBA assay, while for MenW and MenY the results are more similar between the assays."

Table 3 from Year 5 hSBA Immunogenicity Clinical Study Report for Study MenACWY-TT-104

				≥1:4				≥1:8			GMT		
					95% CI				95% CI			95% CI	
Antibody	Vaccine Group	Visit	N	n	%	LL	UL	n	%	LL	UL	Value	LL	UL
hSBA-MenA	ACWY1d	PRE	78	6	7.7	2.9	16.0	6	7.7	2.9	16.0	2.4	2.1	2.8
		PI (M1)	74	71	95.9	88.6	99.2	71	95.9	88.6	99.2	118.0	86.8	160.5
		Y1	70	26	37.1	25.9	49.5	25	35.7	24.6	48.1	6.1	4.1	8.9
		Y3	55	20	36.4	23.8	50.4	20	36.4	23.8	50.4	5.8	3.8	8.9
		Y5	61	17	27.9	17.1	40.8	17	27.9	17.1	40.8	4.4	3.1	6.2
	ACWY2d	PRE	62	6	9.7	3.6	19.9	6	9.7	3.6	19.9	2.6	2.1	3.2
		PI (M1)	66	64	97.0	89.5	99.6	64	97.0	89.5	99.6	132.9	98.1	180.1
		PII (M3)	66	64	97.0	89.5	99.6	64	97.0	89.5	99.6	170.5	126.2	230.2
		Y1	62	22	35.5	23.7	48.7	22	35.5	23.7	48.7	6.4	4.2	10.0
		Y3	50	18	36.0	22.9	50.8	18	36.0	22.9	50.8	5.4	3.6	8.0
		Y5	56	10	17.9	8.9	30.4	10	17.9	8.9	30.4	3.1	2.4	4.0
hSBA-MenC	ACWY1d	PRE	82	3	3.7	0.8	10.3	3	3.7	0.8	10.3	2.2	2.0	2.4
		PI (M1)	78	77	98.7	93.1	100.0	77	98.7	93.1	100.0	151.9	104.8	220.4
		Y1	71	58	81.7	70.7	89.9	57	80.3	69.1	88.8	35.2	22.5	55.2
		Y3	61	40	65.6	52.3	77.3	40	65.6	52.3	77.3	23.6	13.9	40.2
		Y5	61	37	60.7	47.3	72.9	37	60.7	47.3	72.9	18.1	10.9	30.0
	ACWY2d	PRE	66	0	0.0	0.0	5.4	0	0.0	0.0	5.4	2.0	NE	NE
		PI (M1)	70	68	97.1	90.1	99.7	67	95.7	88.0	99.1	160.8	109.8	235.5
		PII (M3)	69	69	100.0	94.8	100.0	69	100.0	94.8	100.0	1753.3	1278.7	2404.2
		Y1	63	59	93.7	84.5	98.2	57	90.5	80.4	96.4	73.4	47.5	113.4
		Y3	56	38	67.9	54.0	79.7	38	67.9	54.0	79.7	27.0	15.6	46.8

				≥1:4				≥1:8			GMT		
					95% CI				95% CI			95% CI	
Antibody	Vaccine Group	Visit	N	n	%	LL	UL	n	%	LL	UL	Value	LL	UL
		Y5	59	40	67.8	54.4	79.4	40	67.8	54.4	79.4	29.4	16.3	52.9
hSBA-MenW-135	ACWY1d	PRE	73	1	1.4	0.0	7.4	1	1.4	0.0	7.4	2.2	1.8	2.6
		PI (M1)	72	45	62.5	50.3	73.6	45	62.5	50.3	73.6	27.5	16.1	46.8
		Y1	72	69	95.8	88.3	99.1	69	95.8	88.3	99.1	209.0	149.9	291.4
		Y3	67	48	71.6	59.3	82.0	48	71.6	59.3	82.0	30.5	18.7	49.6
		Y5	56	33	58.9	45.0	71.9	33	58.9	45.0	71.9	20.8	11.6	37.1
	ACWY2d	PRE	62	0	0.0	0.0	5.8	0	0.0	0.0	5.8	2.0	NE	NE
		PI (M1)	61	42	68.9	55.7	80.1	42	68.9	55.7	80.1	26.2	16.0	43.0
		PII (M3)	70	68	97.1	90.1	99.7	68	97.1	90.1	99.7	756.8	550.1	1041.3
		Y1	65	64	98.5	91.7	100.0	64	98.5	91.7	100.0	232.6	168.3	321.4
		Y3	54	47	87.0	75.1	94.6	47	87.0	75.1	94.6	55.5	35.3	87.1
		Y5	44	28	63.6	47.8	77.6	28	63.6	47.8	77.6	19.5	10.7	35.2
hSBA-MenY	ACWY1d	PRE	65	4	6.2	1.7	15.0	4	6.2	1.7	15.0	2.5	2.0	3.1
		PI (M1)	71	48	67.6	55.5	78.2	48	67.6	55.5	78.2	41.2	23.7	71.5
		Y1	62	57	91.9	82.2	97.3	57	91.9	82.2	97.3	144.4	97.2	214.5
		Y3	64	34	53.1	40.2	65.7	34	53.1	40.2	65.7	17.3	10.1	29.6
		Y5	65	40	61.5	48.6	73.3	40	61.5	48.6	73.3	24.3	14.3	41.1
	ACWY2d	PRE	60	5	8.3	2.8	18.4	5	8.3	2.8	18.4	2.5	2.1	3.0
		PI (M1)	56	36	64.3	50.4	76.6	36	64.3	50.4	76.6	31.9	17.6	57.9
		PII (M3)	64	61	95.3	86.9	99.0	61	95.3	86.9	99.0	513.0	339.4	775.4
		Y1	58	51	87.9	76.7	95.0	51	87.9	76.7	95.0	143.9	88.5	233.8
		Y3	52	32	61.5	47.0	74.7	32	61.5	47.0	74.7	24.1	13.3	43.8
		Y5	48	26	54.2	39.2	68.6	26	54.2	39.2	68.6	16.8	9.0	31.3

Abbreviations: 95% CI = 95% confidence interval; ATP = according-to-protocol; GMT = geometric mean antibody titer calculated for all subjects; hSBA-MenA, hSBA-MenC, hSBA-MenW-135, and hSBA-MenY = serum bactericidal assay using human complement to measure activity against *Neisseria meningitidis* group A, group C, group W-135, and group Y; LL = lower limit; NE = not estimable; UL = upper limit.
N = number of subjects with available data.
n = Number of subjects with titer within the specified range.
% = Percentage of subjects with titer within the specified range.
ACWY1d = subjects who received 1 dose of MenACWY-TT at Month 0.
ACWY2d = subjects who received 2 doses of MenACWY-TT at Month 0 and Month 2.
PRE = at Month 0, before first vaccine dose.
PI (M1) = at Month 1, 1 month after vaccine dose at Month 0.
PII (M3) = at Month 3, 1 month after vaccine dose at Month 2.
Y1 = one (1) year after last primary vaccine dose.
Y3 = three (3) years after last primary vaccine dose.
Y5 = five (5) years after last primary vaccine dose.
Program ID: Study MenACWY-TT-104 (C0921003)/CP IMM_FREQ.SAS. Date of Reporting Dataset Creation: 27MAY2021. Runtime ID: 03JUN2021 01:27. File ID: 28_IMM_H_ATP.HTM.