26 August 2014
EMA/200334/2015
Committee for Medicinal Products for Human Use (CHMP)

Nimenrix

(neisseria meningitidis group A, C, W-135, Y polysaccharide conjugated to tetanus toxoid carrier protein)

Procedure No: EMEA/H/C/002226/P46/0041

CHMP assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No1901/2006

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

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I. Introduction

On 10 July 2014 the MAH submitted a final clinical study report for the paediatric study MenACWY-TT-059 (EXT052) Year 5 for Nimenrix, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

The primary phase study MenACWY-TT-052, as well as the follow-up study after 1 year (MenACWY-TT-059 EXT052 Y1) were submitted as part of the initial MAA for Nimenrix. The 3 year follow-up data (MenACWY-TT-059 EXT052 Y3) was submitted and assessed under Article 46 of Regulation (EC) No. 1901/2006 in September 2012 (Art 46 reference P46-015).

A short critical expert overview has also been provided.

The applicant states that, in accordance with Article 16(2) of Regulation (EC) No 726/2004, the data submitted do not influence the benefit-risk balance for the above mentioned product and therefore do not require taking further regulatory action on the marketing authorisation for the above mentioned product.

II. Scientific discussion

Information on the development program

The MAH stated that study MenACWY-TT-052 is part of a clinical development program.

A line listing of all the concerned studies is annexed.

Information on the pharmaceutical formulation used in the study

Nimenrix is a quadrivalent meningococcal polysaccharide conjugate vaccine composed of Neisseria meningitidis serogroups A, C, W-135, Y conjugated to tetanus toxoid. Nimenrix was authorised on the 20th of April 2012 for active immunisation of individuals from the age of 12 months and above against invasive meningococcal diseases caused by Neisseria meningitidis group A, C, W-135 and Y. A 0.5 ml dose of the reconstituted vaccine is used in all ages.

Clinical aspects

Introduction

The MAH submitted a final report for study MenACWY-TT-052, which investigated the long-term antibody persistence of GSK Biologicals' MenACWY-TT vaccine versus Menactra® in healthy adolescents/adults aged 10-25 years, and booster response to MenACWY-TT vaccine administered at 5 years post-primary vaccination.

Clinical study (MenACWY-TT-052)

Description

MenACWY-TT-052 was a phase II, open, controlled, multi-center study to evaluate the long-term antibody persistence at 1 year, 3 years and 5 years after the administration of one dose of MenACWY-TT versus one dose of Sanofi-Pasteur's meningococcal serogroups A, C, W-135 and Y-diphtheria toxoid conjugate vaccine (Menactra®) in healthy adolescents/adults aged 10-25 years and to evaluate the

safety and immunogenicity of a booster response to MenACWY-TT vaccine administered at 5 years post-primary vaccination with MenACWY-TT or Menactra® and of a primary vaccination of MenACWY-TT in a newly enrolled group aged 15-<31 years.

The clinical study report supplied for this procedure presents the persistence results at 5 years (Month 60) after primary vaccination in study 109377 (MenACWY-TT-052) and immunogenicity and safety up to six month after a booster or primary vaccination of MenACWY-TT administered at Month 60.

Methods

Study MenACWY-TT-059 was conducted in the United States. This study evaluated the immunogenicity induced by Nimenrix as compared to Menactra at 11-25 years of age in terms of the percentage of subjects with N. meningitidis serogroups A, C, W -135 and Y titers ≥1:8 as measured by hSBA (using GSK hSBA assays).

The study included 3 groups:

• ACWY-TT: MenACWY-TT (11-25 years of age)

• ACWY-DT: Menactra (11-25 years of age)

• ACWY<11: MenACWY-TT (10-<11 years of age)

At Year 5, an additional arm of vaccine-naïve 15-<31 year olds was added to receive MenACWY-TT. Subjects who received MenACWY-TT or Menactra in study MenACWY-TT-052 received a booster dose of MenACWY-TT at Year 5 (Month 60).

The primary objective was to evaluate the long-term persistence of the immunogenicity induced by MenACWY-TT vaccine as compared to Menactra at 11-25 years of age in terms of the percentage of subjects with MenA, MenC, MenW-135, and MenY titers ≥1:8 as measured by a serum bactericidal assay using human complement (hSBA).

Secondary objectives included measurement of antibody titers ≥1:4 and geometric mean titers (GMTs), evaluation of the immunogenicity of MenACWY-TT vaccine when given 5 years after a priming dose compared to the immunogenicity in vaccine-naïve subjects.

Results

Persistence phase

Of the 852 subjects in the MenACWY-TT-059 database, 540 did not come to the Year 5 persistence Visit 3, therefore the total cohort at Year 5 included 312 subjects (218 in the ACWY-TT group, 56 in the ACWY-DT group and 38 in the ACWY<11 group) who signed an informed consent and participated in the Year 5 blood draw. The According-to-Protocol (ATP) immunogenicity analysis for persistence at Year 5 contained 215 subjects (144 in the ACWY-TT group, 45 in the ACWY-DT group and 26 in the ACWY<11 group). In the majority of cases, the reasons for subjects not returning for the Year 5 persistence study were: the subjects had been revaccinated with a meningococcal vaccine or the subjects were lost to follow-up. Other reasons fell under the categories of withdrawal of consent or migration to another area.

Across all three vaccine groups the mean age of the subjects in the ATP cohort for persistence at Year 5 was 19.6 years (range 15 to 30 years) with a standard deviation of 3.32. The distribution of males and females was similar (51.6% male and 48.4% female). According to race, 47.4% were

White/Caucasian/European Heritage, 21.9% were Other and 10.7% were American Indian or Alaskan Native.

Table 1. Summary of demographic characteristics (ATP cohort for persistence at Year 5)

		ACWY-TT N = 144		ACWY-DT N = 45		ACWY<11 N = 26		Total N = 215	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**
Age (years) at Year 5	Mean	20.4	-	19.6	-	15.3	-	19.6	-
	SD	3.31	-	2.20	-	0.45	-	3.32	-
	Median	20.0	-	20.0	-	15.0	-	19.0	-
	Minimum	16	-	16	-	15	-	15	-
	Maximum	30	-	26	-	16	-	30	-
Gender	Female	64	44.4	24	53.3	16	61.5	104	48.4
	Male	80	55.6	21	46.7	10	38.5	111	51.6
Race	African Heritage / African American	11	7.6	2	4.4	2	7.7	15	7.0
	American Indian or Alaskan Native	14	9.7	6	13.3	3	11.5	23	10.7
	Asian - Central/South Asian Heritage	0	0.0	0	0.0	0	0.0	0	0.0
	Asian - East Asian Heritage	4	2.8	1	2.2	1	3.8	6	2.8
	Asian - Japanese Heritage	2	1.4	0	0.0	0	0.0	2	0.9
	Asian - South East Asian Heritage	11	7.6	4	8.9	3	11.5	18	8.4
	Native Hawaiian or Other Pacific Islander	0	0.0	1	2.2	0	0.0	1	0.5
	White - Arabic / North African Heritage	0	0.0	0	0.0	1	3.8	1	0.5
	White - Caucasian / European Heritage	71	49.3	20	44.4	11	42.3	102	47.4
	Other	31	21.5	11	24.4	5	19.2	47	21.9

ACWY-TT = Subjects 11-25 years of age in the primary study MenACWY-TT-052 who received MenACWY-TT in that study
ACWY-DT = Subjects 11-25 years of age in the primary study MenACWY-TT-052 who received *Menactra* in that study
ACWY<11 = Subjects <11 years of age in the primary study MenACWY-TT-052 who received MenACWY-TT in that study
N = total number of subjects
n/% = number / percentage of subjects in a given category
Value = value of the considered parameter
SD = standard deviation

The analysis of the 5 year persistence was performed on the ATP cohort for persistence Year 5.

Because the results for the blood samples taken at 1 month after administration of the vaccine and 1, 3 and 5 years after vaccination are based on assays done at different times, comparisons of the kinetics of antibody titer calculations should be interpreted with caution. Note that having serological results 1 year and/or 3 years after primary vaccination was not an entry requirement for the Year 5 persistence of study MenACWY-TT-059EXT:052.

At five years following primary vaccination, the percentage of subjects with hSBA antibody titers ≥1:8 was 48.9%, 92.9%, 87.0% and 94.4% for MenA, MenC, MenW-135 and MenY, respectively, in the ACWY-TT group, and 44.4%, 79.5%, 84.1% and 90.9% for MenA, MenC, MenW-135 and MenY, respectively, in the ACWY-DT group.

The percentage of subjects in the ACWY<11 group with hSBA titers ≥1:8 five years after vaccination was 37.5%, 84.6%, 92.3% and 92.3% for serogroups MenA, MenC, MenW-135 and MenY, respectively.

The GMTs for MenW-135 and MenY at the Year 5 persistence timepoint remained above pre-vaccination titers for all three groups. The GMTs for MenC remained above pre-vaccination titers for the ACWY-TT and ACWY<11 but dropped to almost pre-vaccination levels for the ACWY-DT group at the Year 5 persistence timepoint. In contrast, the MenA GMTs decreased markedly to almost baseline levels for all groups as soon as 1 year after primary vaccination.

Since, for any vaccine group, the percentage of subjects who came back for the Year 5 follow-up with serological results excluded from the ATP cohort was higher than 5%, a second analysis based on the Total cohort at Year 5 was performed to complement the ATP analysis. The descriptive immunogenicity results for the Total cohort at Year 5 were generally consistent with the results for the ATP analysis.

Table 2. Number and percentage of subjects with hSBA-MenA, hSBA-MenC, hSBA-MenW-135 and hSBA-MenY antibody titre equal to or above 1:4 and 1:8 and GMTs (ATP cohort for persistence at Year 5)

				≥ 1:4				≥ 1:8				GMT		
						95% CI				95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
hSBA-MenA	ACWY-TT	PRE	138	21	15.2	9.7	22.3	15	10.9	6.2	17.3	2.7	2.4	3.1
		PI(M1)	137	127	92.7	87.0	96.4	126	92.0	86.1	95.9	92.9	72.0	120.0
		PI(M12)	114	34	29.8	21.6	39.1	34	29.8	21.6	39.1	5.2	3.9	7.0
		PI(M36)	115	44	38.3	29.4	47.8	40	34.8	26.1	44.2	6.0	4.5	8.0
		PI(M60)	141	74	52.5	43.9	60.9	69	48.9	40.4	57.5	8.9	6.8	11.8
	ACWY-DT	PRE	43	9	20.9	10.0	36.0	7	16.3	6.8	30.7	3.1	2.3	4.1
		PI(M1)	41	38	92.7	80.1	98.5	38	92.7	80.1	98.5	90.2	55.0	147.9
		PI(M12)	39	14	35.9	21.2	52.8	14	35.9	21.2	52.8	6.8	3.8	12.2
		PI(M36)	34	16	47.1	29.8	64.9	16	47.1	29.8	64.9	10.1	5.2	19.5
		PI(M60)	45	20	44.4	29.6	60.0	20	44.4	29.6	60.0	7.9	4.8	13.2
	ACWY<11	PRE	26	3	11.5	2.4	30.2	2	7.7	0.9	25.1	2.8	1.8	4.2
		PI(M1)	25	24	96.0	79.6	99.9	24	96.0	79.6	99.9	106.2	69.7	161.8
		PI(M12)	22	8	36.4	17.2	59.3	8	36.4	17.2	59.3	6.5	3.1	13.8
		PI(M36)	23	10	43.5	23.2	65.5	9	39.1	19.7	61.5	7.0	3.5	14.2
		PI(M60)	24	9	37.5	18.8	59.4	9	37.5	18.8	59.4	6.3	3.2	12.2
hSBA-MenC	ACWY-TT	PRE	141	85	60.3	51.7	68.4	85	60.3	51.7	68.4	15.6	11.5	21.3
		PI(M1)	139	137	98.6	94.9	99.8	137	98.6	94.9	99.8	792.9	545.9	1151.7
		PI(M12)	108	104	96.3	90.8	99.0	104	96.3	90.8	99.0	192.8	137.3	270.6
		PI(M36)	117	110	94.0	88.1	97.6	110	94.0	88.1	97.6	124.1	85.5	180.2
		PI(M60)	140	134	95.7	90.9	98.4	130	92.9	87.3	96.5	94.6	65.9	135.9
	ACWY-DT	PRE	43	32	74.4	58.8	86.5	32	74.4	58.8	86.5	24.5	13.9	43.4
		PI(M1)	44	43	97.7	88.0	99.9	43	97.7	88.0	99.9	371.8	213.3	648.3
		PI(M12)	36	28	77.8	60.8	89.9	28	77.8	60.8	89.9	46.8	23.2	94.6
		PI(M36)	35	31	88.6	73.3	96.8	29	82.9	66.4	93.4	40.5	21.8	75.5
		PI(M60)	44	39	88.6	75.4	96.2	35	79.5	64.7	90.2	30.6	17.3	54.4
	ACWY<11	PRE	24	12	50.0	29.1	70.9	12	50.0	29.1	70.9	9.2	4.5	18.7
		PI(M1)	26	26	100	86.8	100	26	100	86.8	100	881.5	394.1	1971.4
		PI(M12)	22	22	100	84.6	100	22	100	84.6	100	306.7	141.4	665.1
		PI(M36)	23	22	95.7	78.1	99.9	22	95.7	78.1	99.9	159.7	67.8	376.3
		PI(M60)	26	24	92.3	74.9	99.1	22	84.6	65.1	95.6	92.9	39.6	217.6
hSBA-MenW-135	ACWY-TT	PRE	126	37	29.4	21.6	38.1	36	28.6	20.9	37.3	6.8	4.8	9.6
		PI(M1)	131	127	96.9	92.4	99.2	127	96.9	92.4	99.2	179.6	138.3	233.3
		PI(M12)	106	104	98.1	93.4	99.8	104	98.1	93.4	99.8	188.5	151.6	234.5
		PI(M36)	117	108	92.3	85.9	96.4	108	92.3	85.9	96.4	117.6	90.3	153.2
		PI(M60)	138	122	88.4	81.9	93.2	120	87.0	80.2	92.1	103.5	76.3	140.5
	ACWY-DT	PRE	38	16	42.1	26.3	59.2	16	42.1	26.3	59.2	12.4	5.8	26.5
		PI(M1)	31	31	100	88.8	100	31	100	88.8	100	230.3	133.6	397.1
		PI(M12)	37	36	97.3	85.8	99.9	36	97.3	85.8	99.9	127.3	72.9	222.2
		PI(M36)	34	31	91.2	76.3	98.1	31	91.2	76.3	98.1	126.0	62.0	256.1
		PI(M60)	44	37	84.1	69.9	93.4	37	84.1	69.9	93.4	70.4	37.2	133.1
	ACWY<11	PRE	24	3	12.5	2.7	32.4	3	12.5	2.7	32.4	3.7	1.8	7.5
		PI(M1)	26	26	100	86.8	100	26	100	86.8	100	170.5	107.5	270.3
		PI(M12)	20	20	100	83.2	100	20	100	83.2	100	273.4	167.9	445.2
		PI(M36)	23	22	95.7	78.1	99.9	22	95.7	78.1	99.9	122.3	70.1	213.3

				≥ 1:4				≥ 1:8				GMT		
						95% CI				95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
		PI(M60)	26	24	92.3	74.9	99.1	24	92.3	74.9	99.1	92.4	50.5	168.8
hSBA-MenY	ACWY-TT	PRE	134	83	61.9	53.2	70.2	81	60.4	51.6	68.8	30.1	20.2	44.8
		PI(M1)	141	140	99.3	96.1	100	140	99.3	96.1	100	334.2	273.5	408.3
		PI(M12)	115	113	98.3	93.9	99.8	113	98.3	93.9	99.8	274.1	221.9	338.6
		PI(M36)	116	113	97.4	92.6	99.5	113	97.4	92.6	99.5	213.4	171.3	265.9
		PI(M60)	142	134	94.4	89.2	97.5	134	94.4	89.2	97.5	224.6	173.9	290.0
	ACWY-DT	PRE	39	29	74.4	57.9	87.0	29	74.4	57.9	87.0	56.4	27.3	116.4
		PI(M1)	45	43	95.6	84.9	99.5	43	95.6	84.9	99.5	202.0	116.8	349.4
		PI(M12)	39	37	94.9	82.7	99.4	37	94.9	82.7	99.4	152.2	89.0	260.4
		PI(M36)	36	33	91.7	77.5	98.2	33	91.7	77.5	98.2	157.8	90.3	275.7
		PI(M60)	44	40	90.9	78.3	97.5	40	90.9	78.3	97.5	129.3	77.4	215.9
	ACWY<11	PRE	26	14	53.8	33.4	73.4	13	50.0	29.9	70.1	19.2	7.3	50.4
		PI(M1)	26	26	100	86.8	100	26	100	86.8	100	417.1	271.4	641.1
		PI(M12)	23	23	100	85.2	100	23	100	85.2	100	343.9	240.9	491.0
		PI(M36)	21	20	95.2	76.2	99.9	20	95.2	76.2	99.9	155.3	86.3	279.5
		PI(M60)	26	24	92.3	74.9	99.1	24	92.3	74.9	99.1	113.7	58.4	221.3

ACWY-TT = Subjects 11-25 years of age in the primary study MenACWY-TT-052 who received MenACWY-TT in that study
ACWY-DT = Subjects 11-25 years of age in the primary study MenACWY-TT-052 who received *Menactra* in that study
ACWY<11 = Subjects <11 years of age in the primary study MenACWY-TT-052 who received MenACWY-TT in that study
GMT = geometric mean antibody titre calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with titre equal to or above specified value
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE = Pre-primary vaccination at Month 0
PI(M1) = Post-primary vaccination at Month 1
PI(M12) = Post-primary vaccination at Month 12
PI(M36) = Post-primary vaccination at Month 36
PI(M60) = Post-primary vaccination and pre-booster vaccination at Month 60

Table 3. Adjusted ratios of ACWY-TT and ACWY-DT GMTs, 5 years after the primary vaccination (ATP cohort for persistence at Year 5)

					Adjusted GMT ratio (ACWY-TT / ACWY-DT)		
	ACWY-TT		ACWY-DT			95% CI	
Antibody	N	Adjusted GMT	N	Adjusted GMT	Value	LL	UL
hSBA-MenA	141	9.5	45	8.3	1.14	0.65	2.00
hSBA-MenC	140	65.7	44	19.5	3.36	1.65	6.84
hSBA-MenW-135	138	88.7	44	59.6	1.49	0.78	2.84
hSBA-MenY	142	219.1	44	126.9	1.73	1.01	2.96

ACWY-TT = Subjects 11-25 years of age in the primary study MenACWY-TT-052 who received MenACWY-TT in that study
ACWY-DT = Subjects 11-25 years of age in the primary study MenACWY-TT-052 who received *Menactra* in that study
Adjusted GMT = geometric mean antibody titre adjusted for age strata
N = Number of subjects with post-vaccination results available
95% CI = 95% confidence interval for the adjusted GMT ratio (Anova model : adjustment for age strata- pooled variance); LL = lower limit, UL = upper limit

Booster phase

A total of 322 subjects received a booster (183 subjects in the ACWYBST group and 38 subjects in the ACWY-DT group) or primary vaccination (101 subjects in the ACWYPRI group). A total of 23 subjects did not complete the booster phase of the study and in the majority of the cases (18 subjects) this was due to the subject being lost to follow-up. The according-to-protocol immunogenicity analysis at Month 61 contained 223 subjects (109 in the ACWYBST group, 29 in the ACWY-DT group and 85 in the ACWYPRI group).

Across all three vaccine groups in the booster phase, the mean age of the subjects in the ATP cohort for immunogenicity at Month 61 was 20.9 years (range 15 to 30 years) with a standard deviation of 4.46. The distribution of males and females was 43.5% male and 56.5% female. According to race, 44.8% were White/Caucasian/European Heritage, 17.0% were American Indian or Alaskan Native and 13.5% were Other.

Table 4. Summary of demographic characteristics (Total Vaccinated Cohort)

		ACWYBST N = 183		ACWY-DT N = 38		ACWYPRI N = 101		Total N = 322	
Characteristics	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%	Value or n	%
Age at vaccination at month 60 (years)	Mean	19.1	-	19.6	-	23.3	-	20.5	-
	SD	3.18	-	2.40	-	4.74	-	4.15	-
	Median	19.0	-	19.5	-	24.0	-	20.0	-
	Minimum	15	-	16	-	15	-	15	-
	Maximum	30	-	26	-	30	-	30	-
Gender	Female	81	44.3	25	65.8	65	64.4	171	53.1
	Male	102	55.7	13	34.2	36	35.6	151	46.9
Race	African Heritage / African American	8	4.4	2	5.3	15	14.9	25	7.8
	American Indian or Alaskan Native	17	9.3	4	10.5	29	28.7	50	15.5
	Asian - Central/South Asian Heritage	0	0.0	0	0.0	1	1.0	1	0.3
	Asian - East Asian Heritage	8	4.4	1	2.6	3	3.0	12	3.7
	Asian - Japanese Heritage	2	1.1	0	0.0	1	1.0	3	0.9
	Asian - South East Asian Heritage	10	5.5	6	15.8	8	7.9	24	7.5
	Native Hawaiian or Other Pacific Islander	0	0.0	1	2.6	5	5.0	6	1.9
	White - Arabic / North African Heritage	1	0.5	0	0.0	0	0.0	1	0.3
	White - Caucasian / European Heritage	98	53.6	16	42.1	37	36.6	151	46.9
	Other	39	21.3	8	21.1	2	2.0	49	15.2

ACWYBST = Pooled subjects 10-25 years of age from ACWY<11 and ACWY-TT groups in the primary study MenACWY-TT-052 who received MenACWY-TT in that study and in current study
ACWY-DT = Subjects 11-25 years of age in the primary study MenACWY-TT-052 who received *Menactra* in that study and MenACWY-TT in current study
ACWYPRI = Subjects 15-<31 years at the time of primary vaccination with MenACWY-TT in current study
N = total number of subjects
n/% = number / percentage of subjects in a given category
Value = value of the considered parameter
SD = standard deviation

- hSBA antibody titers
    - One month after the booster vaccination with MenACWY-TT, the percentage of subjects with hSBA antibody titers ≥1:8 was 99.1% for MenA and MenC and 100% for MenW-135 and MenY in the ACWYBST group, and 100% for all four serogroups in the ACWY-DT group.
    - One month after primary vaccination in the ACWYPRI group, the percentage of subjects with hSBA antibody titers ≥1:8 was 77.2%, 95.1%, 92.5% and 97.6% for MenA, MenC, MenW-135 and MenY, respectively.

- The GMTs ranged from 783.8 (MenA) to 5664.3 (MenY) in the ACWYBST group, from 952.0 (MenA) to 6722.1 (MenC) in the ACWYDT group and from 79.7 (MenA) to 755.1 (MenY) in the ACWYPRI group.

Table 5. Number and percentage of subjects with hSBA-MenA, hSBA-MenC, hSBA-MenW-135 or hSBA-MenY antibody titres equal to or above 1:4 and 1:8 and GMTs (ATP cohort for immunogenicity at Month 61)

				≥ 1:4				≥ 1:8				GMT		
						95% CI				95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
hSBA-MenA	ACWYBST	PI(M60)	104	52	50.0	40.0	60.0	50	48.1	38.2	58.1	7.6	5.7	10.2
		PII(M61)	106	105	99.1	94.9	100	105	99.1	94.9	100	783.8	601.7	1020.9
	ACWY-DT	PI(M60)	29	11	37.9	20.7	57.7	11	37.9	20.7	57.7	6.6	3.5	12.7
		PII(M61)	28	28	100	87.7	100	28	100	87.7	100	952.0	600.9	1508.2
	ACWYPRI	PRE(M60)	79	19	24.1	15.1	35.0	19	24.1	15.1	35.0	3.9	2.9	5.1
		PI(M61)	79	61	77.2	66.4	85.9	61	77.2	66.4	85.9	79.7	46.3	137.4
hSBA-MenC	ACWYBST	PI(M60)	106	101	95.3	89.3	98.5	95	89.6	82.2	94.7	72.1	48.8	106.3
		PII(M61)	109	108	99.1	95.0	100	108	99.1	95.0	100	5020.4	3995.4	6308.4
	ACWY-DT	PI(M60)	28	24	85.7	67.3	96.0	22	78.6	59.0	91.7	28.2	13.7	57.8
		PII(M61)	29	29	100	88.1	100	29	100	88.1	100	6722.1	3950.9	11437.2
	ACWYPRI	PRE(M60)	71	61	85.9	75.6	93.0	51	71.8	59.9	81.9	26.9	16.4	44.1
		PI(M61)	81	78	96.3	89.6	99.2	77	95.1	87.8	98.6	534.7	308.0	928.1
hSBA-MenW-135	ACWYBST	PI(M60)	105	93	88.6	80.9	94.0	92	87.6	79.8	93.2	98.7	70.4	138.5
		PII(M61)	109	109	100	96.7	100	109	100	96.7	100	5517.6	4573.6	6656.4
	ACWY-DT	PI(M60)	28	23	82.1	63.1	93.9	23	82.1	63.1	93.9	75.4	31.0	183.0
		PII(M61)	29	29	100	88.1	100	29	100	88.1	100	3729.0	2415.4	5757.1
	ACWYPRI	PRE(M60)	79	37	46.8	35.5	58.4	37	46.8	35.5	58.4	12.7	7.9	20.4
		PI(M61)	80	74	92.5	84.4	97.2	74	92.5	84.4	97.2	237.7	150.4	375.8
hSBA-MenY	ACWYBST	PI(M60)	106	97	91.5	84.5	96.0	97	91.5	84.5	96.0	178.1	128.6	246.5
		PII(M61)	109	109	100	96.7	100	109	100	96.7	100	5664.3	4590.0	6990.1
	ACWY-DT	PI(M60)	29	27	93.1	77.2	99.2	27	93.1	77.2	99.2	135.7	78.1	235.8
		PII(M61)	29	29	100	88.1	100	29	100	88.1	100	6546.4	4312.3	9938.0
	ACWYPRI	PRE(M60)	78	52	66.7	55.1	76.9	52	66.7	55.1	76.9	35.6	21.6	58.8
		PI(M61)	84	82	97.6	91.7	99.7	82	97.6	91.7	99.7	755.1	522.4	1091.4

ACWYBST = Pooled subjects 10-25 years of age from ACWY<11 and ACWY-TT groups in the primary study MenACWY-TT-052 who received MenACWY-TT in that study and in current study
ACWY-DT = Subjects 11-25 years of age in the primary study MenACWY-TT-052 who received *Menactra* in that study and MenACWY-TT in current study
ACWYPRI = Subjects 15-<31 years at the time of primary vaccination with MenACWY-TT in current study
GMT = geometric mean antibody titre calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with titre equal to or above specified value
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE(M60) = Pre-primary vaccination at Month 60 for ACWYPRI group in current study
PI(M60) = Post-primary vaccination and pre-booster vaccination at Month 60 for ACWY-TT and ACWY-DT groups
PI(M61) = Post-primary vaccination at Month 61 for ACWYPRI groups
PII(M61) = Post-booster vaccination at Month 61 for ACWY-TT and ACWY-DT groups

- hSBA vaccine response
    - One month after booster vaccination with MenACWY-TT, the percentage of subjects with a booster response for hSBA-MenA, hSBA-MenC, hSBA-MenW-135 and hSBA-MenY in the ACWYBST group was 97.0%, 91.5%, 96.2% and 91.5%, respectively, and 85.7%, 96.4%, 85.7% and 93.1% for hSBA-MenA, hSBA-MenC, hSBA-MenW-135 and hSBA-MenY, respectively, in the ACWY-DT group.

- One month after the primary vaccination in the ACWYPRI group, the percentage of subjects with a vaccine response for hSBA-MenA, hSBA-MenC, hSBA-MenW-135 and hSBA-MenY was 68.0%, 69.1%, 67.1% and 67.9%, respectively.

Table 6. Vaccine response for hSBA-MenA, hSBA-MenC, hSBA-MenW-135 and hSBA-MenY antibodies one month post vaccination (ATP cohort for immunogenicity at Month 61)

				Vaccine response			
						95% CI	
Antibody	Group	Pre-vaccination status	N	n	%	LL	UL
hSBA-MenA	ACWYBST	S-	50	49	98.0	89.4	99.9
		S+	51	49	96.1	86.5	99.5
		Total	101	98	97.0	91.6	99.4
	ACWY-DT	S-	17	17	100	80.5	100
		S+	11	7	63.6	30.8	89.1
		Total	28	24	85.7	67.3	96.0
	ACWYPRI	S-	57	42	73.7	60.3	84.5
		S+	18	9	50.0	26.0	74.0
		Total	75	51	68.0	56.2	78.3
hSBA-MenC	ACWYBST	S-	5	4	80.0	28.4	99.5
		S+	101	93	92.1	85.0	96.5
		Total	106	97	91.5	84.5	96.0
	ACWY-DT	S-	4	4	100	39.8	100
		S+	24	23	95.8	78.9	99.9
		Total	28	27	96.4	81.7	99.9
	ACWYPRI	S-	9	7	77.8	40.0	97.2
		S+	59	40	67.8	54.4	79.4
		Total	68	47	69.1	56.7	79.8
hSBA-MenW-135	ACWYBST	S-	12	12	100	73.5	100
		S+	93	89	95.7	89.4	98.8
		Total	105	101	96.2	90.5	99.0
	ACWY-DT	S-	5	5	100	47.8	100
		S+	23	19	82.6	61.2	95.0
		Total	28	24	85.7	67.3	96.0
	ACWYPRI	S-	40	34	85.0	70.2	94.3
		S+	36	17	47.2	30.4	64.5
		Total	76	51	67.1	55.4	77.5
hSBA-MenY	ACWYBST	S-	9	9	100	66.4	100
		S+	97	88	90.7	83.1	95.7
		Total	106	97	91.5	84.5	96.0
	ACWY-DT	S-	2	2	100	15.8	100
		S+	27	25	92.6	75.7	99.1
		Total	29	27	93.1	77.2	99.2
	ACWYPRI	S-	26	24	92.3	74.9	99.1
		S+	52	29	55.8	41.3	69.5
		Total	78	53	67.9	56.4	78.1

ACWYBST = Pooled subjects 10-25 years of age from ACWY<11 and ACWY-TT groups in the primary study MenACWY-TT-052 who received MenACWY-TT in that study and in current study

ACWY-DT = Subjects 11-25 years of age in the primary study MenACWY-TT-052 who received *Menactra* in that study and MenACWY-TT in current study

ACWYPRI = Subjects 15-<31 years at the time of primary vaccination with MenACWY-TT in current study

S- = seronegative subjects (antibody titre < 1:4 for hSBA-MenA, hSBA-MenC, hSBA-MenW-135, hSBA-MenY) prior to vaccination

S+ = seropositive subjects (antibody titre ≥ 1:4 for hSBA-MenA, hSBA-MenC, hSBA-MenW-135, hSBA-MenY) prior to vaccination

Total = subjects either seropositive or seronegative prior to vaccination

Vaccine response defined as:

For initially seronegative subjects: antibody titre ≥ 1:8 at one month after vaccination

For initially seropositive subjects: antibody titre at one month after vaccination ≥ 4 fold the titres before vaccination

N = number of subjects with both pre- and post-vaccination results available

n/% = number/percentage of responders

95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

Safety

- Persistence phase

No SAEs considered to be possibly related to vaccination by the investigator or considered related to study participation were reported during the Year 5 persistence phase of the study.

- Booster phase

During the 4-day follow-up period after booster vaccination, at least one symptom (solicited or unsolicited) was reported in 71.6%, 73.7% and 68.3% of subjects in the ACWYBST, ACWY-DT and ACWYPRI groups, respectively.

Grade 3 symptoms were reported in 5.5%, 2.6% and 6.9% of subjects in the ACWYBST, ACWY-DT and ACWYPRI groups, respectively. In the ACWYBST group, 2.7% of the grade 3 symptoms were general and 4.4% were local. In the ACWY-DT group, only grade 3 local symptoms were reported (2.6%). In the ACWYPRI group, 4.0% of the grade 3 symptoms were general and 3.0% local in the ACWYPRI group.

  - Solicited local adverse events

Pain was the most frequently reported solicited local symptom during the 4-day follow-up period in all three groups (58.8% of subjects in the ACWYBST group, 54.1% of subjects in the ACWT-DT group and 60.4% of subjects in the ACWYPRI group), with grade 3 pain reported in 3.5% of subjects in the ACWYBST group and 1.1% of subjects in the ACWYPRI group. No grade 3 pain was reported in the ACWY-DT group.

Redness was reported in 22.9% of subjects in the ACWYBST group, 16.2% of subjects in the ACWY-DT group and 18.7% of subjects in the ACWYPRI group, with no grade 3 redness reported in any of the groups.

Swelling was reported in 15.9% of subjects in the ACWYBST group, 13.5% of subjects in the ACWY-DT group and 15.4% of subjects in the ACWYPRI group. Grade 3 swelling was reported in 1.2% of subjects in the ACWYBST group, 2.7% of subjects in the ACWY-DT group and 2.2% of subjects in the ACWYPRI group.

Table 7. Incidence of solicited local symptoms reported during the 4-day (Days 0-3) post-vaccination period (Total Vaccinated Cohort)

		ACWYBST					ACWY-DT					ACWYPRI				
					95 % CI					95 % CI					95 % CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Pain	All	170	100	58.8	51.0	66.3	37	20	54.1	36.9	70.5	91	55	60.4	49.6	70.5
	Grade 2 or 3	170	69	40.6	33.1	48.4	37	10	27.0	13.8	44.1	91	35	38.5	28.4	49.2
	Grade 3	170	6	3.5	1.3	7.5	37	0	0.0	0.0	9.5	91	1	1.1	0.0	6.0
	Medical advice	170	0	0.0	0.0	2.1	37	0	0.0	0.0	9.5	91	0	0.0	0.0	4.0
Redness (mm)	All	170	39	22.9	16.9	30.0	37	6	16.2	6.2	32.0	91	17	18.7	11.3	28.2
	>20.0	170	4	2.4	0.6	5.9	37	2	5.4	0.7	18.2	91	2	2.2	0.3	7.7
	>50.0	170	0	0.0	0.0	2.1	37	0	0.0	0.0	9.5	91	0	0.0	0.0	4.0
	Medical advice	170	0	0.0	0.0	2.1	37	0	0.0	0.0	9.5	91	0	0.0	0.0	4.0
Swelling (mm)	All	170	27	15.9	10.7	22.3	37	5	13.5	4.5	28.8	91	14	15.4	8.7	24.5
	>20.0	170	5	2.9	1.0	6.7	37	1	2.7	0.1	14.2	91	4	4.4	1.2	10.9
	>50.0	170	2	1.2	0.1	4.2	37	1	2.7	0.1	14.2	91	2	2.2	0.3	7.7
	Medical advice	170	0	0.0	0.0	2.1	37	0	0.0	0.0	9.5	91	0	0.0	0.0	4.0

- Solicited general adverse events

Fatigue and headache were the most frequently reported solicited general symptoms during the 4-day follow-up period in all three groups.

Fatigue was reported in 34.1%, 18.9% and 33.0% of subjects in the ACWYBST, ACWYDT and ACWYPRI groups, respectively. Grade 3 fatigue symptoms were reported in 1.8% of subjects in the ACWYBST group and 1.1% of subjects in the ACWYPRI group. No subjects reported grade 3 fatigue symptoms in the ACWY-DT group.

Headache was reported in 35.9%, 27.0% and 24.2% of subjects in the ACWYBST, ACWY-DT and ACWYPRI groups, respectively. Grade 3 headache was reported in 1.1% of subjects in the ACWYPRI group. There were no grade 3 symptoms reported for headache in the ACWYBST or ACWY-DT groups.

Gastrointestinal symptoms were reported in 16.5%, 21.6% and 22.0% of subjects in the ACWYBST, ACWY-DT and ACWYPRI groups, respectively. Grade 3 gastrointestinal symptoms were only reported in 2.2% of subjects in the ACWYPRI group.

Fever of any intensity (temperature ≥37.5◦C) was reported in 2.4% of subjects in the ACWYBST group and 3.3% of subjects in the ACWYPRI group with none reported in the ACWY-DT group. None of the subjects in any group had fever >39.5.

Table 8. Incidence of solicited general symptoms reported during the 4-day (Days 0-3) post-vaccination period (Total Vaccinated Cohort)

		ACWYBST					ACWY-DT					ACWYPRI				
					95 % CI					95 % CI					95 % CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Fatigue	All	170	58	34.1	27.0	41.8	37	7	18.9	8.0	35.2	91	30	33.0	23.5	43.6
	Grade 2 or 3	170	23	13.5	8.8	19.6	37	3	8.1	1.7	21.9	91	8	8.8	3.9	16.6
	Grade 3	170	3	1.8	0.4	5.1	37	0	0.0	0.0	9.5	91	1	1.1	0.0	6.0
	Related	170	57	33.5	26.5	41.2	37	6	16.2	6.2	32.0	91	29	31.9	22.5	42.5
	Grade 3*Related	170	3	1.8	0.4	5.1	37	0	0.0	0.0	9.5	91	1	1.1	0.0	6.0
	Medical advice	170	1	0.6	0.0	3.2	37	0	0.0	0.0	9.5	91	0	0.0	0.0	4.0
Gastrointestinal symptoms	All	170	28	16.5	11.2	22.9	37	8	21.6	9.8	38.2	91	20	22.0	14.0	31.9
	Grade 2 or 3	170	7	4.1	1.7	8.3	37	2	5.4	0.7	18.2	91	6	6.6	2.5	13.8
	Grade 3	170	0	0.0	0.0	2.1	37	0	0.0	0.0	9.5	91	2	2.2	0.3	7.7
	Related	170	28	16.5	11.2	22.9	37	8	21.6	9.8	38.2	91	17	18.7	11.3	28.2
	Grade 3*Related	170	0	0.0	0.0	2.1	37	0	0.0	0.0	9.5	91	1	1.1	0.0	6.0
	Medical advice	170	0	0.0	0.0	2.1	37	0	0.0	0.0	9.5	91	0	0.0	0.0	4.0
Headache	All	170	61	35.9	28.7	43.6	37	10	27.0	13.8	44.1	91	22	24.2	15.8	34.3
	Grade 2 or 3	170	17	10.0	5.9	15.5	37	2	5.4	0.7	18.2	91	7	7.7	3.1	15.2
	Grade 3	170	0	0.0	0.0	2.1	37	0	0.0	0.0	9.5	91	1	1.1	0.0	6.0
	Related	170	60	35.3	28.1	43.0	37	10	27.0	13.8	44.1	91	21	23.1	14.9	33.1
	Grade 3*Related	170	0	0.0	0.0	2.1	37	0	0.0	0.0	9.5	91	1	1.1	0.0	6.0
	Medical advice	170	1	0.6	0.0	3.2	37	0	0.0	0.0	9.5	91	0	0.0	0.0	4.0
Temperature/(Axillary) (°C)	All	170	4	2.4	0.6	5.9	37	0	0.0	0.0	9.5	91	3	3.3	0.7	9.3
	≥37.5	170	4	2.4	0.6	5.9	37	0	0.0	0.0	9.5	91	3	3.3	0.7	9.3
	>38.0	170	0	0.0	0.0	2.1	37	0	0.0	0.0	9.5	91	1	1.1	0.0	6.0
	>38.5	170	0	0.0	0.0	2.1	37	0	0.0	0.0	9.5	91	1	1.1	0.0	6.0
	>39.0	170	0	0.0	0.0	2.1	37	0	0.0	0.0	9.5	91	0	0.0	0.0	4.0
	>39.5	170	0	0.0	0.0	2.1	37	0	0.0	0.0	9.5	91	0	0.0	0.0	4.0
	Related	170	2	1.2	0.1	4.2	37	0	0.0	0.0	9.5	91	2	2.2	0.3	7.7
	>39.5*Related	170	0	0.0	0.0	2.1	37	0	0.0	0.0	9.5	91	0	0.0	0.0	4.0
	Medical advice	170	0	0.0	0.0	2.1	37	0	0.0	0.0	9.5	91	0	0.0	0.0	4.0

- Unsolicited adverse events

At least one unsolicited symptom was reported by 21.9 % of subjects in the ACWYBST, 23.7% of subjects in the ACWY-DT group and 15.8% of subjects in the ACWYPRI group during the 31-day period after vaccination. Grade 3 unsolicited events were reported in 4.4% of the subjects in the ACWYBST group. No grade 3 unsolicited symptoms were reported in the ACWY-DT and ACWYPRI groups.

The most commonly reported unsolicited adverse event in the ACWYBST group was nasopharyngitis (4 subjects, 2.2%) followed by upper respiratory tract infection, headache, and oropharyngeal pain (3 subjects, 1.6% for each event). The most commonly reported unsolicited adverse event in the ACWY-DT group was upper respiratory infection (2 subjects, 5.3%) followed by vomiting, chills, injection site pruritus, pain in the extremity, dizziness, dysmenorrhoea, oropharyngeal pain, hypermetropia, and vaginitis bacterial, each reported in 1 subject (2.6%). The most commonly reported unsolicited adverse events in the ACWYPRI group were headache and influenza, each reported in 2 subjects (2.0%).

Vaccine related unsolicited symptoms were reported in 7.7% of subjects in the ACWYBST group, 7.9% of subjects in the ACWY-DT group, and in 5.0% of subjects in the ACWYPRI group. No grade 3 vaccine related unsolicited symptoms were reported in any of the groups.

- Serious adverse events

SAEs were reported for 3 (1.6%) subjects in the ACWYBST group during the 6 month period following booster vaccination and were not considered related to vaccination. All events (acute appendicitis, depression and malaria) had recovered/resolved by the end of the study with one event recovered but with sequelae (subject with depression). No SAEs were reported in the ACWY-DT or ACWYPRI groups. No SAEs were reported within the 31 days after booster vaccination.

Table 9. Listing of SAEs reported following vaccination in the study MenACWY-TT-059 up to end of Extended Safety Follow-up (Total Vaccinated Cohort)

Group	Sub. No.	Case Id	Age at onset (Year)	Sex	Verbatim	Preferred term	System Organ Class	MA type	Dose	Day of onset	Duration	Intensity	Causality	Outcome
ACWYBST	1007	B0844289B	18	F	Acute appendicitis	Appendicitis	Infections and infestations	HO	1	118	3	3	N	Recovered/resolved
	1342	R0024567A	20	M	Depressive disorder	Depression	Psychiatric disorders	HO	1	107	20	3	N	Recovered/resolved with sequelae
	2018	R0024376A	20	M	Malaria	Malaria	Infections and infestations	HO	1	115	18	3	N	Recovered/resolved

No fatal SAEs were reported during the course of the study.

Discussion on clinical aspects

Data from Year 5 of the extension of the original MenACWY-TT-059 study are available from 312 subjects. 852 subjects were randomised at baseline, and 487 returned for the Year 3 visit. Despite the limited number of subjects, particularly in the cohort who were aged under 11 years in the original vaccination phase, the data from Year 5 are consistent with those from Year 3, and generally show a persistence of effect against all four meningitis serogroups targeted by the vaccine. Although the MenA GMTs had dropped close to the pre-vaccination levels by12 months after vaccination, they continued to increase thereafter, up to Year 5. MenC GMTs declined between Years 3 and 5, but remained above baseline levels. The persistence of effect appears better with Nimenrix than with the comparator, Menactra.

In the booster study, the effect of a Nimenrix booster in subjects originally vaccinated with Nimenrix 5 years earlier in the original study was compared against that in subjects originally vaccinated with Menactra, and a cohort of vaccine-naïve subjects were administered a primary dose of Nimenrix as an additional comparison. A strong immunogenic response was observed in both booster groups, and no safety concerns were evident in the booster groups as compared with the vaccine-naïve group.

III. Rapporteur's overall conclusion and recommendation

Overall conclusion

The MAH has provided Year 5 persistence data from the MenACWY-TT-059 (EXT052) study, which are broadly consistent with data from Year 3 of the study. A booster at Year 5 elicited a strong immunogenic response. No new safety concerns are raised.

The SmPC currently includes persistence data up to Year 3 from this study. This is acceptable.

Recommendation

☒ **Fulfilled:**

No further action required, however further data are expected in the context of a variation before any conclusion on product information amendments is made.

Additional clarifications requested

Not applicable.

<Annex. Line listing of all the studies included in the development program>

The studies should be listed by chronological date of completion:

<Non clinical studies>

Product Name: Active substance:

Study title	Study number	Date of completion	Date of submission of final study report

<Clinical studies>

Product Name: Active substance:

Study title	Study number	Date of completion	Date of submission of final study report