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Committee for Medicinal Products for Human Use (CHMP)

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

Nimenrix

meningococcal group a, c, w135 and y conjugate vaccine

Procedure no: EMEA/H/C/002226/P46/054

Note

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

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Table of contents

1. Introduction 4

2. Scientific discussion 4

2.1. Information on the development program 4
2.2. Information on the pharmaceutical formulation used in the study. 4
2.3. Clinical aspects 4
2.3.1. Introduction 4
2.3.2. Clinical study 5
Study MenACWY-TT-099 5
Methods 5
Results 10
2.3.3. Discussion on clinical aspects 15

3. CHMP overall conclusion and recommendation 16

☒ Fulfilled: 16

1. Introduction

On 12 July 2019, the MAH submitted data from a completed paediatric study for Nimenrix, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

These data are submitted as part of this post-authorisation measure (PAM) P46/054.

A short overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that Study MenACWY-TT-099 is a stand-alone study.

In addition to this study, two other studies have recently been completed, MenACWY-TT-100 (C0921004) under review at the time of submission of P46/054 (procedure EMEA/H/C/002226/P46/053) and an adult study MenACWYTT-101 (C0921005). All these studies assessed long-term antibody persistence up to 10 years after vaccination with MenACWY-TT, or comparator vaccine and the immunogenicity and safety of a booster dose of MenACWY-TT administered 10 years after primary vaccination. After complete data from all three of these studies are available, Pfizer proposes to submit a variation to update the SmPC with long term antibody persistence and booster data based on the complete data set from these studies. Pfizer anticipates submitting this variation in either September or October 2019.

2.2. Information on the pharmaceutical formulation used in the study.

Nimenrix powder and solvent for solution for injection in pre-filled syringe Meningococcal group A, C, W-135 and Y conjugate vaccine.

2.3. Clinical aspects

2.3.1. Introduction

- Protocol MenACWY-TT-099 (C0921002); formerly GlaxoSmithKline 116725

A Phase IIIb, Open, Multi-Center Study to Evaluate the Long-Term Antibody Persistence at 6, 7, 8, 9 and 10 Years After the Administration of One Dose of Meningococcal Conjugate Vaccine MenACWY-TT Versus 1 Dose of Meningococcal Polysaccharide Vaccine Mencevax® ACWY, and to Evaluate the Safety and Immunogenicity of a Booster Dose of MenACWY-TT Vaccine Administered 10 Years After Primary Vaccination of 11-55 Year Old Subjects With MenACWY-TT or Mencevax® ACWY.

Study MenACWY-TT-099 (C0921002) was an extended follow-up study to evaluate antibody persistence 6, 7, 8, 9, and 10 years after primary vaccination. In the original study, MenACWY-TT-015 (107386), 500 healthy subjects between 11 and 55 years of age were randomized using a 3:1 ratio to receive either a single dose of the quadrivalent meningococcal conjugate vaccine MenACWY-TT (ACWY-TT group) or the meningococcal quadrivalent polysaccharide vaccine Mencevax ACWY (MenPS group). Antibody persistence was evaluated up to 5 years after vaccination in extension studies MenACWY-TT-016 through -020. The primary vaccination study MenACWY-TT-015 was conducted in Saudi Arabia and in the Philippines. Study MenACWY-TT-099 was conducted only in the Philippines. The study provides a summary of the immunogenicity and safety results up to 10 years after vaccination. Results

are also presented for evaluations of the safety and immunogenicity of a booster dose of MenACWY-TT administered to all eligible subjects 10 years after the primary vaccination.

2.3.2. Clinical study

Study MenACWY-TT-099

Methods

Objective(s)

The main purpose of this study was to evaluate antibody persistence 6, 7, 8, 9, and 10 years after primary vaccination with MenACWY-TT as compared to Mencevax ACWY when given to healthy participants 11 to 55 years of age. The safety and immunogenicity of a booster dose of MenACWY-TT administered to all participants 10 years after the primary vaccination was evaluated

Objectives	Endpoints
Primary Immunogenicity	
• To evaluate the long-term persistence of the serum bactericidal (antibody) titers induced by MenACWY-TT as compared to Mencevax ACWY when administered to individuals 11-55 years of age.	• The percentage of subjects with rSBA-MenA, rSBA-MenC, rSBA-MenW-135 and rSBA-MenY antibody titers ≥1:8 and ≥1:128 and GMTs.
Secondary Immunogenicity	
• To evaluate immunogenicity one month after booster vaccination with MenACWY-TT.	• The percentage of subjects with rSBA-MenA, rSBA-MenC, rSBA-MenW-135, and rSBA-MenY antibody titers ≥1:8 and ≥1:128 and GMTs. • The percentage of subjects with rSBA-MenA, rSBA-MenC, rSBA-MenW-135, rSBA-MenY vaccine response[a].
• To evaluate anti-TT concentrations before and one month after booster vaccination with MenACWY-TT.	• The percentage of subjects with anti-TT concentrations ≥0.1 IU/mL and ≥1.0 IU/mL and GMCs.
Secondary Safety	
• To evaluate the safety and reactogenicity of a booster vaccination dose of MenACWY-TT in terms of solicited events, unsolicited events, serious adverse events (SAEs), and new-onset chronic illnesses (NOCIs) (eg, autoimmune disorders, asthma, Type I diabetes, and allergies).	• Occurrence of solicited local and general events on Days 0-3 following the booster vaccination. • Occurrence of unsolicited events up to 31 days following booster vaccination. • Occurrence of SAEs, NOCIs (eg, autoimmune disorders, asthma, Type 1 diabetes, and allergies), Guillain-Barré syndrome, and meningococcal disease from administration of the vaccine dose until study end.
Abbreviations: GMC = geometric mean concentration; GMT = geometric mean titer; 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; TT = tetanus toxoid. [a] rSBA vaccine responses for serogroups A, C, W-135, and Y are defined as: For initially seronegative subjects (prevaccination titer below the cutoff of 1:8): rSBA antibody titers ≥1:32 one month after vaccination, and for initially seropositive subjects (prevaccination titer ≥1:8): rSBA antibody titers at least 4 times the prevaccination antibody titers, one month after vaccination.	

Booster Phase

Booster starting at Visit 5 (Month 120 [Year 10] after primary vaccination) and ending at the phone contact visit (Month 126 or 6 months after booster vaccination).

There were 2 parallel groups in this study:

- ACWY-TT group: all participants vaccinated with MenACWY-TT in Study MenACWY-TT-015 (107386)
- MenPS group: all participants vaccinated with Mencevax ACWY in Study MenACWY-TT-015 (107386)

Four hundred (400) subjects (299 in the ACWY-TT group and 101 in the MenPS group) were enrolled and vaccinated in Study MenACWY-TT-015 (107386) in the Philippines. The subjects who completed the vaccination phase of Study MenACWY-TT-015 (107386) and received either MenACWY-TT or Mencevax ACWY were eligible for this study if they met the inclusion criteria and no exclusion criteria. Participants were followed up for 5 years after vaccination. The subjects were allowed to return at any visit during the persistence phase.

Study design

Study MenACWY-TT-099 (C0921002) was a Phase 3b, open-label study with 2 parallel groups that was designed to evaluate the persistence of meningococcal antibodies 6, 7, 8, 9, and 10 years after primary vaccination with MenACWY-TT or Mencevax ACWY in Study MenACWY-TT-015. However, the Year 6 study visit was not completed, and thus there are no data for Year 6. At 10 years after primary vaccination, a booster dose of MenACWY-TT was administered to subjects in both vaccine groups, and the immunogenicity, safety, and reactogenicity of the booster dose was evaluated.

All subjects who completed the vaccination phase of Study MenACWY-TT-015 were eligible for Study MenACWY-TT-099 if they met the inclusion criteria and none of the exclusion criteria. During the persistence phase of the study, subjects attended visits once a year, when blood samples were drawn for determination of antibody titers at the following time points: Year 7 (Month 84); Year 8 (Month 96); Year 9 (Month 108); Year 10 (Month 120). At the Year 10 visit, subjects received a single booster dose of MenACWY-TT and returned 1 month later for a blood draw for determination of antibody titers. Bactericidal activity was measured by serum bactericidal assays using rabbit complement (rSBA) to measure activity against Neisseria meningitidis group A (rSBA-MenA), group C (rSBA- MenC), group W-135 (rSBA-MenW-135), and group Y (rSBA-MenY).

At each persistence phase visit, serious adverse events (SAEs) related to study participation, fatal SAEs, SAEs leading to withdrawal from the study, and any occurrence of meningococcal disease were to be reported. Unsolicited adverse events (AEs) and pregnancies were reported from the time of booster vaccination through the 31-day postbooster visit. Solicited local events (pain, redness, swelling) and solicited general events (fever ≥37.5°C, fatigue, gastrointestinal symptoms, and headache) were recorded daily in a diary for 4 days after the vaccination. Serious adverse events, new-onset chronic illnesses (NOCIs), and Guillain Barré Syndrome (GBS) were reported from the time of booster vaccination through the 6-month follow-up telephone contact.

Study population /Sample size

A total of 311 subjects were enrolled in the study: 235 in the ACWY-TT group and 76 in the MenPS group. Mean age at enrollment was 25.2 years; approximately 48% of subjects were female, and all subjects were of Asian/Southeast Asian heritage. The proportions of subjects attending each of the annual visits were approximately 93% at Year 7, 90% at Year 8, 82% at Year 9, and 74% at Year 10. Overall, 80 subjects (approximately 26%) withdrew from the study during the persistence phase, with

the most frequent reasons for withdrawal being moved from study area (41 subjects) and "other reason" (30 subjects); the most common "other reasons" cited for withdrawal were a busy work schedule, conflict with work schedule, or ineligibility as per eligibility criteria. A total of 220 subjects received the booster dose: 164 in the ACWY-TT group and 56 in the MenPS group, and 5 subjects were withdrawn from the study during the booster phase (due to 'moved from area' or lost to follow-up).

Treatments

Investigational Product Name	Manufacturer	Vaccine/ Component Name	Formulation	Presentation	Volume to Be Administered	Lot Number
Primary vaccine (1 through 10 years)						
MenACWY-TT	GlaxoSmithKline Biologicals	MenACWY-TT	5 µg of PSA conjugated to TT 5 µg of PSC conjugated to TT 5 µg of PSW-135 conjugated to TT 5 µg of PSY conjugated to TT ~44 µg of TT	Lyophilized pellet to be reconstituted with saline diluent	0.5 mL	DMECA007A Diluent: AD02B076B
Meningococcal serogroup ACWY vaccine	GlaxoSmithKline Biologicals	Mencevax ACWY	50 µg of PSA 50 µg of PSC 50 µg of PSW-135 50 µg of PSY	Lyophilized pellet to be reconstituted with saline diluent	0.5 mL	AMENB036A Diluent: AD02B118A
Year 10 booster dose						
MenACWY-TT	GlaxoSmithKline Biologicals (vaccine acquired by Pfizer on 01Oct2015)	MenACWY-TT	5 µg of PSA conjugated to TT 5 µg of PSC conjugated to TT 5 µg of PSW-135 conjugated to TT 5 µg of PSY conjugated to TT ~44 µg of TT	Lyophilized pellet to be reconstituted with saline diluent	0.5 mL	Vendor Lot Number/Lot Number[a] (Pfizer) R98867/16-005696 Diluent: R98866/16-005753

Abbreviations: PSA, PSC, PSW-135, and PSY = polysaccharide *Neisseria meningitidis* groups A, C, W-135, and Y; TT = tetanus toxoid.
[a] Lot number assigned to the investigational product by Pfizer Global Clinical Supply.

Outcomes/endpoints

See Objectives in the beginning of this chapter for endpoints.

Statistical Methods

The analysis cohorts:

- Total Cohort at Year X
- According-to-protocol (ATP) Cohort for Persistence at Year X
- Adapted ATP Cohort (denotes, for each time point, that subjects belong to the corresponding ATP Cohort for Immunogenicity or persistence at that time point)
- Total Enrolled Cohort
- Booster Total Vaccinated Cohort at Year 10
- Booster ATP Cohort for Safety at Year 10
- Booster ATP Cohort for Immunogenicity at Year 10

Analysis of Persistence

For each Year X: The analysis of antibody persistence was based on the ATP cohort for antibody persistence at Year X. If, for any vaccine group, the percentage of subjects who come back for the Year X follow-up with serological results excluded from the ATP cohort is higher than 5%, a second analysis based on the total cohort at Year X was performed to complement the ATP analysis.

Within Group Analysis

For each vaccine group, at each blood sampling time point in Study MenACWY-TT-099, for each antigen assessed:

- GMTs with 95% CIs will be tabulated.
- Percentages of subjects with titers above the proposed cut-offs with exact 95% Cis will be calculated.
- The distribution of antibody titers will be tabulated and also presented using reverse cumulative distribution curves.

In addition, the following analyses will also be performed by age stratum:

- GMTs with 95% CIs will be tabulated.
- Percentages of subjects with titers above the proposed cut-offs with exact 95% Cis will be calculated.
- Geometric mean anti-TT concentrations (GMCs) with 95% CIs will be tabulated.

Modelling prediction

In order to complement the descriptive analyses of observed persistence per time point and minimize the bias that may have occurred due to the loss to follow-up after the vaccination, a longitudinal analysis will be performed at the last time point for rSBA-MenA, C, W-135, and Y at Year 10.The longitudinal analyses will include all titers from:

- The pre- and post-primary vaccination analysis (Month 0 and Month 1 in Study MenACWY-TT-015) for subjects belonging in the ATP cohort for immunogenicity defined in Study MenACWY-TT-015.
- Year 1, 2, 3, 4, and 5 (in Study MenACWY-TT-016, -017,- 018,- 019, and -020 respectively) for subjects belonging in the ATP cohort for persistence defined in each study respectively, and
- Year 7, 8, 9, and 10 (in Study MenACWY-TT-099) for subjects belonging in the ATP cohort for persistence at Year 7 (Month 84) up to Year 10 (Month 120), respectively.

Note that since the Year 6 (Month 72) visit was not done the ATP cohort for persistence at Year 6 is not applicable. A longitudinal model taking into account the vaccine group, age cohort, and all available immunogenicity time points from pre-primary time point (in Study MenACWY-TT-015) until the last persistence time point at Year 10 (in Study MenACWY-TT-099) will be fitted. This model will be primarily aimed at evaluating the selection effect in the group and the time points will be considered as categorical.

MenACWY-TT Antibody Response

Bactericidal antibodies specific for meningococcal antigens are recognized as surrogate markers of protection against meningococcal disease. A serum bactericidal assay using rabbit complement (rSBA) with a cut-off of 1:8 was shown to be the most consistent with observed efficacy at 4 weeks after vaccination with the meningococcal group C conjugate vaccine in post-licensure efficacy estimates in the United Kingdom. Following common practice, the 1:8 cut-off for the rSBA to measure activity against *N. meningitidis* group C (rSBA-MenC) was extended for rSBA to measure activity against *N. meningitidis* group A (rSBA-MenA), rSBA to measure activity against *N. meningitidis* group W-135 (rSBA-MenW-135), and rSBA to measure activity against *N. meningitidis* group Y (rSBA-MenY).

Functional anti-meningococcal serogroup bactericidal activity (ie, rSBA-MenA, rSBA-MenC, rSBA-MenW-135, and rSBA-MenY) was determined by an rSBA according to the Centers for Disease Control and Prevention (CDC) protocol.11 rSBA titers were expressed as the reciprocal of the highest serum last dilution resulting in at least a 50% reduction of meningococcal colony-forming units.

Specific antibody against TT was measured by dLIA. The cut-off of the assay was 0.037 international unit (IU)/mL.

Laboratories Performing rSBAs by Time Point.

Study MenACWY-	Time Point	GSK	PHE
TT-015	Prevaccination	X	
	Month 1	X	
TT-016	Year 1	X	
TT-017	Year 2	X	
TT-018	Year 3	X	
TT-019	Year 4		X
TT-020	Year 5		X
TT-099	Month 84 (Year 7)		X
	Month 96 (Year 8)		X
	Month 108 (Year 9)		X
	Month 120 (Year 10)		X
	Month 121		X

GSK = GlaxoSmithKline; PHE = Public Health England; rSBA = serum bactericidal assay using rabbit complement

Results

Recruitment/ Number analysed

Table 1. Study Population – Persistence Phase (Total Cohort at Months 84, 96, 108, and 120)

	Vaccine Group		
	ACWY-TT[a]	MenPS[b]	Total
Planned[c], N	252	84	336
Enrolled, N[d] (total enrolled cohort)	235	76	311
Completed Month 84 (Visit 2), n[e] (%)[f]	219 (93.2)	69 (90.8)	288 (92.6)
Completed Month 96 (Visit 3), n[e] (%)[f]	212 (90.2)	67 (88.2)	279 (89.7)
Completed Month 108 (Visit 4), n[e] (%)[f]	193 (82.1)	61 (80.3)	254 (81.7)
Completed Month 120 (Visit 5), n[e] (%)[f]	173 (73.6)	58 (76.3)	231 (74.3)
Demographic information			
Females:males	108:127	40:36	148:163
Mean age at enrollment, years (SD)	25.3 (8.2)	25.2 (8.4)	25.2 (8.2)
Median age, years (minimum, maximum)	22.0 (18, 60)	22.0 (18, 55)	22.0 (18, 60)
Race			
Asian - South East Asian heritage, n[e] (%)[f]	235 (100.0)	76 (100.0)	311 (100.0)
Ethnicity			
Not American Hispanic or Latino, n[e] (%)[f]	235 (100.0)	76 (100.0)	311 (100.0)

Note: Date of birth, sex, race, and ethnicity were collected in primary study MenACWY-TT-015.
Note: Subjects were randomized and the primary vaccinations were administered at 11 to 55 years of age in primary study MenACWY-TT-015; all subjects who were given the booster vaccination in Study MenACWY-TT-099 (C0921002) received MenACWY-TT at Month 120.
Note: The age is computed based on the date of enrollment visit in Study MenACWY-TT-099 (C0921002).
a. ACWY-TT = vaccinated with MenACWY-TT in Study MenACWY-TT-015.
b. MenPS = vaccinated with Mencevax ACWY in Study MenACWY-TT-015.
c. Planned number of subjects was based on an assumption that approximately 10% of the potential subjects would not participate at Visit 1 (Month 72).
d. N = number of subjects.
e. n = Number of subjects within each category.
f. % = Percentage of subjects within each category was calculated based on total enrolled cohort in persistence phase.

Table 2. Study Population – Booster Phase (Booster Total Vaccinated Cohort)

	Vaccine Group		
	ACWY-TT[a]	MenPS[b]	Total
Enrolled, N[c] (booster total vaccinated cohort)	164	56	220
Completed Month 121 (Visit 6), n[d] (%)[e]	159 (97.0)	53 (94.6)	212 (96.4)
Completed Month 126 (phone call), n[d] (%)[e]	161 (98.2)	54 (96.4)	215 (97.7)
Demographic information			
Females:males	71:93	27:29	98:122
Mean age at booster vaccination, years (SD)	26.8 (7.9)	27.4 (8.7)	26.9 (8.1)
Median age, years (minimum, maximum)	24.0 (21, 63)	24.5 (21, 56)	24.0 (21, 63)
Race			
Asian - South East Asian heritage, n[d] (%)[e]	164 (100.0)	56 (100.0)	220 (100.0)
Ethnicity			
Not American Hispanic or Latino, n[d] (%)[e]	164 (100.0)	56 (100.0)	220 (100.0)

Note: Date of birth, sex, race, and ethnicity were collected in primary study MenACWY-TT-015.
Note: The age is computed on the date of booster dose visit in Study MenACWY-TT-099 (C0921002).
Note: Subjects were randomized and the primary vaccinations were administered at 11 to 55 years of age in primary study MenACWY-TT-015; all subjects who were given the booster vaccination in Study MenACWY-TT-099 (C0921002) received MenACWY-TT at Month 120.

Note: The booster total vaccinated cohort includes all vaccinated subjects in primary study MenACWY-TT-015 with a documented booster vaccination.

g. ACWY-TT = vaccinated with MenACWY-TT in Study MenACWY-TT-015.
h. MenPS = vaccinated with Mencevax ACWY in Study MenACWY-TT-015.
i. N = number of subjects.
j. n = Number of subjects within each category.
k. % = Percentage of subjects within each category was calculated based on booster total vaccinated cohort in booster phase.

Baseline data

Efficacy results

The mean GMTs observed for rSBA-MenA, rSBA-MenW-135, and rSBA-MenY were higher in the ACWY-TT group in comparison to the MenPS group. GMTs for rSBA-MenC were similar for both vaccine groups. GMTs remained generally similar across all time-points in the persistence phase for both vaccine groups.

The numbers and percentages of subjects with rSBA titers greater than or equal to 1:8 and 1:128 and GMTs for the total enrolled cohort were similar to those observed for the adapted ATP cohort.

In the ACWY-TT vaccine group, the percentage of subjects with rSBA-MenA, rSBA-MenC, rSBA-MenW-135, and rSBA-MenY titers ≥1:8 increased from 71.4% to 90.9% at Month 120 to 100.0% at Month 121 (1 month after booster vaccination). In the MenPS vaccine group, the percentage of subjects with rSBA-MenA, rSBA-MenC, rSBA-MenW-135, andrSBA-MenY titers ≥1:8 increased from 21.2% to 88.5% at Month 120 to 98.1% to 100.0% at Month 121 (1 month after booster vaccination).

The mean GMTs observed at 1 month after booster vaccination were greater in the ACWY-TT group in comparison to the MenPS group, particularly for rSBA-MenC, rSBA-MenW-135, and rSBA-MenY.

Table 3. Number (%) of Subjects With rSBA-MenA, rSBA-MenC, rSBA-MenW-135, or rSBA-MenY Titers ⩾1:8 and ⩾1:128 and GMTs at Each Visit After Primary Vaccination (Adapted ATP Cohort)

				≥1:8				≥1:128				GMT		
					95% CI[a]				95% CI[a]			95% CI[b]		
Antibody	Vaccine Group	Visit[c]	N[d]	n[e]	%[f]	LL	UL	n[e]	%[f]	LL	UL	Value	LL	UL
rSBA-MenA	ACWY-TT[g]	M84	206	182	88.3	83.2	92.4	152	73.8	67.2	79.7	220.8	167.2	291.5
		M96	208	158	76.0	69.6	81.6	126	60.6	53.6	67.3	104.8	77.1	142.4
		M108	190	157	82.6	76.5	87.7	143	75.3	68.5	81.2	227.8	165.0	314.5
		M120	162	124	76.5	69.3	82.8	110	67.9	60.1	75.0	142.5	100.4	202.1
	MenPS[h]	M84	65	44	67.7	54.9	78.8	30	46.2	33.7	59.0	54.5	31.1	95.8
		M96	67	38	56.7	44.0	68.8	27	40.3	28.5	53.0	44.1	24.3	80.0
		M108	61	40	65.6	52.3	77.3	36	59.0	45.7	71.4	81.2	44.2	149.4
		M120	54	38	70.4	56.4	82.0	31	57.4	43.2	70.8	73.7	40.9	132.8
rSBA-MenC	ACWY-TT[g]	M84	206	170	82.5	76.6	87.4	127	61.7	54.6	68.3	105.3	79.7	139.1
		M96	204	176	86.3	80.8	90.7	139	68.1	61.3	74.5	155.4	118.3	204.0
		M108	190	170	89.5	84.2	93.5	127	66.8	59.7	73.5	173.3	129.9	231.1
		M120	161	146	90.7	85.1	94.7	117	72.7	65.1	79.4	181.4	134.6	244.4
	MenPS[h]	M84	65	50	76.9	64.8	86.5	40	61.5	48.6	73.3	156.7	82.7	297.1
		M96	67	54	80.6	69.1	89.2	43	64.2	51.5	75.5	240.6	125.4	461.8
		M108	61	55	90.2	79.8	96.3	41	67.2	54.0	78.7	264.9	147.7	474.9
		M120	54	48	88.9	77.4	95.8	37	68.5	54.4	80.5	234.0	122.3	447.9
rSBA-MenW-135	ACWY-TT[g]	M84	206	125	60.7	53.7	67.4	108	52.4	45.4	59.4	83.2	57.0	121.5
		M96	207	137	66.2	59.3	72.6	126	60.9	53.9	67.6	119.7	82.8	173.1
		M108	190	106	55.8	48.4	63.0	96	50.5	43.2	57.8	71.7	48.0	107.0
		M120	161	113	70.2	62.5	77.1	104	64.6	56.7	72.0	161.5	104.8	248.9
	MenPS[h]	M84	65	15	23.1	13.5	35.2	11	16.9	8.8	28.3	10.0	6.3	15.9
		M96	67	16	23.9	14.3	35.9	11	16.4	8.5	27.5	10.8	6.7	17.5
		M108	61	6	9.8	3.7	20.2	6	9.8	3.7	20.2	6.7	4.5	10.0
		M120	54	13	24.1	13.5	37.6	12	22.2	12.0	35.6	11.9	6.8	21.0
rSBA-MenY	ACWY-TT[g]	M84	206	165	80.1	74.0	85.3	158	76.7	70.3	82.3	270.2	195.2	373.8
		M96	206	157	76.2	69.8	81.9	146	70.9	64.2	77.0	181.6	130.2	253.3
		M108	190	170	89.5	84.2	93.5	164	86.3	80.6	90.9	460.6	346.2	612.7
		M120	161	140	87.0	80.8	91.7	134	83.2	76.5	88.6	387.0	274.1	546.4
	MenPS[h]	M84	65	30	46.2	33.7	59.0	25	38.5	26.7	51.4	32.7	17.8	60.1
		M96	67	27	40.3	28.5	53.0	25	37.3	25.8	50.0	26.0	14.5	46.6
		M108	61	35	57.4	44.1	70.0	31	50.8	37.7	63.9	57.8	30.6	109.2

		M120	54	35	64.8	50.6	77.3	29	53.7	39.6	67.4	63.2	33.4	119.6

Table 4. Number (%) of Subjects With rSBA-MenA, rSBA-MenC, rSBA-MenW-135 and rSBA-MenY Titers ≥1:8 and ≥1:128 and GMTs Before and 1 Month After Booster Vaccination Visit (Booster ATP Cohort for Immunogenicity)

				≥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	ACWY-TT	M120	155	121	78.1	70.7	84.3	108	69.7	61.8	76.8	153.8	108.1	218.6
		M121	155	155	100.0	97.6	100.0	155	100.0	97.6	100.0	4059.5	3383.8	4870.2
	MenPS	M120	52	37	71.2	56.9	82.9	30	57.7	43.2	71.3	75.1	41.4	136.4
		M121	52	52	100.0	93.2	100.0	52	100.0	93.2	100.0	3584.8	2750.7	4672.0
rSBA-MenC	ACWY-TT	M120	154	140	90.9	85.2	94.9	112	72.7	65.0	79.6	192.8	140.6	264.4
		M121	155	155	100.0	97.6	100.0	155	100.0	97.6	100.0	13823.5	10839.7	17628.7
	MenPS	M120	52	46	88.5	76.6	95.6	35	67.3	52.9	79.7	212.4	109.6	411.8
		M121	52	51	98.1	89.7	100.0	50	96.2	86.8	99.5	3444.3	1998.5	5936.0
rSBA-MenW-135	ACWY-TT	M120	154	110	71.4	63.6	78.4	100	64.9	56.8	72.4	166.2	107.1	257.9
		M121	155	155	100.0	97.6	100.0	155	100.0	97.6	100.0	23431.0	17351.4	31640.7
	MenPS	M120	52	11	21.2	11.1	34.7	10	19.2	9.6	32.5	10.9	6.1	19.3
		M121	52	51	98.1	89.7	100.0	51	98.1	89.7	100.0	5792.6	3585.9	9357.4
rSBA-MenY	ACWY-TT	M120	154	133	86.4	79.9	91.4	127	82.5	75.5	88.1	363.7	254.6	519.4
		M121	155	155	100.0	97.6	100.0	155	100.0	97.6	100.0	8958.4	7601.6	10557.5
	MenPS	M120	52	32	61.5	47.0	74.7	26	50.0	35.8	64.2	56.0	28.8	109.1
		M121	52	52	100.0	93.2	100.0	52	100.0	93.2	100.0	5137.8	3528.2	7481.6

Estimated rSBA Predicted by Modeling

rSBA GMTs were predicted by modeling for pre-vaccination and postvaccination (1 month) time points (from Study MenACWY-TT-015 [107386]) and Months 12, 24, 36, 48, 60, 84, 96, 108, and 120 after primary vaccination. For both vaccine groups the estimated GMTs at Months 84 to 120 were generally similar to the observed values, with no indication of bias caused by subjects lost to follow-up during the persistence phase.

Immune Response to MenACWY-TT Anti-TT Concentration ≥0.1 IU/mL and ≥1.0 IU/mL and GMCs

A secondary objective of this study was to evaluate the percentage of subjects with anti-TT concentrations ≥0.1 IU/mL and ≥1.0 IU/mL and geometric mean concentrations (GMCs) before and 1 month after booster vaccination.

Between Month 120 and Month 121 (1 month after booster vaccination), the percentage of subjects with anti-TT concentrations ≥0.1 IU/mL increased from 86.5% to 99.4% in the ACWY-TT group, and from 61.5% to 98.1% in the MenPS group. Similarly, the percentage of subjects with anti-TT concentrations ≥1.0 IU/mL increased from 44.5% to 94.8% in the ACWY-TT group, and from 23.1% to 88.5% in the MenPS group.

Immunogenicity Conclusions

In general, vaccine meningococcal antibodies persisted from Months 84 to 120 after primary vaccination with MenACWY-TT or Mencevax ACWY. The percentage of subjects with rSBA titers greater than or equal to the cut-off values (1:8 and 1:128) and GMTs for the adapted ATP cohort remained generally stable across all time points. The persistence of the rSBA-MenA, rSBA-MenW-135, and rSBA-MenY immune response was generally higher for subjects in the ACWY-TT group in comparison to the MenPS group. The persistence of the rSBA-MenC immune response over time was similar for the ACWY-TT and MenPS groups.

The mean GMTs observed for rSBA-MenA, rSBA-MenW-135, and rSBA-MenY were higher in the ACWY-TT group in comparison to the MenPS group. GMTs for rSBA-MenC were similar for both vaccine groups.

For subjects who received a booster vaccination 10 years after the primary vaccination, a robust booster vaccination response was observed. In both the ACWY-TT and MenPS groups, the percentage of subjects with rSBA-MenA, rSBA-MenC, rSBA-MenW-135, and rSBA-MenY titers ≥1:8 increased from 21.1% to 90.9% at Month 120 to 98.1% to 100.0% at Month 121 (1 month after booster vaccination). The GMTs observed in response to booster vaccination were greater in the ACWY-TT group in comparison to the MenPS group, particularly for rSBA-MenC, rSBA-MenW-135, and rSBA-MenY.

The percentage of subjects in the ACWY-TT and MenPS groups with anti-TT antibody concentrations ≥ 0.1 IU/mL increased from 86.5% and 61.5% at Month 120 to 99.4% and 98.1% at Month 121, respectively.

No clinically relevant differences were observed in vaccine response between subjects who were initially seronegative and those who were initially seropositive before the booster vaccination.

Safety results

Solicited local and general events (pain, redness, and swelling at the injection site; and fatigue, fever, gastrointestinal events [nausea, vomiting, diarrhea, and/or abdominal pain], and headache) were monitored and recorded by subjects on diary cards for 4 days after the booster vaccination.

The proportion of subjects reporting pain was similar in both vaccine groups (27.0% versus 26.4% in the ACWY-TT and MenPS groups, respectively), and the majority of these events were mild in severity. Few subjects in either vaccine group reported redness (5.7% versus 3.8% in the ACWY-TT and MenPS groups, respectively) or swelling (3.8% versus 5.7% in the ACWY-TT and MenPS groups, respectively) at the injection site.

Most solicited general events were mild in severity. The proportion of subjects reporting solicited general events in the ACWY-TT and MenPS vaccine groups was 14.5% and 15.1% for fatigue, 6.9% and 5.7% for fever, 4.4% and 1.9% for gastrointestinal events, and 15.7% and 9.4% for headache, respectively. Grade 3 solicited general events occurred within the ACWY TT group, with 1 report of Grade 3 fatigue (0.6%), 1 report of Grade 3 gastrointestinal event (0.6%), and 2 reports of Grade 3 headache (1.3%); all were assessed as being related to the investigational vaccine by the investigator.

The proportion of subjects reporting at least 1 AE during the 31-day post-booster vaccination period was 9.1% (15 subjects) in the ACWY-TT group and 3.6% (2 subjects) in the MenPS group. Most reported unsolicited AEs were in the system organ class (SOC) of infections and infestations (7 [4.3%] in the ACWY-TT group and 2 [3.6%] in the MenPS group).

Three AEs in the ACWY-TT group were assessed as being related to the investigational vaccine (1 report each of dizziness, hypoesthesia, and oropharyngeal pain), and none of the AEs in the MenPS group were assessed as being related to the investigational vaccine.

No related Grade 3 AEs were reported during this study.

No deaths, SAEs, NOCIs, or other significant AEs (including GBS or meningococcal disease) were reported during the study, and no subjects were withdrawn from the study due to safety-related reasons.

2.3.3. Discussion on clinical aspects

Antibody persistence at Years 7 to 10 after primary vaccination was higher among subjects primed with MenACWY-TT compared with subjects primed with Mencevax ACWY, as measured by the percentage of subjects with rSBA-MenA, rSBA-MenW-135, and rSBA-Men-Y titers greater than or equal to predefined cutoff values. Antibody persistence for MenC was similar for both vaccine groups. While a robust MenACWY-TT booster vaccination response was observed in both vaccine groups, greater GMTs were observed in subjects primed with MenACWY-TT compared with subjects primed with Mencevax ACWY at 1 month after booster vaccination.

No new safety concerns or adverse reactions for Nimenrix were identified in this long-term persistence study of subjects 11 to 55 years of age who received a primary vaccination of either MenACWY-TT or Mencevax ACWY (Study MenACWY-TT-015 [107386]) and who subsequently received a booster dose of MenACWY-TT 10 years after primary vaccination.

Overall, the results of the analysis at 7 to 10 years after primary vaccination and up to 6 months after booster vaccination continue to support a favourable benefit-risk assessment of MenACWY-TT in this age group.

3. CHMP overall conclusion and recommendation

The percentage of subjects with rSBA titers ≥1:8 or ≥1:128 and GMTs at time points 7, 8, 9 and 10 years after the primary vaccination are quite stable. No hSBA data are available from this study, or from the previous reports from the primary vaccination or previous extension studies. There is a good consistency in the rSBA data from PHE (Public Health England) from year 4 after the primary vaccination through the years 7-10. Based on a smaller sample size analysed by PHE from 1 month after the primary vaccination and year 1 and 2, it is evident that the largest drop in rSBA is seen the two first years after the primary dose.

Study TT-99 shows that a booster dose of Nimenrix administered 10 years after primary vaccination in adolescents and adults 11-55 years of age elicited a robust immune responses against each of the 4 serogroups.

Safety results demonstrate that the booster dose was well tolerated, and no new safety concerns were identified.

CHMP agrees that the data from Study MenACWY-TT-99 do not change the benefit-risk profile of Nimenrix.

Long-term antibody persistence data up to 10 years after primary vaccination in 1-10 year old subjects with Nimenrix and the effect of a booster dose (MenACWY-TT-100) was recently reviewed (procedure EMEA/H/C/002226/P46/053). Study (MenACWY-TT-99) provides the same type of data in adolescents and adults 11-55 years of age. In addition, an adult study MenACWYTT-101 is expected to be received for a review. The MAH Pfizer proposes to submit a variation to update the SmPC with long-term antibody persistence and booster data based on the complete data set from these three studies.

The task for the MAH will be closed when the variation application to update the SmPC is assessed and finalised.

☒ Fulfilled:

No further action required.

However, further data are expected in the context of a variation prior to any conclusion on product information amendments being made. The MAH is expected to submit this variation application when study MenACWYTT-101 has been reviewed.