EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Human Medicines Evaluation Division

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

Nimenrix

meningococcal group a, c, w135 and y conjugate vaccine

Procedure no: EMEA/H/C/002226/P46/052

Note

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

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1. Introduction

On 04/05/2018, the MAH submitted the final Clinical Study Report for study MENACWY-TT-102 (C0921001) for which the paediatric data are being submitted in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that MENACWY-TT-102 (C0921001) is a stand-alone study.

2.2. Information on the pharmaceutical formulation used in the study

No investigational products were administered in this antibody persistence study.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- Study MenACWY-TT-102 (C0921001)

2.3.2. Clinical study MenACWY-TT-102 (C0921001)

Description

MenACWY-TT-102 is a phase III, open, multicentre, controlled study to **evaluate the long-term antibody persistence at 2, 3, 4, 5, 6 Years**, after a booster dose of Meningococcal serogroup A, C, W-135, Y -tetanus toxoid conjugate vaccine (MenACWY-TT) or Meningitec® administered in healthy 5 year-old children in study MenACWY-TT-048 EXT: 039 Y2, 3, 4, 5 (112036), who were primed with the same vaccine in study MenACWY-TT-039 (109670) at 12 through 23 months of age.

Methods

Objective(s)

Immunogenicity

Persistence

At 2, 3, 4, 5, 6 years after booster vaccination of children with MenACWY-TT or Meningitec

To evaluate the persistence of meningococcal A, C, W-135, Y Abs as the % of subjects with:

Primary objective: rSBA antibody titres ≥1:8 for each of the 4 serogroups: A, C, W, Y

Secondary objective

- **rSBA titres ≥1:128** and geometric mean titres (GMTs) *presented here* AND
- **hSBA titres ≥1:4 and ≥1:8** and GMTs *yet to be presented*

  for each of the 4 serogroups A, C, W, Y.

Safety

- To describe SAEs related to vaccination and any event related to lack of vaccine efficacy (i.e. meningococcal disease) from the subject's last visit in Study MenACWY-TT-048 up to each yearly visit in the current study in a retrospective manner.

Study design

This study was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with the relevant ICH Good Clinical Practice (GCP) guidelines. This study was undertaken by GSK and conducted at multiple sites in Finland. Sponsorship of the study was transferred to Pfizer, Inc on 12 April 2016, after all subjects had completed Visit 3 (Year 4).

Study population /Sample size

Overall study plan

This was an open-label single-country study with 2 parallel groups to evaluate persistence of meningococcal Abs up to 6 years after booster vaccination in children who had participated in study 112036 (MenACWY-TT-048). At enrolment, the mean age of subjects in Study 112036 (MenACWY-TT-048) was 40.4 months (range: 37 to 45 months) (according-to-protocol [ATP] cohort for persistence at Month 24). There were 2 parallel groups with the subjects in this study being allocated to the same groups and retaining the same subject numbers as the previous study:

- ACWY-TT group: Subjects vaccinated and boosted with MenACWY-TT
- MenCCRM group: Subjects vaccinated and boosted with Meningitec

Sample size

Sample size was driven by the sample size of Study MenACWY-TT-048. The maximum number of subjects who could return at Visit 1 (Month 24) was 248 subjects in total: 206 in the ACWY-TT group and 42 in the MenCCRM group. Based on experience with studies in a similar age group, it was assumed that ~ 10% of potential subjects would not participate to the persistence study at Visit 1 (Month 24). Therefore, a total of 223 subjects (185 in the ACWY-TT group and 38 in the MenCCRM group) were expected to participate at Visit 1 (Month 24). The total duration of the study for each subject was approximately 4 years.

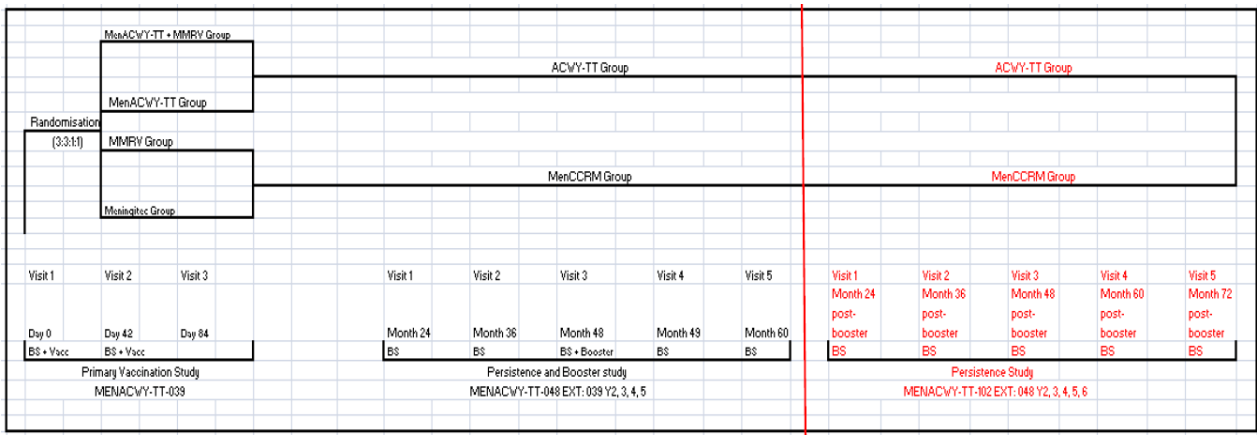
Epochs

- Epoch 001: Persistence Visit 1 (Year 2 [Month 24] after booster vaccination)
- Epoch 002: Persistence Visit 2 (Year 3 [Month 36] after booster vaccination)
- Epoch 003: Persistence Visit 3 (Year 4 [Month 48] after booster vaccination)
- Epoch 004: Persistence Visit 4 (Year 5 [Month 60] after booster vaccination)

- Epoch 005: Persistence Visit 5 (Year 6 [Month 72] after booster vaccination)

A subject could join at any visit in the study

Study design Overview Diagram



Source: menacwy-tt-102-200088-report-body Fig 1

Primary study MenACWY-TT-039: Vaccines administered at 12 to 23 months of age

Booster study MenACWY-TT-048: booster vaccine administered at 5 years of age

ACWY-TT Group = pooled groups from MenACWY-TT-039, primed and boosted with MenACWY-TT, (MenACWY-TT + MMRV group also received 2 doses of MMRV, measles, mumps, rubella, chickenpox/ varicella vaccine, 2nd dose after 84 days as Co-Ad subjects; MenACWY-TT received MenACWY-TT followed by 2 doses of MMRV vaccine after 42 and 84 days respectively).

MenCCRM Group = pooled groups from MenACWY-TT-039, primed and boosted with Meningitec, (MMRV group = MMRV vaccine followed by Meningitec after 42 days & 2nd dose of MMRV after 84 days; MenCCRM group = Meningitec followed by 2 doses of MMRV vaccine after 42 & 84 days respectively).

In protocol amendment 1 (4 Jan 2016) blood sample volume was increased to 10 mL for Visits 4, 5.

Entry criteria were male or female subjects who had received primary and booster vaccination with MenACWY-TT or Meningitec in studies MenACWY-TT-039 and MenACWY-TT-048, respectively, able to provide appropriate consent via parent(s) or guardian(s).

Subjects were excluded if they had a history of meningococcal disease; or confirmed or suspected immunosuppression or immunodeficiency; or a bleeding disorders or requirement for anti-coagulants; or receipt of meningococcal polysaccharide or conjugate vaccine outside of these studies.

ATP, according to protocol, cohort: Satisfy entry criteria and have assay results for at least one tested Ag at month X

Adapted ATP cohort: applies the ATP cohort for each time point when presenting different timepoints

Total enrolled cohort: all subjects enrolled irrespective of the visit at which they were enrolled.

Treatments

No vaccines were administered in this persistence study.

Information was sought at each study visit from the subject's parent/guardian about any other vaccination received by the subject

Immunogenicity Measurements

Whole venous blood samples, ~7 mL at Visits 1, 2, 3 and ~10 mL at Visits 4, 5 were collected using Vacutainer tubes with serum separator, then after blood centrifugation and serum separation, samples were stored at -20°C or below until collection by the sponsor. The laboratories in charge of the assay testing were blinded to the vaccine groups.

Laboratories

Organization	Address	Service(s) Provided
GSK Biologicals Global Vaccine Clinical Laboratory, Wavre-Nord Noir Epine[a]	Karl Walravens Avenue Fleming, 20 - B-1300 Wavre - Belgium	Clinical specimen management
Pfizer Vaccine Research & Development[a]	John Sorrentino Vice President & Chief Operating Officer Vaccine Research & Development 401 N Middletown Road Pearl River, NY 10965 USA	Clinical specimen management
Public Health England (PHE) Manchester Medical Microbiology Partnership (formerly HPA Laboratory, Vaccine Evaluation Unit, Health Protection Agency North West)	Ray Borrow Head Vaccine Evaluation Meningococcal Reference Unit PO Box 209, 2nd Floor Clinical Sciences Building II Manchester Royal Infirmary Oxford Road Manchester, M13 9WZ United Kingdom	rSBA-MenA, rSBA-MenC, rSBA-MenW-135, and rSBA-MenY testing
NÉOMED-LABS (formerly GSK Biologicals Global Vaccine Clinical Laboratory, North America – Laval, Biospecimen Reception – Clinical Serology)	Luc Gagnon Vice President Lab Operations and Technologies 525 Cartier Boulevard West Laval, Quebec, H7V 3S8 Canada	hSBA-MenA, hSBA-MenC, hSBA-MenW-135, and hSBA-MenY testing

a. Clinical specimen management was handled by GSK for Years 2, 3, 4 and Pfizer for Years 5, 6.

Laboratory Assays

System	Component	Method	Unit	Cutoff
Humoral	*Neisseria meningitidis* Group A L10 3125 Ab	rSBA	1/dilution	8
Humoral	*Neisseria meningitidis* Group C L3v C11 Ab	rSBA	1/dilution	8
Humoral	*Neisseria meningitidis* Group W L3v MP01240070 Ab	rSBA	1/dilution	8
Humoral	*Neisseria meningitidis* Group Y L3v S1975 Ab	rSBA	1/dilution	8
Humoral	*Neisseria meningitidis* Group A L10 3125 Ab	hSBA	1/dilution	4
Humoral	*Neisseria meningitidis* Group C L3v C11 Ab	hSBA	1/dilution	4
Humoral	*Neisseria meningitidis* Group W L3v MP01240070 Ab	hSBA	1/dilution	4
Humoral	*Neisseria meningitidis* Group Y L3v S1975 Ab	hSBA	1/dilution	4

Abbreviations: Ab = antibody; hSBA = serum bactericidal assay using human complement; rSBA = serum bactericidal assay using rabbit complement.

Bactericidal antibodies are recognized as *surrogate markers of protection*. In particular, rSBA titres ≥1:8 against N meningitidis group C (rSBA-MenC) are consistent with observed efficacy at 4 weeks postvaccination with the meningococcal group C conjugate vaccine in post-licensure efficacy estimates in UK. The threshold for protection for other serogroups is *undefined* but it is common to extend the 1:8 titre cutoff to serum bactericidal Abs for rSBA-MenA, rSBA-MenW-135, rSBA-MenY.

For hSBA against N meningitidis group C, hSBA-MenC, a titre ≥1:4 is an established correlate of protection commonly extended as the correlate of protection for groups A, W-135, Y.

Results

Recruitment/ Number analysed /Demographics

Timelines

1st Subject 1st Visit: 16 Jul 2013

Last Subject Last Visit: 08 Nov 2017

Serology Completion: 25 Jan 2018

Summary of Demographic Characteristics for ATP Cohorts at Months 24, 36, 48, 60 and 72

		Vaccine Group					
		ACWY-TT N[a]=123		MenCCRM N[a]=21		Total N[a]=144	
Characteristic	Parameter or Category	Value[b] or n[c]	%[d]	Value[b] or n[c]	%[d]	Value[b] or n[c]	%[d]
Age at Month 24 (months)	Mean	88.83		88.90		88.84	
	SD	1.93		1.95		1.92	
	Median	89.0		89.0		89.0	
	Minimum	85		86		85	
	Maximum	94		93		94	
Sex	Female	58	47.2	8	38.1	66	45.8
	Male	65	52.8	13	61.9	78	54.2
Race	White - Caucasian /European heritage	122	99.2	21	100.0	143	99.3

Characteristic	Parameter or Category	Vaccine Group ACWY-TT N[a]=135 Value[b] or n[c]	%[d]	MenCCRM N[a]=22 Value[b] or n[c]	%[d]	Total N[a]=157 Value[b] or n[c]	%[d]
Age at Month 36 (months)	Mean	99.69		99.91		99.72	
	SD	2.18		2.00		2.15	
	Median	99.0		100.0		100.0	
	Minimum	95		96		95	
	Maximum	106		104		106	
Sex	Female	64	47.4	9	40.9	73	46.5
	Male	71	52.6	13	59.1	84	53.5
Race	White - Caucasian /European heritage	134	99.3	22	100.0	156	99.4

Characteristic	Parameter or Category	Vaccine Group ACWY-TT N[a]=139 Value[b] or n[c]	%[d]	MenCCRM N[a]=23 Value[b] or n[c]	%[d]	Total N[a]=162 Value[b] or n[c]	%[d]
Age at Month 48 (months)	Mean	111.91		111.74		111.88	
	SD	2.18		2.03		2.15	
	Median	112.0		112.0		112.0	
	Minimum	108		108		108	
	Maximum	118		115		118	
Sex	Female	65	46.8	9	39.1	74	45.7
	Male	74	53.2	14	60.9	88	54.3
Race	White - Caucasian /European heritage	138	99.3	23	100.0	161	99.4

Characteristic	Parameter or Category	Vaccine Group ACWY-TT N[a]=137 Value[b] or n[c]	%[d]	MenCCRM N[a]=23 Value[b] or n[c]	%[d]	Total N[a]=160 Value[b] or n[c]	%[d]
Age at Month 60 (months)	Mean	124.08		124.35		124.12	
	SD	2.16		2.08		2.14	
	Median	124.0		125.0		124.0	
	Minimum	119		120		119	
	Maximum	130		127		130	
Sex	Female	67	48.9	9	39.1	76	47.5
	Male	70	51.1	14	60.9	84	52.5
Race	White - Caucasian /European heritage	136	99.3	23	100.0	159	99.4

Characteristic	Parameter or Category	Vaccine Group ACWY-TT N[a]=134 Value[b] or n[c]	%[d]	MenCCRM N[a]=23 Value[b] or n[c]	%[d]	Total N[a]=157 Value[b] or n[c]	%[d]
Age at Month 72 (months)	Mean	134.72		134.57		134.70	
	SD	1.85		1.70		1.82	
	Median	135.0		134.0		135.0	
	Minimum	131		131		131	
	Maximum	140		137		140	
Sex	Female	64	47.8	9	39.1	73	46.5
	Male	70	52.2	14	60.9	84	53.5
Race	White - Caucasian /European heritage	133	99.3	23	100.0	156	99.4

Source: menacwy-tt-102-200088-report-body Tables 6-10

The total enrolled / ATP cohorts at month 24 were 167 / 144 (86.2%), increasing to 170 – 174 at later time points with the ATP cohort comprising 91.8%, 93.1%, 94.1%, 90.2% at months 36, 48, 60, 72. The most common reason for exclusion from the ATP cohort for persistence was exclusion from the booster ATP cohort for immunogenicity or ATP cohort for persistence at Month 60 in Study MenACWY-TT-048.

Efficacy results

In the ACWY-TT group, the percentage of subjects with rSBA-MenC titres ≥1:8 declined from 97.6% (Month 24) to 71.6% (Month 72) and in the MenCCRM group from 100.0% to 65.2% respectively. The percentage of subjects with rSBA-MenC titers ≥1:8 was generally comparable between the ACWY-TT and the MenCCRM groups at all time points. Although the small numbers in the latter group limits comparisons.

In the ACWY-TT group, the percentage of subjects with rSBA-MenA titres ≥1:8 declined from 98.4% (Month 24) to 92.5% (Month 72), for rSBA-MenW-135 from 96.7% to 85.8%, rSBA-MenY from 100.0% to 94.0% respectively.

Number, % Subjects with rSBA titres for MenA, C, W, Y ≥1:8, ≥1:128 and GMTs (Adapted ATP Cohort)

					≥1:8				≥1:128			GMT		
						95% CI				95% CI			95% CI	
Antibody	Vaccine Group	Visit[a]	N[b]	n[c]	%[d]	LL	UL	n[c]	%[d]	LL	UL	Value	LL	UL
rSBA-MenA	ACWY-TT	M24	123	121	98.4	94.2	99.8	117	95.1	89.7	98.2	1071.2	821.9	1396.2
		M36	135	129	95.6	90.6	98.4	112	83.0	75.5	88.9	376.3	280.7	504.3
		M48	139	132	95.0	89.9	98.0	116	83.5	76.2	89.2	413.2	310.3	550.2
		M60	137	123	89.8	83.4	94.3	100	73.0	64.7	80.2	229.0	163.0	321.9
		M72	134	124	92.5	86.7	96.4	105	78.4	70.4	85.0	297.4	214.4	412.5
	MenCCRM	M24	21	5	23.8	8.2	47.2	3	14.3	3.0	36.3	9.1	3.9	21.6
		M36	22	4	18.2	5.2	40.3	3	13.6	2.9	34.9	8.8	3.9	19.6
		M48	23	6	26.1	10.2	48.4	4	17.4	5.0	38.8	10.8	4.7	24.7
		M60	23	0	0.0	0.0	14.8	0	0.0	0.0	14.8	4.0	NE	NE
		M72	23	2	8.7	1.1	28.0	2	8.7	1.1	28.0	5.7	3.4	9.6
rSBA-MenC	ACWY-TT	M24	123	120	97.6	93.0	99.5	92	74.8	66.2	82.2	174.5	137.5	221.5
		M36	135	119	88.1	81.5	93.1	63	46.7	38.0	55.4	70.6	53.3	93.3
		M48	139	123	88.5	82.0	93.3	64	46.0	37.6	54.7	69.0	52.5	90.7
		M60	137	110	80.3	72.6	86.6	65	47.4	38.9	56.1	66.0	48.1	90.5
		M72	134	96	71.6	63.2	79.1	54	40.3	31.9	49.1	39.6	28.6	54.6
	MenCCRM	M24	21	21	100.0	83.9	100.0	18	85.7	63.7	97.0	224.3	134.1	375.4
		M36	22	17	77.3	54.6	92.2	9	40.9	20.7	63.6	54.7	25.0	119.5
		M48	23	23	100.0	85.2	100.0	11	47.8	26.8	69.4	62.1	32.1	120.3
		M60	23	18	78.3	56.3	92.5	10	43.5	23.2	65.5	47.3	19.0	117.9
		M72	23	15	65.2	42.7	83.6	8	34.8	16.4	57.3	33.0	14.7	74.2
rSBA-MenW-135	ACWY-TT	M24	123	119	96.7	91.9	99.1	116	94.3	88.6	97.7	859.9	641.6	1152.3
		M36	135	132	97.8	93.6	99.5	119	88.1	81.5	93.1	544.5	418.0	709.4
		M48	138	120	87.0	80.2	92.1	102	73.9	65.8	81.0	224.7	158.6	318.2
		M60	137	121	88.3	81.7	93.2	95	69.3	60.9	76.9	184.3	130.3	260.6
		M72	134	115	85.8	78.7	91.2	90	67.2	58.5	75.0	171.9	117.5	251.4
	MenCCRM	M24	21	2	9.5	1.2	30.4	2	9.5	1.2	30.4	6.6	3.2	13.4
		M36	22	2	9.1	1.1	29.2	2	9.1	1.1	29.2	6.4	3.3	12.7
		M48	23	4	17.4	5.0	38.8	4	17.4	5.0	38.8	9.3	4.1	21.1
		M60	23	3	13.0	2.8	33.6	3	13.0	2.8	33.6	8.0	3.6	17.8
		M72	23	3	13.0	2.8	33.6	3	13.0	2.8	33.6	7.3	3.7	14.6
rSBA-MenY	ACWY-TT	M24	123	123	100.0	97.0	100.0	116	94.3	88.6	97.7	734.4	584.6	922.5
		M36	135	128	94.8	89.6	97.9	114	84.4	77.2	90.1	416.9	313.3	554.9
		M48	139	132	95.0	89.9	98.0	114	82.0	74.6	88.0	335.1	254.7	440.9
		M60	137	127	92.7	87.0	96.4	106	77.4	69.4	84.1	265.2	190.9	368.4
		M72	134	126	94.0	88.6	97.4	101	75.4	67.2	82.4	260.0	188.6	358.5
	MenCCRM	M24	21	7	33.3	14.6	57.0	7	33.3	14.6	57.0	18.9	6.6	53.7
		M36	22	8	36.4	17.2	59.3	8	36.4	17.2	59.3	20.6	7.6	56.1
		M48	23	10	43.5	23.2	65.5	10	43.5	23.2	65.5	28.4	10.3	77.8
		M60	23	6	26.1	10.2	48.4	5	21.7	7.5	43.7	13.0	5.2	32.3
		M72	23	3	13.0	2.8	33.6	3	13.0	2.8	33.6	8.8	3.5	21.8

Source: menacwy-tt-102-200088-report-body Tables 11

In the ACWY-TT group, the percentage of subjects with rSBA-MenC titres ≥128 declined from 74.8% (Month 24) to 40.3% (Month 72) compared with the MenCCRM group where rates fell from 85.7% to 34.8% respectively.

The GMTs followed similar time trends declining for rSBA-MenC from 174.5 to 39.6 (ACWY-TT) versus 224.3 to 33.0 (MenCCRM) from Months 24 to 72, and in the ACWY-TT group from 1071.2 to 297.4 for rSBA-MenA, rSBA-MenW-135 859.9 to 171.9, and 734.4 to 260.0 for rSBA-MenY, respectively.

Exploratory Comparison: rSBA Titres >8, >128, GMTs for ACWY-TT vs MenCCRM: Adapted ATP cohort

			Vaccine Group						Difference in Percentage (ACWY-TT Minus MenCCRM)		
			ACWY-TT			MenCCRM				95%CI	
Antibody	Type	Visit[a]	N[b]	n[c]	%[d]	N[b]	n[c]	%[d]	%	LL	UL
rSBA-MenC	≥1:8	M24	123	120	97.6	21	21	100.0	-2.4	-6.95	13.18
		M36	135	119	88.1	22	17	77.3	10.9	-3.45	32.26
		M48	139	123	88.5	23	23	100.0	-11.5	-17.90	3.12
		M60	137	110	80.3	23	18	78.3	2.0	-12.48	23.19
		M72	134	96	71.6	23	15	65.2	6.4	-11.79	28.17
	≥1:128	M24	123	92	74.8	21	18	85.7	-10.9	-24.07	10.62
		M36	135	63	46.7	22	9	40.9	5.8	-16.43	25.69
		M48	139	64	46.0	23	11	47.8	-1.8	-22.92	18.86
		M60	137	65	47.4	23	10	43.5	4.0	-17.62	24.00
		M72	134	54	40.3	23	8	34.8	5.5	-16.51	24.00

		Vaccine Group				GMT Ratio (ACWY-TT/MenCCRM)		
		ACWY-TT		MenCCRM			95% CI	
Antibody	Visit[a]	N[b]	GMT	N[b]	GMT	Value	LL	UL
rSBA-MenC	M24	123	174.5	21	224.3	0.8	0.42	1.43
	M36	135	70.6	22	54.7	1.3	0.61	2.74
	M48	139	69.0	23	62.1	1.1	0.54	2.28
	M60	137	66.0	23	47.3	1.4	0.60	3.25
	M72	134	39.6	23	33.0	1.2	0.52	2.78

Source: menacwy-tt-102-200088-report-body Tables 12, 13

Modelling analyses indicated that for both ACWY-TT and MenCCRM groups the estimated GMTs at Months 24 to 72 were similar to the observed values with no indication of bias caused by subjects lost to follow-up after the booster vaccination.

Safety results

No fatal or related SAEs were reported through 6 years after booster vaccination with either MenACWY-TT or MenCCRM. During the study period a single nonserious AE of juvenile idiopathic arthritis was reported on Day 859 after booster vaccination; the subject was in the ACWY-TT group and the AE was assessed as unrelated to investigational vaccine. No subjects were withdrawn for safety-related reasons i.e. due to an AE or SAE during the reporting period for this study.

2.3.3. Discussion on clinical aspects

In the ACWY-TT group, bactericidal Abs persist from months 24 to 72 after booster vaccination but the percentage of subjects with titres of rSBA-MenC ≥8 or ≥128 decrease most between months 24 to 36, from 97.6% to 88.1% or 74.8% to 46.7% for ACWY-TT versus from 100% to 77.3% or 85.7% to 40.9% for MenCCRM respectively. This early decrease in the percentage of subjects with threshold titres of rSBA-MenC Abs is consistent with changes in GMTs, with relatively stable rates or GMTs thereafter. In the ACWY-TT group bactericidal Abs for serogroups A, W, Y, follow a similar early decline

in GMTs from months 24 to 36, rSBA-MenA GMTs fall from 1071.2 to 376.3, rSBA-MenW GMTs from 859.9 to 544.5, rSBA-MenY GMTs from 734.4 to 416.9 respectively, although this feature is less evident when considering the percentage of subjects with titres ≥8, ≥128.

The seminal study supporting SBA levels as surrogate markers of protection demonstrated hSBA titres ≥1:4 protected military recruits from disease during exposure to an epidemic of Men C infection, whilst virtually all clinical cases had baseline titres <1:4 when measured using human serum complement, hSBA (Goldschneider 1969). Rabbit complement is known to augment bactericidal titres, for example, a titre of >1:128 by rSBA was needed to predict with >80% certainty a positive titre of >1:4 in the hSBA (Goldschneider) assay. High bactericidal titres by rSBA are predictive of protection against Men C in vaccinated toddlers or older children, but no threshold titre is both sensitive and specific for predicting a positive titre by hSBA (Santos 2001). In the current absence of hSBA titres, a cautious interpretation of the rSBA data would suggest that **by 36 months** after booster vaccination with ACWY-TT at 5 years of age, **the percentage of subjects susceptible to meningococcal infection may have increased** significantly. **The effect estimate (effect size) is unclear** although rSBA titres ≥128 suggest susceptibility rates might be as high as 17% (MenA), 53.3% (MenC), 11.9% (MenW-135) and 15.6% (MenY). The MenCCRM group show similar values for rSBA-MenC and generally low levels of naturally acquired immunity for the remaining serotypes except for MenY where 43.5% of subjects (82% after ACWY-TT) at month 48 had rSBA titres ≥128.

No new safety concerns were identified during the study period otherwise since study 112036 (MenACWY-TT-048) through 6 years after booster vaccination with either MenACWY-TT or MenCCRM.

The results of the analysis at 2 to 6 years after booster vaccination continue to support a favourable benefit risk assessment of MenACWY-TT in this age group, **although there are potential concerns about an increase in susceptibility to MenC infection by 36 months after booster** immunisation given at 5 years old.

3. CHMP overall conclusion and recommendation

MenACWY-TT-102 is a stand-alone study examining persistence of bactericidal Abs 2 – 6 years after a booster dose of MenACWY-TT or Meningitec® administered in healthy 5 year-old children in study MenACWY-TT-048 after priming with the same vaccine in study MenACWY-TT-039 at 12 through 23 months of age. Bactericidal Abs for each serogroup are determined separately using rabbit complement, rSBA, and human complement, hSBA, balancing the convenience of rSBA with the potentially greater accuracy of hSBA in terms of correlates of protection for MenC which are extrapolated across the serogroups. **Only the rSBA titres are provided for this assessment, with the hSBA titres to follow.**

The implication of waning titres of rSBA titres is uncertain, but the time course of infection indicates that protection against meningococcal infection is dependent on circulating bactericidal Ab levels rather than the anamnestic response to challenge. Therefore, by extrapolation from correlates of protection, the percentage of subjects susceptible to MenC infection after a prime -boost schedule might increase from 2.4% at month 24 to 11.9% at month 36 applying rSBA-MenC titres ≥8 or from 25.2% to 53.3% applying rSBA-MenC titres of ≥128 as the threshold - given that an rSBA titre of >1:128 may be required to predict with >80% certainty a positive titre of >1:4 in the hSBA assay. **The waning of rSBA titres overtime suggests there may be a significant increase in**

susceptibility to MenC infection when the interval after booster vaccination is >24 months although the effect estimate is uncertain. The rSBA analysis should be supplemented by the hSBA titres together with an analysis of the epidemiology of meningococcal infection in this age group to guide a summary data table in the SmPC.

There are no new safety concerns otherwise.

The benefit/risk balance remains positive.

☒ Not fulfilled:

Data from MenACWY-TT-102 on the persistence of hSBA titres 2, 3, 4, 5, 6 years after boosting vaccination age 5 years have yet to be provided although the LPLV date is 08 Nov 2017 and the serology completion date is 25 Jan 2018.

4. Additional clarification requested

Based on the data submitted, the MAH should address the following questions as part of this procedure:

The outstanding hSBA data should be provided promptly together with a discussion on the interpretation of waning titres of bactericidal Abs after a prime-boost vaccination schedule in the context of current epidemiological data on the age-related incidence of meningococcal infection, to guide an appropriate summary as a product information amendment.

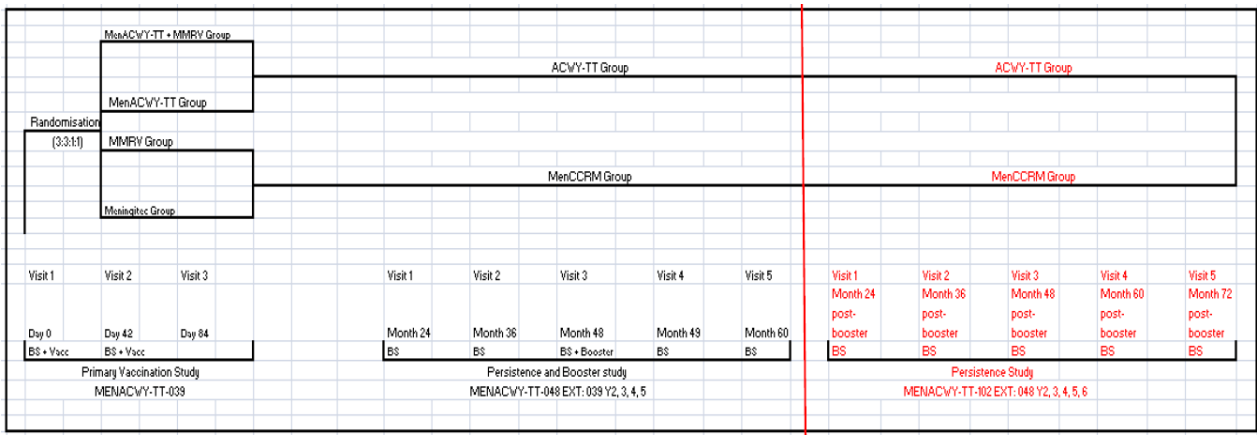
The timetable is a 30 day response timetable with clock stop if this is justified.

Assessment report endorsed by 3 MS.

MAH responses to Request for supplementary information

The study design overview is repeated here to aid interpretation of the regimen where a booster dose of MenACWY-TT or MenC-CRM is administered in healthy 5 year-old children in study MenACWY-TT-048 primed with the same vaccine in study MenACWY-TT-039 at 12 through 23 months of age.

Study design Overview Diagram



Source: menacwy-tt-102-200088-report-body Fig 1

The number of subjects in MenCCRM with hSBA results is much smaller than ACWY-TT (particularly for hSBAs for MenA, MenW-135, and MenY), limiting between group comparisons.

hSBA-MenA, -MenC, -MenW-135, -MenY Titres ≥1:4, ≥1:8 and GMTs in the Adapted ATP Cohort

				≥1:4				≥1:8				GMT		
					95% CI				95% CI				95% CI	
Antibody	Vaccine Group	Visit[a]	N[b]	n[c]	%[d]	LL	UL	n[c]	%[d]	LL	UL	Value	LL	UL
hSBA-MenA	ACWY-TT	M24	120	84	70.0	61.0	78.0	84	70.0	61.0	78.0	33.2	22.9	48.3
		M36	133	103	77.4	69.4	84.2	103	77.4	69.4	84.2	44.6	32.2	61.7
		M48	129	94	72.9	64.3	80.3	92	71.3	62.7	78.9	27.7	20.2	38.1
		M60	135	72	53.3	44.6	62.0	72	53.3	44.6	62.0	13.2	9.6	18.3
		M72	130	76	58.5	49.5	67.0	76	58.5	49.5	67.0	14.4	10.5	19.7
	MenCCRM	M24	21	3	14.3	3.0	36.3	3	14.3	3.0	36.3	2.9	1.9	4.4
		M36	21	3	14.3	3.0	36.3	2	9.5	1.2	30.4	2.6	1.9	3.5
		M48	23	8	34.8	16.4	57.3	8	34.8	16.4	57.3	4.2	2.6	6.6
		M60	23	0	0.0	0.0	14.8	0	0.0	0.0	14.8	2.0	NE	NE
		M72	23	3	13.0	2.8	33.6	3	13.0	2.8	33.6	2.8	1.9	4.0
hSBA-MenC	ACWY-TT	M24	121	121	100.0	97.0	100.0	120	99.2	95.5	100.0	510.8	389.8	669.3
		M36	131	131	100.0	97.2	100.0	130	99.2	95.8	100.0	343.3	270.2	436.2
		M48	133	131	98.5	94.7	99.8	130	97.7	93.5	99.5	232.3	176.6	305.6
		M60	136	135	99.3	96.0	100.0	135	99.3	96.0	100.0	337.1	261.3	434.9
		M72	130	128	98.5	94.6	99.8	127	97.7	93.4	99.5	259.1	194.7	344.7
	MenCCRM	M24	21	21	100.0	83.9	100.0	21	100.0	83.9	100.0	424.9	188.3	958.9
		M36	22	22	100.0	84.6	100.0	22	100.0	84.6	100.0	226.7	135.5	379.4
		M48	22	22	100.0	84.6	100.0	22	100.0	84.6	100.0	182.6	109.9	303.3
		M60	23	23	100.0	85.2	100.0	23	100.0	85.2	100.0	241.3	138.7	419.8
		M72	23	23	100.0	85.2	100.0	22	95.7	78.1	99.9	169.4	94.1	304.8
hSBA-MenW-135	ACWY-TT	M24	120	120	100.0	97.0	100.0	120	100.0	97.0	100.0	991.3	852.0	1153.5
		M36	134	134	100.0	97.3	100.0	134	100.0	97.3	100.0	738.8	640.6	852.0
		M48	137	137	100.0	97.3	100.0	137	100.0	97.3	100.0	600.0	506.0	711.5
		M60	136	136	100.0	97.3	100.0	136	100.0	97.3	100.0	326.8	275.6	387.5
		M72	133	131	98.5	94.7	99.8	131	98.5	94.7	99.8	314.4	255.1	387.6
	MenCCRM	M24	20	3	15.0	3.2	37.9	3	15.0	3.2	37.9	3.4	1.9	6.1
		M36	22	4	18.2	5.2	40.3	4	18.2	5.2	40.3	3.5	2.0	6.1
		M48	23	1	4.3	0.1	21.9	1	4.3	0.1	21.9	2.3	1.7	3.0
		M60	22	1	4.5	0.1	22.8	1	4.5	0.1	22.8	2.4	1.6	3.6
		M72	21	2	9.5	1.2	30.4	2	9.5	1.2	30.4	2.5	1.8	3.4
hSBA-MenY	ACWY-TT	M24	120	120	100.0	97.0	100.0	120	100.0	97.0	100.0	575.4	488.3	678.1

Antibody	Vaccine Group	Visit[a]	N[b]	≥1:4 n[c]	≥1:4 %[d]	≥1:4 95% CI LL	≥1:4 95% CI UL	≥1:8 n[c]	≥1:8 %[d]	≥1:8 95% CI LL	≥1:8 95% CI UL	GMT Value	GMT 95% CI LL	GMT 95% CI UL
		M36	134	133	99.3	95.9	100.0	133	99.3	95.9	100.0	691.9	579.8	825.6
		M48	132	128	97.0	92.4	99.2	128	97.0	92.4	99.2	495.0	393.4	622.7
		M60	137	134	97.8	93.7	99.5	134	97.8	93.7	99.5	398.7	320.8	495.4
		M72	131	128	97.7	93.5	99.5	128	97.7	93.5	99.5	315.6	252.7	394.0
	MenCCRM	M24	21	6	28.6	11.3	52.2	6	28.6	11.3	52.2	4.6	2.5	8.5
		M36	20	8	40.0	19.1	63.9	8	40.0	19.1	63.9	7.4	3.4	16.2
		M48	21	6	28.6	11.3	52.2	6	28.6	11.3	52.2	5.0	2.5	10.1
		M60	22	9	40.9	20.7	63.6	9	40.9	20.7	63.6	7.6	3.5	16.4
		M72	21	7	33.3	14.6	57.0	7	33.3	14.6	57.0	8.0	3.1	20.8

Source: EMA/H/C/00226/P46 052/102 – RSI – Article 46: Study MenACWY-TT-102 (C0921001) Table 1

Key: a = months after booster dose administered

Exploratory Comparison of ACWY-TT vs MenC-CRM: % Subjects with hSBA-MenC Titres ≥1:4 and ≥1:8 for Each Visit After the Booster Vaccination (Adapted ATP Cohort)

Antibody	Type	Visit[a]	Vaccine Group ACWY-TT N[b]	ACWY-TT n[c]	ACWY-TT %[d]	MenCCRM N[b]	MenCCRM n[c]	MenCCRM %[d]	Difference in Percentage (ACWY-TT Minus MenCCRM) %	95%CI LL	95%CI UL
hSBA-MenC	≥1:4	M24	121	121	100.0	21	21	100.0	0.0	-3.10	15.56
		M36	131	131	100.0	22	22	100.0	0.0	-2.87	14.95
		M48	133	131	98.5	22	22	100.0	-1.5	-5.34	13.48
		M60	136	135	99.3	23	23	100.0	-0.7	-4.06	13.67
		M72	130	128	98.5	23	23	100.0	-1.5	-5.46	12.89
	≥1:8	M24	121	120	99.2	21	21	100.0	-0.8	-4.55	14.75
		M36	131	130	99.2	22	22	100.0	-0.8	-4.22	14.20
		M48	133	130	97.7	22	22	100.0	-2.3	-6.44	12.75
		M60	136	135	99.3	23	23	100.0	-0.7	-4.06	13.67
		M72	130	127	97.7	23	22	95.7	2.0	-3.57	18.86

Source: EMA/H/C/00226/P46 052/102 – RSI – Article 46: Study MenACWY-TT-102 (C0921001) Table 2

Exploratory Comparison of ACWY-TT vs MenC-CRM: hSBA-MenC GMTs for Each Visit After the Booster Vaccination (Adapted ATP Cohort)

Antibody	Visit[a]	Vaccine Group ACWY-TT N[b]	ACWY-TT GMT	MenCCRM N[b]	MenCCRM GMT	GMT Ratio (ACWY-TT/MenCCRM) Value	95% CI LL	95% CI UL
hSBA-MenC	M24	121	510.8	21	424.9	1.2	0.58	2.48
	M36	131	343.3	22	226.7	1.5	0.82	2.81
	M48	133	232.3	22	182.6	1.3	0.63	2.57
	M60	136	337.1	23	241.3	1.4	0.72	2.69
	M72	130	259.1	23	169.4	1.5	0.75	3.14

Source: EMA/H/C/00226/P46 052/102 – RSI – Article 46: Study MenACWY-TT-102 (C0921001) Table 3

Epidemiology of Invasive Meningococcal Disease (IMD) in Europe

IMD notifications to the European Centre for Disease Prevention and Control (ECDC) indicate an overall notification rate in 2016 of 0.6 cases per 100,000 population among 30 EU/EEA member states, similar to 2015, with 3031 (92%) of 3280 IMD cases of known serogroups where 54% were serogroup B.

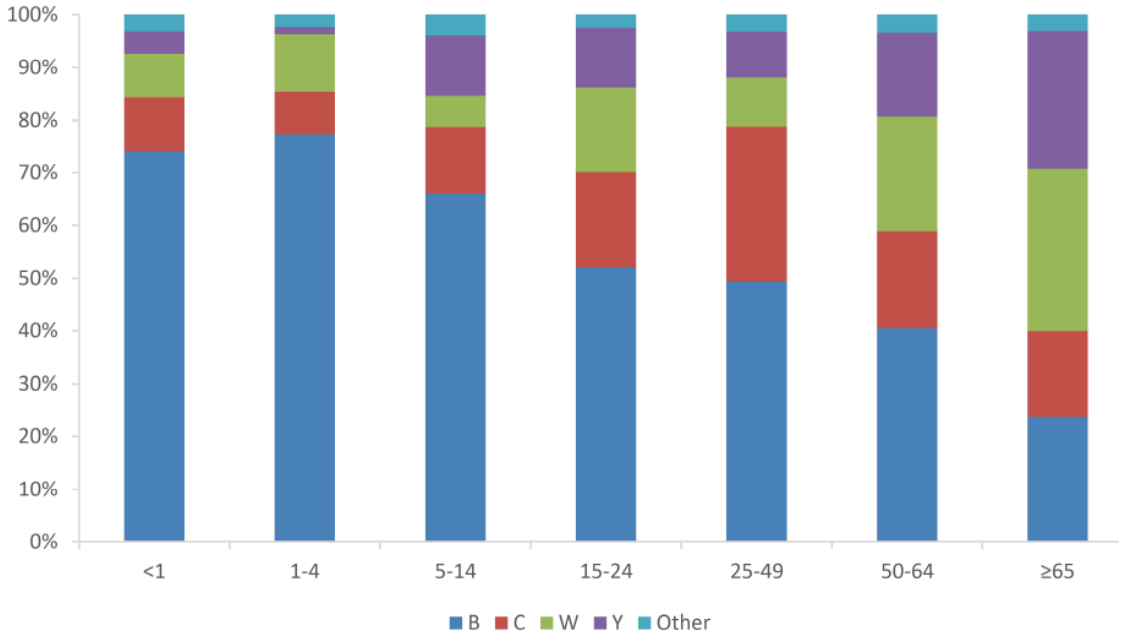
Serogroup Distribution of Confirmed Invasive Meningococcal Disease Cases, EU/EEA, (ECDC 2016)

Serogroup	Cases	%
B	1647	54
C	485	16
W	464	15
Y	344	11
Other	91	3
Total	3031	100

Source: EMA/H/C/00226/P46 052/102 – RSI – Article 46: Study MenACWY-TT-102 (C0921001) Table 4

Key: Other = all cases reported as serogroup A, X, 29E, non-groupable or 'other'.

Serogroup Distribution of Confirmed IMD by Age Group in Years EU/EEA (ECDC 2016)



Source: EMA/H/C/00226/P46 052/102 – RSI – Article 46: Study MenACWY-TT-102 (C0921001) Fig 1

Recent trends over Time

Serogroup C

In Europe, serogroup C has shown a stable low notification rate at 0.11 cases per 100,000 in 2012 vs 0.10 in 2016 among the 26 Member States that consistently reported serogroup data. In 2016, serogroup C was most prominent in adults aged 25 to 49 years accounting for 29% of cases in this age group. Among children in the age group 5 to 14 years, representing the age group of subjects evaluated for seropersistence from 2 to 6 years following a booster dose of MenACWY-TT or MenC-CRM in study MenACWY-TT-102, serogroup C disease was reported in approximately 10%.

Serogroup A, Serogroup Y

In Europe serogroup A has largely disappeared, whilst serogroup Y has shown a stable trend in the EU, although several countries have reported increases.

Serogroup W

Serogroup W has shown a notable increase in notification rate related to the rapid epidemic expansion of a single clone originating in the UK in 2009–2010 – most cases were among the elderly and in adolescents, but in the UK, cases also occurred among young children (especially <1 year of age). The Netherlands has also experienced a significant increase of serogroup W disease, with the reported incidence increasing >10-fold from 2005 - 2014 (0.02 per 100,000) to 2016 (0.29 per 100,000) where Q4 data indicate a further increase in incidence to 0.40 per 100,000 representing 33% of all IMD cases in the country in 2016. France and Sweden have also experienced an increase of IMD due to the emergence of the same serogroup W clone since 2015.

Changes in Immunisation Regimens

The UK and the Netherlands recently joined Austria, the Czech Republic, Greece, Italy and introduced the quadrivalent conjugate vaccine Men ACWY into their routine vaccination schedules, predominantly as booster doses for adolescents.

By 2016, meningococcal C conjugate (MCC) vaccine was included in national routine childhood immunisation programmes of 14 EU/EEA countries and in these, 15% of IMD cases were attributed to serogroup C. Conversely, in countries without national routine MCC vaccination, serogroup C accounted for 21% of IMD cases. Currently, most countries recommend an MCC vaccine in the second year of life.

Immunogenicity Discussion and Conclusions

In the Men-ACWY-TT group at 60 months post booster 4 years after primary vaccination in toddlers, the lower limit of the 95% CI for percentage of subjects with hSBA titres $\geq$1 in 4 for Men A, C, W, Y was 44.6%, 96.0%, 97.3%, 93.7% respectively, with a similar trend in GMTs.

For MenA, the waning in persistence of hSBA responses confirms previously available rSBA data from study MenACWY-TT-102 and similar observations in previous studies, but the clinical significance is unclear given the epidemiology of serotype A. The current MenACWY-TT PI contains the guidance that if an individual is considered at continued risk of serogroup A disease, an additional dose of MenACWY-TT could be considered.

For MenC, whilst decreases in persistence of the bactericidal Abs from 2 to 6 years after booster vaccination in the ACWY-TT group were observed for rSBA the hSBA, titres remained almost unaltered.

- rSBA-MenC titres $\geq$1:8 month 24 vs 72 = 97.6% vs 71.6%
- rSBA-MenC titres $\geq$1:128 month 24 vs 72 = 74.8% vs 40.3%
- hSBA-MenC titres $\geq$1:4 month 24 vs 72 = 100% vs 98.5%
- hSBA-MenC titres $\geq$1:8 month 24 vs 72 = 99.2% vs 97.7%

In Europe, the IMD notification rates, including serogroup C, in the age group studied are low and the need for a booster dose of a meningococcal vaccine is not evident. The current strategy being adopted by several member states is to recommend a meningococcal ACWY conjugate vaccine for adolescents when an increase in notification rates for any of the 4 serogroups occurs.

In summary, in children receiving primary vaccination with MenACWY TT aged 12 months through 23 months, and booster vaccination 4 years later, hSBA levels 2 to 6 years after

booster vaccination continue to support a favourable benefit-risk assessment of MenACWY TT in toddlers.

5. CHMP Updated overall conclusion and recommendation

The current indication for MenACWY-TT vaccine is for the active immunisation of children (from 6 weeks of age), adolescents and adults at risk of exposure to *Neisseria meningitidis* groups A, C, W135 and Y, to prevent invasive disease, according to national recommendations. The recommended posology is for a single dose in children (from 12 months of age), adolescents and adults. A booster dose may be given, noting the need for and timing of a booster dose in subjects previously vaccinated with MenACWY-TT is to be defined based on national recommendations.

MenACWY-TT-102 is a stand-alone study examining persistence of bactericidal Abs 2 – 6 years after a booster dose of MenACWY-TT or Meningitec® administered in healthy 5 year-old children in study MenACWY-TT-048 after priming with the same vaccine in study MenACWY-TT-039 at 12 through 23 months of age. There is a high level of Ab persistence 6 years after a boosting dose of MenACWY-TT, given some 4 years after the primary vaccination series in toddlers, with the lower 95% CI for hSBA titres $\geq$1 in 8 of 94.6%, 94.7%, 93.5% for Men C, -W, -Y. At the same time point hSBA titres $\geq$1 in 4 for MenA were achieved by only 49.5% of subjects but IMD due to serotype A is uncommon and the clinical significance of this finding is unclear. ECDC data on Invasive Meningococcal Disease in Europe highlights the increase in serotype W disease, particularly in the elderly and adolescents, with cases in young children also reported in the UK.

There are no new safety concerns. No amendments to the PI are proposed.

The benefit / risk balance remains positive.

☒ **Fulfilled**