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EMA/49111/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Nimenrix

International non-proprietary name: Meningococcal group A, C, W135 and Y conjugate vaccine

Procedure No. EMEA/H/C/002226/II/0096

Note

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

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1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Pfizer Europe MA EEIG submitted to the European Medicines Agency on 14 November 2019 an application for a variation.

The following changes were proposed:

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

Update of section 5.1 of the SmPC based on final results from 3 extended follow-up paediatric studies (MenACWY-TT-099, MenACWY-TT-100 and MenACWY-TT-101) as well as paediatric study MenACWY-TT-102. Studies MenACWY-TT-099, MenACWY-TT-100 and MenACWY-TT-102 were previously submitted (P46 054, P46 053 and P46 052, respectively).

The Package Leaflet is updated accordingly. In addition, the opportunity is taken to bring the PI in line with the latest QRD template version 10.1.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet.

GLP/GCP Inspections

No clinical study sites were inspected in connection to this variation.

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

The results from 4 persistence and booster studies have been submitted to support a revision to the Nimenrix SmPC to update information regarding:

- The persistence of serum bactericidal antibody after an initial vaccination of Nimenrix or another meningococcal vaccine;
- The immune response to a booster dose of Nimenrix or other meningococcal vaccine; and
- The persistence of serum bactericidal antibody after a booster dose of Nimenrix or other meningococcal vaccine.

The data cover primary vaccination with Nimenrix in age groups 1 – 55 years, the persistence of antibodies against all serogroups for up to 10 years, the response to a booster dose and persistence of the booster for up to 6 years. Serum bactericidal antibodies were measured by rSBA (rabbit complement) and hSBA (human complement) at different time points. Titres (GMT), the percentage of subjects with titres above thresholds regarded as protective against disease (rSBA ≥1:8 and 1:128, hSBA≥1:4 and 1:8) and seroresponses (defined increase in titres from baseline) were measured. Nimenrix was compared with Meningitec (serogroup C conjugated vaccine) or Mencevax (plain polysaccharide vaccine with serogroups A, C, W, Y).

The study report for TT-101 was submitted together with the variation application. The results and the assessment for TT-101 is therefore presented in this report. For details on methods and results from

the 3 other studies that have been assessed previously, see the separate assessments and CSRs:

- MenACWY-TT-100 procedure EMEA/H/C/2226/P46/053 (AR included as Appendix in this AR)
- MenACWY-TT-099 procedure EMEA/H/C/2226/P46/054 (AR available in the Nimenrix EPAR)
- MenACWY-TT-102 procedure EMA/H/C/00226/P46/052 (AR available in the Nimenrix EPAR)

No changes to the SmPC regarding posology or undesirable effects have been proposed based on the persistence and booster data. The data are not considered to change the benefit-risk profile of Nimenrix, but they add knowledge to the persistence of antibodies in different age categories and the response to a booster dose. Changes to the section 5.1 of the SmPC are therefore proposed where the new results on antibody persistence and booster are presented. Changes relate to:

- *Antibody persistence up to 10 years after vaccination at 12-23 month of age and 2-10 years of age; Response to a booster dose administered 10 years after primary vaccination (Studies 027, 032, and 100).*

The percentage of subjects with rSBA ≥ 1:8 at the 10 year time point: Serogroup A: Nimenrix < 2 years 65%, Nimenrix ≥ 2 years 88%, serogroup C: Nimenrix < 2 years 82%, Nimenrix ≥ 2 years 84%, serogroup W: Nimenrix < 2 years 31%, Nimenrix ≥ 2 years 67%, serogroup Y: Nimenrix < 2 years 43%, Nimenrix ≥ 2 years 65%.

The percentages of subjects with rSBA titres or hSBA ≥1:8 for serogroup C at the 10 year time point were high and similar for all vaccines and age groups (1-10 years). The hSBA against serogroup A at the 10 year time point was rather low, 31-34% of subjects with titres ≥ 1:4 for Nimenrix. Study TT-100 shows that a booster dose of Nimenrix administered 10 years after primary vaccination elicited robust immune responses against each of the 4 serogroups.

- *Antibody persistence up to 10 years after vaccination at 11-17 years of age; Response to a booster dose administered 10 years after primary vaccination (Studies 036, 043, and 101).*

The percentage of subjects with rSBA ⩾ 1:8 at the 10 year time point for Nimenrix: Serogroup A: 85%, serogroup C: 90%, serogroup W: 71%, serogroup Y: 90%. Nimenrix has higher levels of protective antibodies against all serogroups compared to Mencevax at the 10 year time point.

High antibody levels were observed after the booster dose of Nimenrix given 10 years after primary vaccination with a single dose of Nimenrix or Mencevax. All subjects in the Nimenrix arm and nearly all subjects in the Mencevax arm had rSBA ≥1: 128 after the booster dose.

- *Antibody persistence up to 10 years after vaccination at 11-55 years of age; Response to a booster dose administered 10 years after primary vaccination (Studies 015, 020, and 099).*

The percentage of subjects with rSBA ⩾ 1:8 at the 10 year time point for Nimenrix: Serogroup A: 76%, serogroup C: 90%, serogroup W: 70%, serogroup Y: 87%.

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 robust immune responses against each of the 4 serogroups. All subjects in the Nimenrix groups had rSBA ≥ 1:128, and 99-100% of the Mencevax group.

- *Antibody persistence up to 4 years after vaccination at 12-23 months of age; Response to a booster dose administered 4 years after primary vaccination, and Antibody persistence up to 6 years after the booster dose (studies 039, 048, and 102).*

The percentage of subjects with rSBA ⩾ 1:8 at the 6 year time point after booster for Nimenrix: Serogroup A: 92%, serogroup C: 71%, serogroup W: 85%, serogroup Y: 94%.

The persistence of rSBA against serogroup C was similar in the Nimenrix and Meningitec groups. For

subjects in the Nimenrix group, the percentages of subjects with hSBA titres ≥1:8 remained very high (≥97.0%) across all time points for serogroups C, W and Y. For serogroup A the percentage of subjects with hSBA ≥ 1:8 was 58% at the 6 year time point.

The current recommendations in the SmPC regarding the need for a booster vaccine are sufficient for the time being: the use of Nimenrix for booster vaccination is mentioned in SmPC section 4.2 Posology and in section 4.4 Special warnings and precautions for use. No changes to these sections other than minor wording adjustments are proposed. Section 4.4 mentions the potential need for a booster dose linked to waning serogroup A titres as measured with hSBA in some studies. Also, because of a general decline of antibody titres over time for all serogroups a booster may be beneficial for subjects with a high risk of exposure (see SmPC section 4.4). It is agreed that no changes to these sections are necessary.

The results are consistent with the safety profile that has been established for primary vaccination with Nimenrix, and no new adverse reactions for Nimenrix were identified.

The benefit-risk balance of Nimenrix remains positive.

3. Recommendations

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

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

Update of section 5.1 of the SmPC based on final results from 3 extended follow-up paediatric studies (MenACWY-TT-099, MenACWY-TT-100 and MenACWY-TT-101) as well as paediatric study MenACWY-TT-102. Studies MenACWY-TT-099, MenACWY-TT-100 and MenACWY-TT-102 were previously submitted (P46 054, P46 053 and P46 052, respectively).

The Package Leaflet is updated to make it consistent with the SmPC by including information on infant coadministration. In addition, the opportunity is taken to bring the PI in line with the latest QRD template version 10.1.

☒ is recommended for approval.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I and IIIB are recommended.

4. EPAR changes

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

Scope

Please refer to the Recommendations section above

Summary

Please refer to Scientific Discussion 'Nimenrix-H/C/002226-II-96'

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

5. Introduction

Pfizer's meningococcal polysaccharide groups A, C, W-135, and Y tetanus toxoid conjugate vaccine (MenACWY-TT), marketed as Nimenrix, consists of *Neisseria meningitides* capsular polysaccharides A, C, W-135, and Y, each coupled to tetanus toxoid as a carrier protein. Nimenrix is indicated for active immunization of individuals from 6 weeks of age against invasive meningococcal diseases caused by *Neisseria meningitidis* serogroups A, C, W-135 and Y.

The results from 4 persistence and booster studies have been submitted to support a revision to the Nimenrix SmPC to update information regarding:

- The **persistence** of serum bactericidal antibody after an initial vaccination of Nimenrix or another meningococcal vaccine;
- The immune response to a **booster** dose of Nimenrix or other meningococcal vaccine; and
- The persistence of serum bactericidal antibody after a booster dose of Nimenrix or other meningococcal vaccine.

Data are now available from 3 recently completed extended follow-up studies (Studies MenACWY-TT-100, MenACWY-TT-099, and MenACWY-TT-101) that describe the persistence of serum bactericidal antibodies up to 10 years after primary vaccination with either Nimenrix or another meningococcal vaccine administered to toddlers, children, adolescents, or adults (subjects from 1 to 55 years of age), as well as the response to a booster dose of Nimenrix administered 10 years after initial vaccination.

Data from a previously submitted study (MenACWY-TT-102) has also been submitted to describe antibody persistence up to 6 years after a booster vaccination of Nimenrix or meningococcal C conjugate vaccine (MenCCRM) given to subjects who had received primary vaccination with these vaccines at 12 to 23 months of age.

The study report for TT-101 was submitted together with the variation application. The results and the assessment for TT-101 is therefore presented below, followed by summaries of the 3 other studies. For details on methods and results from the 3 other studies that have been assessed previously, see the separate assessments and CSRs:

- MenACWY-TT-100 procedure EMEA/H/C/2226/P46/053
- MenACWY-TT-099 procedure EMEA/H/C/2226/P46/054
- MenACWY-TT-102 procedure EMA/H/C/00226/P46/052

6. Clinical Efficacy aspects

6.1. Study MenACWY-TT-101

Final Report: A Phase IIIb, Open Study to Evaluate the Immunogenicity, Reactogenicity and Safety of a Booster Dose of MenACWY-TT Vaccine Administered 10 Years After Healthy Subjects Aged 11 to 17 Years Received Either MenACWY-TT Vaccine (Nimenrix®) or Mencevax ACWY®.

Protocol Number: Protocol MenACWY-TT-101 (C0921005); former GlaxoSmithKline 116724

Study description

This was a Phase IIIb, open-label, uncontrolled study with 2 parallel groups. At Visit 1 (Month 120 after primary vaccination), 1 dose of MenACWY-TT was administered to the participants in both study groups. This study was an extension of the following studies:

MenACWY-TT-036 and MenACWY-TT-043.

The study consisted of a single epoch, with a duration of approximately 1 month for each subject starting at Visit 1 (Month 120 [Year 10] after primary vaccination) and ending at Visit 2 (Month 121 or 1 month after booster vaccination).

There were 2 parallel groups in this study:

- ACWY-TT group: all participants vaccinated with MenACWY-TT in Study MenACWY-TT-036;
- MenPS group: all participants vaccinated with Mencevax ACWY in Study MenACWY-TT-036

First Subject First Visit: 01 August 2017

Last Subject Last Visit: 11 April 2018 (last Visit 2 [Month 121] blood draw)

Serology Completion Date: 01 March 2019

Study Center(s): This study was undertaken by GlaxoSmithKline (GSK) at one site in the Philippines. Sponsorship of the study was transferred to Pfizer, Inc on 01 October 2015.

6.1.1. Methods

Study participants

According to the protocol, 200 subjects from the Philippines were expected to participate in the TT-101 booster study. The protocol also says that all subjects that were vaccinated in the MenACWY-TT-036 at the participating site will be invited to participate. It was estimated that approximately 10% of the subjects will not be evaluable and that around 180 subjects would be included in the Booster ATP cohort of immunogenicity (135 in the ACWY-TT group and 45 in the MenPS group).

Inclusion criteria included: healthy male or female subjects who completed the vaccination in Study MenACWY-TT-036 as per protocol.

Exclusion criteria included administration of immune-modifying drugs or meningococcal vaccine, acute illness and fever, history of serious illness (specified).

Treatments

Nimenrix:

Treatment name	Vaccine/ product name	Formulation	Presentation	Volume to be administered	Number of doses
MenACWY-TT	MenACWY-TT *	PSA=5µg TT; PSC=5µg TT; PSW_{135}=5µg TT; PsY=5µg TT; TT~=44µg Tris-HCL, pH 6.8 ± 0.3 1.6 mM; Sucrose 28 mg	Lyophilized pellet to be reconstituted with saline diluent	0.5 mL	1
	NaCl	NaCl=150mM	liquid		

*The lyophilized pellet of MenACWY-TT vaccine is to be reconstituted with the supplied saline solution.

Objectives/endpoints

Primary objective:

To evaluate the immunogenicity of a booster dose of MenACWY-TT conjugate vaccine 1 month after booster vaccination with MenACWY-TT.

Endpoint: The percentage of subjects with an rSBA-MenA, rSBA-MenC, rSBA-MenW-135, rSBA-MenY booster response. rSBA **vaccine responses** for serogroups A, C, W-135 and Y are defined as:

For initially seronegative subjects (prevaccination titre below the cutoff of 1:8): rSBA antibody titres ≥1:32 one month after vaccination, and for initially seropositive subjects (prevaccination titre ≥1:8): rSBA antibody titres at least 4 times the prevaccination antibody titres, one month after vaccination.

Secondary Immunogenicity

Secondary endpoint for booster dose: The percentage of subjects with rSBA-MenA, rSBA-MenC, rSBA-MenW-135, and rSBA-MenY antibody titres ≥1:8, ≥1:128, and GMTs.

Objective: To evaluate the **long-term antibody persistence** induced by MenACWY-TT conjugate vaccine as compared to Mencevax ACWY when administered to individuals 11 to 17 years of age. **Endpoint:** The percentage of subjects with rSBA-MenA, rSBA-MenC, rSBA-MenW-135, and rSBA-MenY antibody titres ≥1:8, ≥1:128, and GMTs.

Objective: To evaluate **anti-TT concentrations** before and 1 month after booster vaccination with MenACWY-TT. **Endpoint:** The percentage of subjects with anti-TT concentrations ≥0.1 IU/mL and ≥1.0 IU/mL and GMCs.

Sample size

The sample size of this study with respect to the postbooster analysis of safety and immunogenicity was driven by the sample size of the primary vaccination study MenACWY-TT-036 (109069), the enrollment rate in the persistence extension study MenACWY-TT-036 (MenACWY-TT-043 EXT:036 Y2, 3, 4 and 5) and the estimated number of potential participating subjects based on the feedback from the site participating in this extension study.

Randomisation

There was no randomization in this open-label study. Participants who completed Study MenACWY-TT-036 and who received either MenACWY-TT or Mencevax ACWY were allocated to the same groups as in the primary vaccination study. Subjects retained the same subject number as in MenACWY-TT-036, but were allocated a new container number.

Blinding (masking)

This study was not blinded.

Laboratory assays

Serological assays will be performed at Public Health England (PHE; Manchester, UK) using standardised and validated procedures.

Table 1. ***Humoral Immunity (Antibody determination)***

Component	Method	Test kit/ Manufacturer	Unit	Cut-off	Laboratory
Neisseria meningitidis Serogroup A L10 3125 Ab	rSBA	NA	1/DIL	8	PHE*
Neisseria meningitidis Serogroup C L3v C11 Ab	rSBA	NA	1/DIL	8	PHE*
Neisseria meningitidis Serogroup W L3v MP01240070 Ab	rSBA	NA	1/DIL	8	PHE*
Neisseria meningitidis Serogroup Y L3v S1975 Ab	rSBA	NA	1/DIL	8	PHE*
Clostridium tetani.Tetanus Toxoid Ab.IgG	dLIA**	NA	IU/mL	0.1	***PPD

rSBA = Serum Bactericidal Assay (using baby rabbit complement) 1/DIL = Dilution for at least 50% killing
*PHE = Public Health England (previously the Health Protection Agency [HPA])
**dLIA – Direct Luminex Immunoassay
***PPD – Pharamceutical Product Development, Inc. Bioanalytical Laboratories

Statistical methods

The analysis cohorts:

- Booster total vaccinated cohort
- Booster according-to-protocol (ATP) cohort for immunogenicity
- Total cohort at Month 120
- ATP cohort for persistence at Month 120
- Adapted ATP cohort (denotes that subjects belong to the corresponding ATP cohort for immunogenicity for that time point)

GMTs and GMCs will be obtained by log transformations of indicated values, averaging the log values, then exponentiating the result. The 2-sided 95% CI will be obtained by calculating the CI in log scale, referencing the t-distribution, and then exponentiating the lower and upper limits.

Within Group Immunogenicity Methods

For each group, at each blood sampling time point (Month 120 and Month 121), for each antigen assessed:

- Percentage of subjects with rSBA booster response with 95% CIs will be calculated.
- GMTs/GMCs with 95% CIs will be tabulated.
- Percentages of subjects with titres/concentrations above proposed cutoffs and with 95% CIs will be calculated.
- The antibody titres/concentrations will be tabulated and also presented using reverse cumulative distribution curves.

Between Group Immunogenicity Methods

An exploratory evaluation of the differences in the immune response 1 month after the booster vaccination will be performed for each group.

- Differences in the percentage of subjects with rSBA titres ≥1:8 and ≥1:128 between the ACWY-TT group and the MenPS group, with their standardized asymptotic 95% CIs.
- Differences in the percentage of subjects with booster response between the ACWY-TT and the MenPS group, with their standardized asymptotic 95% CIs.
- Ratio of GMTs between the ACWY-TT group and the MenPS group, with their standardized asymptotic 95% CIs. This will be performed using an analysis of variance (ANOVA) model on the logarithm10 transformation of the titres using the vaccine group as fixed effect. The difference in percentage is defined as ACWY-TT minus MenPS. The ratio of GMTs will be ACWY-TT divided by MenPS.

Modelling Prediction

In order to complement the descriptive analyses of observed persistence per time point and identify bias that may have occurred due to the loss to follow-up after the vaccination, a longitudinal analysis will be performed for each group.

This analysis will include:

- all pre- and post-primary vaccination results (Month 0 and Month 1 in Study MenACWY-TT-036) from subjects who belong to the ATP cohort for immunogenicity
- results from Years 2, 3, 4, 5 (in Study MenACWY-TT-043) for subjects who belong to the ATP cohort for persistence in the indicated year
- results from Month 120 (in Study MenACWY-TT-101[C0921005]) for subjects who belong to the ATP persistence cohort for Month 120.

For a specific group, the model will include assay results from a time point provided that the subjects were part of the ATP cohort for that time point. Titres below the cutoff will be set at half the value of the cutoff. Titres will be log transformed. Only titres from Public Health England (PHE) will be used. The bactericidal assay was performed by PHE on a subset of samples at Months 0, 1 and 24 (Year 2), and on all samples at Months 36 (Year 3), 48 (Year 4), 60 (Year 5) and 120 (Year 10).

Only subjects from the Philippines will be included because all Month 120 subjects will be from the Philippines. Subjects may be included for a later visit even if an earlier visit is missed.

6.1.2. Results

Participant flow

Table 2. ***Study Population (Total Cohort at Month 120 and Booster Total Vaccinated Cohort)***

	Vaccine Group		
	ACWY-TT[a]	MenPS[b]	Total
Enrolled, N[c] (total cohort at Month 120)	170	59	229
Completed Month 120 (Visit 1), n[d] (%)[e]	170 (100.0)	59 (100.0)	229 (100.0)
Completed Month 121 (Visit 2), n[d] (%)[e]	169 (99.4)	58 (98.3)	227 (99.1)
Demographic information			
Females: males	80:90	23:36	103:126
Mean age at enrollment, years (SD)	24.2 (1.9)	24.0 (2.0)	24.1 (2.0)
Median age, years (minimum, maximum)	24.0 (21, 27)	24.0 (21, 28)	24.0 (21, 28)
Race			
Asian - South East Asian heritage, n[d] (%)[e]	170 (100.0)	59 (100.0)	229 (100.0)
Ethnicity			
Not American Hispanic or Latino, n[d] (%)[e]	169 (99.4)	59 (100.0)	228 (99.6)
American Hispanic or Latino, n[d] (%)[e]	1 (0.6)	0 (0.0)	1 (0.4)

Note: Date of birth, sex, race, and ethnicity were collected in primary study MenACWY-TT-036.
Note: Subjects were randomized and the primary vaccinations were administered at 11 to 17 years of age in primary study MenACWY-TT-036; all subjects who were given the booster vaccination in Study MenACWY-TT-101 (C0921005) received MenACWY-TT at Month 120.
Note: The age was computed based on the date of enrollment visit in Study MenACW-TT-101 (C0921005).
a. ACWY-TT = vaccinated with MenACWY-TT in Study MenACWY-TT-036.
b. MenPS = vaccinated with Mencevax ACWY in Study MenACWY-TT-036.
c. N = number of subjects in each vaccine group. These values are used as the denominators for the percentage calculations.
d. n = Number of subjects in a given category.
e. % = Percentage of subjects in a given category.

Table 3. ***Number of Subjects in Booster Total Vaccinated Cohort and Booster ATP Cohort for Immunogenicity as Well as the Number of Subjects Excluded From Booster ATP Cohort for Immunogenicity, With Reasons for Exclusion***

	ACWY-TTa	MenPSb	Total	
	N	N	N	%d
Total cohort at Month 120	170	59	229	100.0
Did not receive booster dose at Month 120	0	0	0	0.0
Booster Total Vaccinated Cohort at Month 120	170	59	229	100.0
Excluded from booster ATP cohort for immunogenicity	8	8	16	7.0
Ineligible subjects as per eligibility criteria	0	1	1	0.4
Did not receive primary study vaccine MenACWY-TT or Mencevax	0	0	0	0.0
The Administration site of the vaccine is unknown	0	0	0	0.0
Administration of drug(s) forbidden in the protocol	0	0	0	0.0
Noncompliance with booster vaccination or blood sampling schedule[e]	5	5	10	4.4
Essential serological data missing at Month 121	1	1	2	0.9
Had a history of meningococcal group A, C, W-135, or Y disease	0	0	0	0.0
Had an immunocompromising medical condition	0	0	0	0.0
Excluded from the the primary study and/or persistence cohorts	2	1	3	1.3
Booster ATP cohort for immunogenicity	162	51	213	93.0

The ATP cohort at month 120 (10 years) for persistence had 163 subjects in the Nimenrix arm and 53 in the MenPC arm.

Outcomes and estimation

The primary objective of this study was to evaluate the immunogenicity of MenACWY-TT 1 month after booster vaccination in terms of the percentage of subjects with an rSBA-MenA, rSBA-MenC, rSBA-MenW-135, rSBA-MenY vaccine response.

The table below presents the number and percentage of subjects with a vaccine response at 1 month after booster vaccination and by prebooster vaccination status, for the booster ATP cohort for immunogenicity. Vaccine response was defined as an antibody titre ≥1:32 at 1 month after booster vaccination for initially seronegative subjects (S-) or an antibody titre at least 4 times the prevaccination antibody titre at 1 month after booster vaccination for initially seropositive subjects (S+). Seronegative subjects (S-) have rSBA < 1:8.

Regardless of prevaccination status, for each serogroup a vaccine response was observed in the majority of subjects in both vaccine groups (range: 81.5% to 95.7% for the ACWY-TT group; 66.7% to 94.1% for the MenPS group). No clinically relevant differences were observed in vaccine response between subjects who were initially seronegative before the booster vaccination and those who were initially seropositive before the booster vaccination.

Table 4. ***Vaccine Response for rSBA-MenA, rSBA-MenC, rSBA-MenW-135, or rSBA-MenY Titres 1 Month After Booster Vaccination (Booster ATP Cohort for Immunogenicity)***

Antibody	Vaccine Group	Prevaccination Status[c]	Vaccine response[a] N[d]	n[e]	%[f]	95% CI[b] LL	UL
rSBA-MenA	ACWY-TT[g]	S-	24	24	100.0	85.8	100.0
		S+	138	108	78.3	70.4	84.8
		Total	162	132	81.5	74.6	87.1
	MenPS[h]	S-	10	10	100.0	69.2	100.0
		S+	41	33	80.5	65.1	91.2
		Total	51	43	84.3	71.4	93.0
rSBA-MenC	ACWY-TT[g]	S-	16	16	100.0	79.4	100.0
		S+	146	127	87.0	80.4	92.0
		Total	162	143	88.3	82.3	92.8
	MenPS[h]	S-	9	9	100.0	66.4	100.0
		S+	42	25	59.5	43.3	74.4
		Total	51	34	66.7	52.1	79.2
rSBA-MenW-135	ACWY-TT[g]	S-	46	46	100.0	92.3	100.0
		S+	116	109	94.0	88.0	97.5
		Total	162	155	95.7	91.3	98.2
	MenPS[h]	S-	29	28	96.6	82.2	99.9
		S+	22	20	90.9	70.8	98.9
		Total	51	48	94.1	83.8	98.8
rSBA-MenY	ACWY-TT[g]	S-	15	15	100.0	78.2	100.0
		S+	147	126	85.7	79.0	90.9
		Total	162	141	87.0	80.9	91.8
	MenPS[h]	S-	26	24	92.3	74.9	99.1
		S+	25	22	88.0	68.8	97.5
		Total	51	46	90.2	78.6	96.7

Abbreviations: ATP = according-to-protocol; LL = lower limit; rSBA-MenA, rSBA-MenC, rSBA-MenW-135, and rSBA-MenY = serum bactericidal assay using rabbit complement to measure activity against *Neisseria meningitidis* group A, group C, group W-135, and group Y; UL = upper limit.
Note: Subjects were randomized and the primary vaccinations were administered at 11 to 17 years of age in primary study MenACWY-TT-036; all subjects who were given the booster vaccination in Study MenACWY-TT-1011(C0921005) received MenACWY-TT at Month 120.

a. Vaccine response defined as follows: For initially seronegative subjects: antibody titre ⩾1:32 after the booster vaccination; for initially seropositive subjects: antibody titre after the booster vaccination ⩾4-fold higher than the pre‑booster vaccination antibody titre.
b. Exact 2-sided CI based upon the observed proportion of subjects, using the Clopper and Pearson method.
c. S- = initially seronegative subjects (antibody titre <1:8) prior to booster vaccination; S+ = initially seropositive subjects (antibody titre ⩾1:8) prior to booster vaccination.
d. N = number of subjects with before and after booster vaccination results available.
e. n = Number of subjects with a vaccine response.
f. Vaccine response defined as follows: For initially seronegative subjects: antibody titre ≥1:32 after the booster vaccination; for initially seropositive subjects: antibody titre after the booster vaccination ≥4-fold higher than the pre–booster vaccination antibody titre.
g. Exact 2-sided CI based upon the observed proportion of subjects, using the Clopper and Pearson method.
h. S- = initially seronegative subjects (antibody titre <1:8) prior to booster vaccination; S+ = initially seropositive subjects (antibody titre ≥1:8) prior to booster vaccination.
i. N = number of subjects with before and after booster vaccination results available.
j. n = Number of subjects with a vaccine response.
k. % = Percentage of subjects with a vaccine response.
l. ACWY-TT = vaccinated with MenACWY-TT in Study MenACWY-TT-036.
m. MenPS = vaccinated with Mencevax ACWY in Study MenACWY-TT-036.

Table 5. ***Number and Percentage of Subjects With rSBA-MenA, rSBA-MenC, rSBA-MenW-135, or rSBA-MenY Titres ≥1:8 and ≥1:128 and GMTs (Booster ATP Cohort for Immunogenicity)***

				≥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]	M120 (Visit 1)	162	138	85.2	78.8	90.3	132	81.5	74.6	87.1	248.4	181.4	340.2
		M121 (Visit 2)	162	162	100.0	97.7	100.0	162	100.0	97.7	100.0	3760.1	3268.3	4325.9
	MenPS[h]	M120 (Visit 1)	51	41	80.4	66.9	90.2	39	76.5	62.5	87.2	142.7	80.5	252.9
		M121 (Visit 2)	51	51	100.0	93.0	100.0	51	100.0	93.0	100.0	2956.0	2040.5	4282.1
rSBA-MenC	ACWY-TT[g]	M120 (Visit 1)	162	146	90.1	84.5	94.2	125	77.2	69.9	83.4	244.2	181.6	328.5
		M121 (Visit 2)	162	162	100.0	97.7	100.0	162	100.0	97.7	100.0	8697.7	7391.2	10235.1
	MenPS[h]	M120 (Visit 1)	51	42	82.4	69.1	91.6	32	62.7	48.1	75.9	177.4	86.1	365.3
		M121 (Visit 2)	51	51	100.0	93.0	100.0	51	100.0	93.0	100.0	3879.3	2714.6	5543.7
rSBA-MenW-135	ACWY-TT[g]	M120 (Visit 1)	162	116	71.6	64.0	78.4	105	64.8	56.9	72.1	145.5	97.6	217.1
		M121 (Visit 2)	162	162	100.0	97.7	100.0	162	100.0	97.7	100.0	11243.4	9366.8	13496.0
	MenPS[h]	M120 (Visit 1)	51	22	43.1	29.3	57.8	13	25.5	14.3	39.6	16.4	9.2	29.4
		M121 (Visit 2)	51	51	100.0	93.0	100.0	50	98.0	89.6	100.0	3674.0	2353.9	5734.4
rSBA-MenY	ACWY-TT[g]	M120 (Visit 1)	162	147	90.7	85.2	94.7	138	85.2	78.8	90.3	446.5	332.7	599.1
		M121 (Visit 2)	162	162	100.0	97.7	100.0	162	100.0	97.7	100.0	7584.8	6748.4	8524.7
	MenPS[h]	M120 (Visit 1)	51	25	49.0	34.8	63.4	20	39.2	25.8	53.9	32.9	17.1	63.3
		M121 (Visit 2)	51	50	98.0	89.6	100.0	49	96.1	86.5	99.5	3295.5	1998.7	5433.7

Abbreviations: ATP = according-to-protocol; GMT = geometric mean titre; LL = lower limit; rSBA-MenA, rSBA-MenC, rSBA-MenW-135, and rSBA-MenY = serum bactericidal assay using rabbit complement to measure activity against *Neisseria meningitidis* group A, group C, group W-135, and group Y; UL = upper limit.

Note: Subjects were randomized and the primary vaccinations were administered at 11 to 17 years of age in primary study MenACWY-TT-036; all subjects who were given the booster vaccination in Study MenACWY-TT-1011(C0921005) received MenACWY-TT at Month 120.

a. Exact 2-sided CI based upon the observed proportion of subjects, using the Clopper and Pearson method.
b. CIs are back transformations of confidence levels based on the Student t distribution for the mean logarithm of the titres, or the mean of the ratio.
c. M120 (Visit 1) = Month 120, 120 months after primary vaccination in Study MenACWY-TT-036; M121 (Visit 2) = Month 121, 121 months after primary vaccination in Study MenACWY-TT-036.
d. N = number of subjects.
e. n = Number of subjects in a given category.
f. % = Percentage of subjects in a given category.
g. ACWY-TT = vaccinated with MenACWY-TT in Study MenACWY-TT-036.
h. MenPS = vaccinated with Mencevax ACWY in Study MenACWY-TT-036.

Table 6. ***Estimated rSBA-MenC GMTs as Predicted by Modeling (Adapted ATP Cohort)***

Antibody	Vaccine Group	Visit[b]	GMT Value	95% CI[a] LL	UL
rSBA-MenC	ACWY-TT[c]	M0	5.3	4.0	7.0
		M1	4168.0	3356.9	5175.1
		M24	335.9	269.5	418.7
		M36	369.1	300.8	452.8
		M48	392.5	326.2	472.3
		M60	393.4	319.9	483.7
		M120 (Visit 1)	256.1	200.3	327.5
	MenPS[d]	M0	5.6	3.7	8.4
		M1	2407.3	1726.4	3356.8
		M24	277.7	193.3	398.9
		M36	252.2	174.9	363.5
		M48	297.0	213.0	414.0
		M60	287.4	201.3	410.3
		M120 (Visit 1)	219.0	142.7	336.2

Abbreviations: ATP = according-to-protocol; GMT = geometric mean titre; LL = lower limit; rSBA-MenC = serum bactericidal assay using rabbit complement to measure activity against *Neisseria meningitidis* group C; UL = upper limit.

Note: Subjects were randomized and the primary vaccinations were administered at 11 to 17 years of age in primary study MenACWY-TT-036; all subjects who were given the booster vaccination in Study MenACWY-TT-101 (C0921005) received MenACWY-TT at Month 120.

Note: Only subjects from the Philippines were enrolled in Study MenACWY-TT-101 (C0921005). Subjects enrolled in the primary study MenACWY-TT-036 who were from India and Taiwan were excluded from primary study visits.

a. CIs are back transformations of confidence levels based on the Student t distribution for the mean logarithm of the titres, or the mean of the ratio.
b. M0 = Month 0, primary vaccination in Study MenACWY-TT-036; M1 = Month 1, 1 month after primary vaccination in Study MenACWY-TT-036; M24 = Month 24, 24 months after primary vaccination in Study MenACWY-TT-036; M36 = Month 36, 36 months after primary vaccination in Study MenACWY-TT-036; M48 = Month 48, 48 months after primary vaccination in Study MenACWY-TT-036; M60 = Month 60, 60 months after primary vaccination in Study MenACWY-TT-036; M120 (Visit 1) = Month 120, 120 months after the primary vaccination in Study MenACWY-TT-036.
c. ACWY-TT = vaccinated with MenACWY-TT in Study MenACWY-TT-036.
d. MenPS = vaccinated with Mencevax ACWY in Study MenACWY-TT-036.

Table 7. ***Number and Percentage of Subjects With Anti -Tetanus Toxoid (Anti-TT) Concentrations ⩾0.1 IU/mL and ⩾1.0 IU/mL and GMCs (Booster ATP Cohort for Immunogenicity)***

					≥0.1 IU/mL			≥1.0 IU/mL				GMC		
						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**
Antitetanus	ACWY-TT[g]	M120 (Visit 1)	162	140	86.4	80.2	91.3	62	38.3	30.8	46.2	0.608	0.476	0.775
		M121 (Visit 2)	162	160	98.8	95.6	99.9	149	92.0	86.7	95.7	5.057	4.274	5.984
	MenPS[h]	M120 (Visit 1)	51	28	54.9	40.3	68.9	14	27.5	15.9	41.7	0.252	0.154	0.411
		M121 (Visit 2)	51	49	96.1	86.5	99.5	42	82.4	69.1	91.6	5.115	3.073	8.514

Abbreviations: ATP = according-to-protocol; GMC = geometric mean concentration; LL = lower limit; UL = upper limit.

Note: Subjects were randomized and the primary vaccinations were administered at 11 to 17 years of age in primary study MenACWY-TT-036; all subjects who were given the booster vaccination in Study MenACWY-TT-1011(C0921005) received MenACWY-TT at Month 120.

a. Exact 2-sided CI based upon the observed proportion of subjects, using the Clopper and Pearson method.

b. CIs are back transformations of confidence levels based on the Student t distribution for the mean logarithm of the concentrations, or the mean of the ratio.

c. M120 (Visit 1) = Month 120, 120 months after primary vaccination in Study MenACWY-TT-036; M121 (Visit 2) = Month 121, 121 months after primary vaccination in Study MenACWY-TT-036.

d. N = number of subjects.

e. n = Number of subjects in a given category.

f. % = Percentage of subjects in a given category.

g. ACWY-TT = vaccinated with MenACWY-TT in Study MenACWY-TT-036.

h. MenPS = vaccinated with Mencevax ACWY in Study MenACWY-TT-036.

6.2. Discussion study TT-101

Design and conduct of clinical study

The study was an extension of study TT-036 where a single dose of Nimenrix was administered to adolescents 11-17 years. In that study the immune response to Nimenrix was compared to the response after a dose of plain polysaccharide vaccine Mencevax. While study TT-036 covers the primary vaccination of Nimenrix and Mencevax, study TT-043 measured antibodies at time points 3 and 5 years. In the present study TT-101, the primary objective is to measure the response to a single booster dose of Nimenrix to both arms 10 years after the primary dose. In addition, the persistence of antibodies against all serogroups A, C, W and Y up to 10 years after the primary dose were measured. Antibodies were measured by the Public Health England using rSBA.

The study TT-036 included 674 subjects in the Nimenrix arm and 224 in the Mencevax arm. Antibodies were measured at 3 and 5 years time points after the primary dose and the number of participants fell to a lower number for each time point. At the booster time point (this study) the ATP cohort included 162 subjects that had received Nimenrix as a primary dose and 51 subjects that had received Mencevax as a primary dose. A reduction in subjects available over a period of 10 years is expected.

The presence of antibodies against serogroups A, C, W and Y were measured 10 years after the primary dose of Nimenrix or Mencevax. At the same time a booster dose of Nimenrix was administered to both arms (Nimenrix or Mencevax primary dose) and the response to the booster was measured 30 days after.

In addition, tetanus toxoid antibodies were measured before and after the booster dose and the percentage of subjects with GMC ≥ 0.1 IU/ml or 1.0 IU/ml were calculated.

Efficacy data and additional analyses

The fraction of seronegative subjects (rSBA<1:8) before the booster dose, 10 years after the primary vaccination, was 9-28% for Nimenrix and 18-57% for MenPS for the different serogroups. The highest percentage of subjects being seronegative was seen in serogroup W. A high vaccine response was observed after the booster dose of Nimenrix. The booster response varied from 82-96% in subjects previously vaccinated with Nimenrix and 67-94% in subjects previously vaccinated with Mencevax. The lowest response was seen against serogroup A in the Nimenrix group and against serogroup C in the Mencevax group. There was a tendency of higher response in seronegative subjects.

The percentage of subjects with rSBA ≥ 1:128 after booster was 100% for all groups, except in the Mencevax arm serogroup W with 98.0% and serogroup Y with 96.1%.

At the 10 year persistence time point a majority of subjects had levels of antibodies (rSBA) that is considered associated with protection against disease. The exception was the Mencevax group where less than 50% had protective levels against serogroup W and Y.

The percentage of subjects with rSBA ≥ 1:128 or ≥ 1:8 at the 10 year time point:

	Serogroup A (%)	Serogroup C (%)	Serogroup W (%)	Serogroup Y (%)
rSBA ≥ 1:128				
Nimenrix	81.5	77.2	64.8	85.2
Mencevax	76.5	62.7	25.5	39.2
rSBA ≥ 1:8				
Nimenrix	84.7	90.2	71.8	90.8
Mencevax	81.1	83.0	41.5	49.1

Nimenrix has higher levels of protective antibodies against all serogroups compared to Mencevax after 10 years. The difference between the vaccines are largest for serogroups W and Y.

The antibodies against tetanus toxoid increased from the 10 year persistence time point to 30 days after the booster dose: the percentage of subjects with anti-tetanus toxoid concentrations ≥ 1.0 IU/mL increased from 38.3% to 92.0% in the Nimenrix group, and from 27.5% to 82.4% in the Mencevax group.

6.2.1. Conclusions study TT-101

A high response in antibody levels was observed after the booster dose of Nimenrix given 10 years after primary vaccination with a single dose of Nimenrix or Mencevax. The booster response varied from 82-96% in subjects previously vaccinated with Nimenrix and 67-94% in subjects previously vaccinated with Mecevax. All subjects in the Nimenrix arm and nearly all subjects in the Mencevax arm had rSBA ≥1: 128 after the booster dose.

Nimenrix has higher levels of protective antibodies against all serogroups compared to Mencevax at the 10 year time point, the range of percentage of subjects with rSBA ≥ 1:128 was 64.8 – 85.2% for Nimenrix and 25.5 – 76.5% for Mencevax for all serogroups.

Both the persistence of antibodies against all serogroups and the response to a booster dose of Nimenrix have been reported according to the intention of the study. The results have been included in the proposal for change in the SmPC.

6.3. Methods – analysis of data submitted

The 3 recently completed studies supporting the present SmPC updates were extended follow-up studies that evaluated the persistence of bactericidal antibody titres against meningococcal groups A, C, W-135, and Y at one or more time points up to 10 years after administration of a single dose of either MenACWY-TT or a comparator meningococcal vaccine to subjects between 1 and 55 years of age.

All 3 studies also evaluated the safety and immunogenicity of a booster dose of MenACWY-TT administered to all eligible subjects (regardless of primary vaccination group) 10 years after the primary vaccination. Bactericidal antibody was measured by serum bactericidal assays using rabbit complement (rSBA) and/or by serum bactericidal assays using human complement (hSBA).

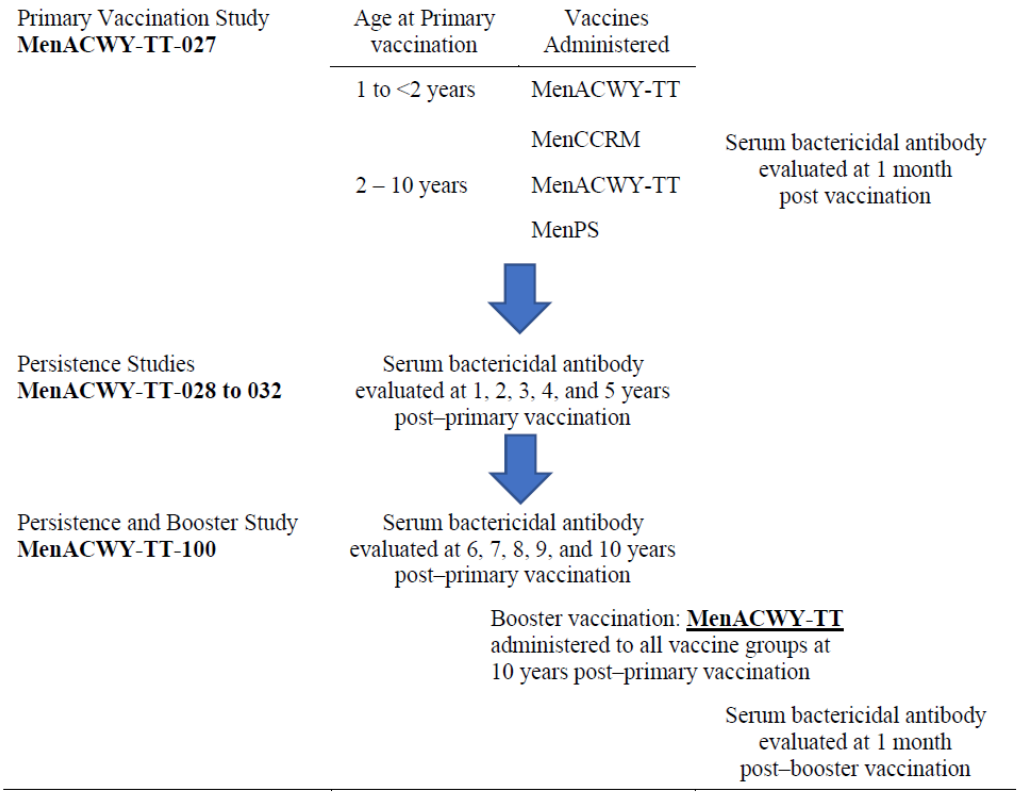
The design of the fourth study, MenACWY-TT-102 (C0921001), submitted previously, differs from the design of the first 3 studies, and thus will be described separately.

Table 8. ***Overview of Vaccines Administered in Primary Study and Antibody Persistence Time Points Evaluated***

Study	Age at Vaccination in Primary Study	Vaccine Group	Vaccine Administered in Primary Study	Antibody Persistence Time Points[a]
MenACWY-TT-100 (C0921004)	1 to 10 years			Year 6, 7, 8, 9, 10
	1 to <2 years	ACWY<2	MenACWY-TT	
		MenCCRM	Meningitec[b]	
	2 – 10 years	ACWY≥2	MenACWY-TT	
		MenPS	Mencevax ACWY[c]	
MenACWY-TT-099 (C0921002)	11 – 55 years	ACWY-TT	MenACWY-TT	Year 7, 8, 9, 10
		MenPS	Mencevax ACWY[c]	
MenACWY-TT-101 (C0921005)	11 – 17 years	ACWY-TT	MenACWY-TT	Year 10
		MenPS	Mencevax ACWY[c]	

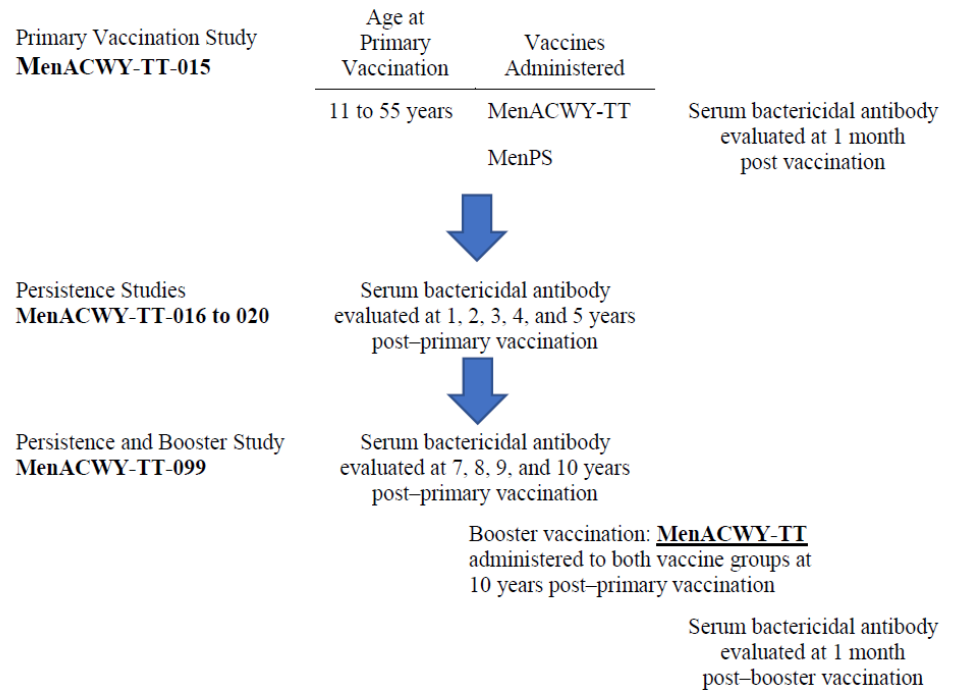
a. Years after primary vaccination
b. Meningitec = meningococcal C conjugate vaccine (MenCCRM)
c. Mencevax ACWY = quadrivalent meningococcal polysaccharide vaccine (MenPS)

Figure 1. Studies MenACWY-TT-027/ -028 to -032 / -100



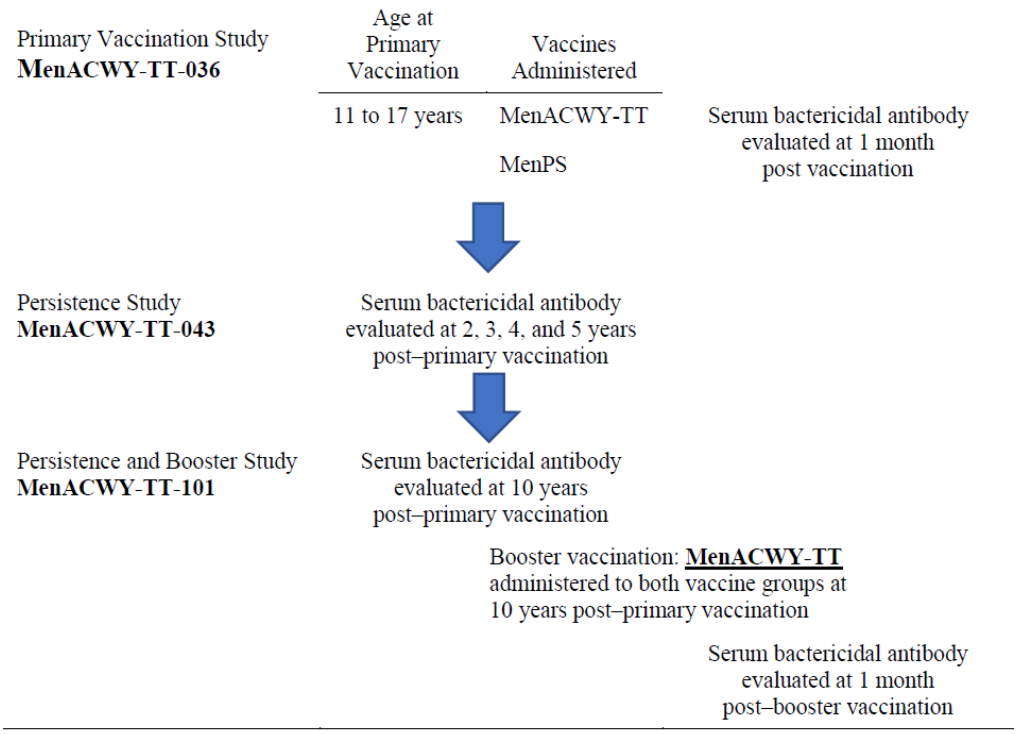
Note: rSBA assays were performed at GlaxoSmithKline laboratories for the 1 month and Year 1, 2, and 3 post vaccination time points; rSBA assays were performed at Public Health England for all determinations after Year 3.

Figure 2. ***Studies MenACWY-TT-015 / -016 to -020 / -099***



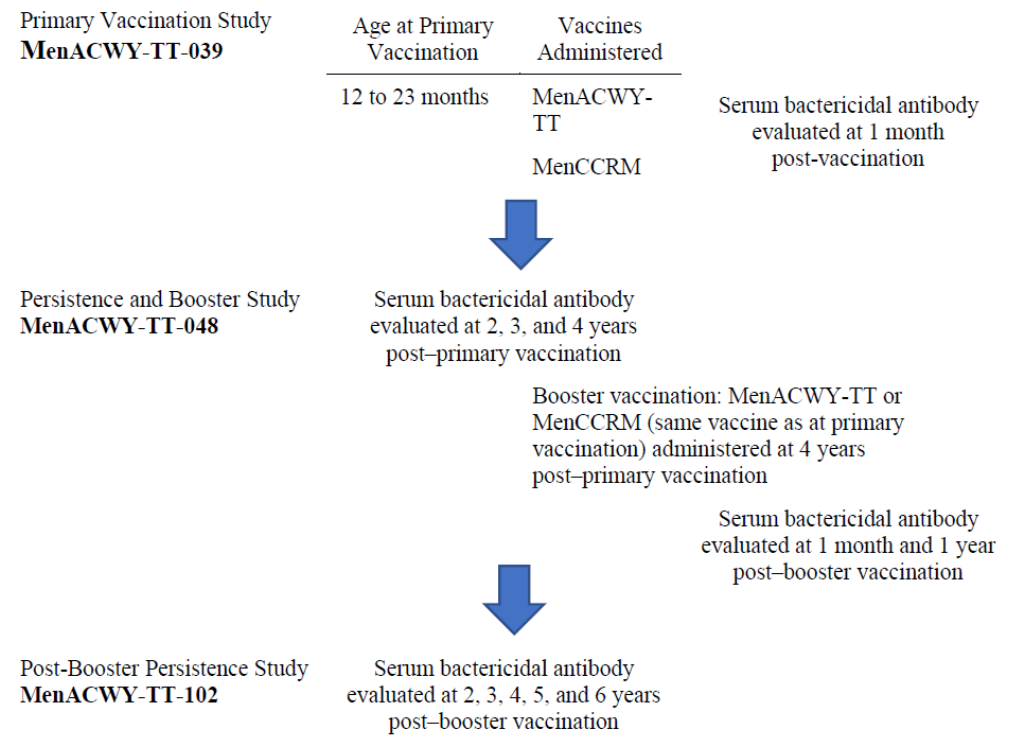
Note: rSBA assays were performed at GlaxoSmithKline laboratories for the 1 month and Year 1, 2, and 3 post vaccination time points; rSBA assays were performed at Public Health England for all determinations after Year 3.

Figure 3. ***Studies MenACWY-TT-036 / -043 / -101***



Note: rSBA assays were performed at GlaxoSmithKline laboratories for the 1 month and Year 2 post vaccination time points; rSBA assays were performed at Public Health England for all determinations after Year 2.

Figure 4. ***Studies MenACWY-TT-039 / -048 / -102***



Note: rSBA assays were performed at GlaxoSmithKline laboratories for the 1 month and Year 2 post vaccination time points; rSBA assays were performed at Public Health England for all determinations after Year 2.

Serum bactericidal antibody assay using rabbit complement (rSBA-MenA, rSBA-MenC, rSBA-MenW-135, and rSBA-MenY) – In all 4 studies, serum bactericidal antibody was determined by a serum bactericidal assay according to the (United States) Centers for Disease Control and Prevention protocol1 using rabbit complement. Titres are expressed as the reciprocal of the last (highest) dilution resulting in at least 50% reduction of meningococcal colony-forming units. The cut-off for the assay is a titre of 1:8. The rSBA testing for all 4 studies was performed at the laboratory of Public Health England in the United Kingdom. It should be noted that for the preceding primary studies (MenACWY TT-027, -015, -036, and -039) and for some time points in the interim persistence studies, rSBA assays were performed at GlaxoSmithKline (GSK) Biologicals Laboratories.

Serum bactericidal antibody assay using human complement (hSBA-MenA, hSBA-MenC, hSBA-MenW-135, and hSBA-MenY) – In Study 100 and Study 102, bactericidal antibodies were also determined by a serum bactericidal assay using human complement. hSBA titres are expressed as the reciprocal of the interpolated serum dilution resulting in 50% reduction of meningococcal colony-forming units. The cut-off for the assay is a titre of 1:4. The hSBA testing for both studies was performed at the Neomed Institute (Laval, Quebec).

An rSBA booster response to meningococcal antigens A, C, W-135, and Y was defined as:

- **For initially seronegative subjects** (prevaccination rSBA titre below 1:8), an rSBA titre ≥1:32, one month after vaccination;
- **For initially seropositive subjects** (prevaccination rSBA titre ≥1:8), an rSBA titre at least 4 times the prevaccination antibody titres, one month after vaccination.

An hSBA booster response to meningococcal antigens A, C, W-135, and Y was defined as:

- **For initially seronegative subjects** (prevaccination hSBA titre below 1:4), hSBA titre ≥ 1:8, one month after vaccination;
- **For initially seropositive subjects** (prevaccination hSBA titre ≥1:4), an hSBA titre at least 4 times the prevaccination antibody titres, one month after vaccination

6.4. Results

TT-100 (primary vaccination as toddlers 1- <2 years and children 2-10 years)

Primary Objectives:

Long-term persistence phase: 6, 7, 8, 9, and 10 years after primary vaccination with meningococcal polysaccharide groups A, C, W-135, Y tetanus toxoid conjugate vaccine (MenACWY-TT), Meningitec, or Mencevax ACWY, in Study MenACWY-TT-027

- To evaluate the long-term persistence of the serum bactericidal (antibody) titres induced by MenACWY-TT as compared to Meningitec when administered to individuals 1 to <2 years of age in terms of the percentage of subjects with serogroup A, C, W and Y ≥1:8, ≥1:128 and rSBA geometric mean titres (GMTs) in those subjects who received MenACWY-TT, and serogroup C (MenC) rSBA titres ≥1:8, ≥1:128, and GMTs in those subjects who received Meningitec.
- To evaluate the long-term persistence of the serum bactericidal (antibody) titres induced by MenACWY-TT as compared to Mencevax ACWY when administered to individuals 2 to 10 years of age in terms of the percentage of subjects with rSBA MenA, MenC, MenW-135, and MenY titres ≥1:8, ≥1:128 and GMTs as measured by rSBA.

Booster phase

One (1) month after booster vaccination with MenACWY-TT 10 years after primary vaccination:

- To evaluate the immunogenicity of a booster dose of MenACWY-TT with respect to the percentage of subjects with rSBA-MenA, rSBA-MenC, rSBA-MenW-135, and rSBA-MenY antibody titres ≥1:8, ≥1:128, and GMTs.
- To evaluate the immunogenicity of a booster dose of MenACWY-TT with respect to the percentage of subjects with hSBA-MenA, hSBA-MenC, hSBA-MenW-135, and hSBA-MenY antibody titres ≥1:4, ≥1:8, and GMTs.
- To evaluate the immunogenicity of a booster dose of MenACWY-TT conjugate vaccine in terms of the percentage of subjects with an rSBA-MenA, rSBA-MenC, rSBA-MenW-135, rSBA-MenY booster response.

Table 9. ***Number (%) of Subjects With rSBA-MenA, rSBA-MenC, rSBA-MenW-135, or rSBA-MenY Titres ≥1:8 and ≥1:128 and GMTs at Each Visit After Primary Vaccination (Adapted ATP Cohort) (Study 100)***

				≥1:8				≥1:128				GMT		
					95% CI[a]				95% CI[a]			95% CI[b]		
Antibody	Vaccine Group	Visitc	N	n	%	LL	UL	n	%	LL	UL	Value	LL	UL
rSBA-MenA	ACWY<2	M78	54	28	51.9	37.8	65.7	9	16.7	7.9	29.3	16.0	9.8	26.1
		M90	60	35	58.3	44.9	70.9	13	21.7	12.1	34.2	20.4	12.1	34.4
		M102	65	31	47.7	35.1	60.5	15	23.1	13.5	35.2	15.8	9.8	25.6
		M114	64	43	67.2	54.3	78.4	20	31.3	20.2	44.1	28.4	16.5	48.9
		M126	64	42	65.6	52.7	77.1	17	26.6	16.3	39.1	29.3	16.8	51.3
	MenCCRM	M78	16	3	18.8	4.0	45.6	1	6.3	0.2	30.2	5.9	3.1	11.3
		M90	21	2	9.5	1.2	30.4	2	9.5	1.2	30.4	6.1	3.3	11.4
		M102	22	1	4.5	0.1	22.8	1	4.5	0.1	22.8	4.8	3.3	7.2
		M114	21	1	4.8	0.1	23.8	1	4.8	0.1	23.8	5.2	3.0	9.0
		M126	17	3	17.6	3.8	43.4	1	5.9	0.1	28.7	5.8	3.2	10.6
	ACWY≥2	M78	98	78	79.6	70.3	87.1	54	55.1	44.7	65.2	107.3	66.0	174.3
		M90	104	77	74.0	64.5	82.1	46	44.2	34.5	54.3	65.3	40.5	105.4
		M102	100	70	70.0	60.0	78.8	45	45.0	35.0	55.3	51.3	31.5	83.4
		M114	93	74	79.6	69.9	87.2	53	57.0	46.3	67.2	118.8	71.1	198.6
		M126	81	72	88.9	80.0	94.8	40	49.4	38.1	60.7	106.0	63.7	176.4
	MenPS	M78	24	3	12.5	2.7	32.4	2	8.3	1.0	27.0	5.8	3.5	9.6
		M90	27	5	18.5	6.3	38.1	3	11.1	2.4	29.2	7.4	4.0	13.8
		M102	25	6	24.0	9.4	45.1	3	12.0	2.5	31.2	7.8	4.2	14.3
		M114	25	6	24.0	9.4	45.1	4	16.0	4.5	36.1	10.9	4.5	26.2
		M126	21	6	28.6	11.3	52.2	3	14.3	3.0	36.3	9.1	4.0	20.7
rSBA-MenC	ACWY<2	M78	54	42	77.8	64.4	88.0	38	70.4	56.4	82.0	161.3	84.7	307.1
		M90	60	47	78.3	65.8	87.9	37	61.7	48.2	73.9	104.0	58.0	186.3
		M102	65	51	78.5	66.5	87.7	42	64.6	51.8	76.1	110.2	65.9	184.3
		M114	64	52	81.3	69.5	89.9	42	65.6	52.7	77.1	166.0	92.3	298.7
		M126	64	53	82.8	71.3	91.1	41	64.1	51.1	75.7	132.2	74.5	234.6
	MenCCRM	M78	16	12	75.0	47.6	92.7	9	56.3	29.9	80.2	103.1	31.9	333.3
		M90	21	15	71.4	47.8	88.7	11	52.4	29.8	74.3	54.3	18.5	158.9
		M102	22	17	77.3	54.6	92.2	11	50.0	28.2	71.8	64.0	26.0	157.4
		M114	21	18	85.7	63.7	97.0	12	57.1	34.0	78.2	92.0	32.7	259.1
		M126	17	15	88.2	63.6	98.5	10	58.8	32.9	81.6	81.7	29.2	229.2
	ACWY≥2	M78	98	81	82.7	73.7	89.6	67	68.4	58.2	77.4	192.9	121.0	307.5
		M90	101	85	84.2	75.6	90.7	62	61.4	51.2	70.9	139.0	87.8	220.0
		M102	100	85	85.0	76.5	91.4	61	61.0	50.7	70.6	140.1	91.3	214.9
		M114	93	80	86.0	77.3	92.3	60	64.5	53.9	74.2	176.4	106.8	291.3
		M126	82	69	84.1	74.4	91.3	54	65.9	54.6	76.0	175.0	104.7	292.4
	MenPS	M78	24	19	79.2	57.8	92.9	15	62.5	40.6	81.2	98.7	42.2	230.7
		M90	27	22	81.5	61.9	93.7	18	66.7	46.0	83.5	101.6	42.1	245.0
		M102	25	22	88.0	68.8	97.5	16	64.0	42.5	82.0	121.1	52.2	281.1
		M114	25	21	84.0	63.9	95.5	17	68.0	46.5	85.1	164.3	66.5	405.8
		M126	21	17	81.0	58.1	94.6	14	66.7	43.0	85.4	105.0	37.2	296.4

				≥1:8					≥1:128				GMT		
						95% CI[a]				95% CI[a]				95% CI[b]	
Antibody	**Vaccine Group**	**Visit[c]**	**N**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**Value**	**LL**	**UL**
rSBA-MenW	ACWY<2	M78	54	18	33.3	21.1	47.5	16	29.6	18.0	43.6	18.0	9.8	32.9
		M90	60	16	26.7	16.1	39.7	14	23.3	13.4	36.0	13.0	7.6	22.3
		M102	65	19	29.2	18.6	41.8	18	27.7	17.3	40.2	15.3	9.0	26.3
		M114	64	21	32.8	21.6	45.7	17	26.6	16.3	39.1	17.3	9.7	30.8
		M126	64	20	31.3	20.2	44.1	18	28.1	17.6	40.8	16.7	9.5	29.3
	MenCCRM	M78	16	2	12.5	1.6	38.3	1	6.3	0.2	30.2	6.2	3.1	12.3
		M90	21	2	9.5	1.2	30.4	2	9.5	1.2	30.4	6.8	3.0	15.3
		M102	22	3	13.6	2.9	34.9	2	9.1	1.1	29.2	6.4	3.3	12.4
		M114	21	2	9.5	1.2	30.4	2	9.5	1.2	30.4	6.6	3.2	13.6
		M126	17	0	0.0	0.0	19.5	0	0.0	0.0	19.5	4.0	NE	NE
	ACWY≥2	M78	98	72	73.5	63.6	81.9	72	73.5	63.6	81.9	265.2	154.9	454.1
		M90	102	75	73.5	63.9	81.8	71	69.6	59.7	78.3	206.0	120.9	350.9
		M102	100	76	76.0	66.4	84.0	76	76.0	66.4	84.0	252.5	154.3	413.2
		M114	92	70	76.1	66.1	84.4	66	71.7	61.4	80.6	274.0	155.8	481.7
		M126	82	55	67.1	55.8	77.1	54	65.9	54.6	76.0	187.2	101.0	347.1
	MenPS	M78	24	3	12.5	2.7	32.4	3	12.5	2.7	32.4	7.6	3.7	15.6
		M90	27	3	11.1	2.4	29.2	2	7.4	0.9	24.3	6.3	3.7	10.9
		M102	25	5	20.0	6.8	40.7	5	20.0	6.8	40.7	11.8	4.7	29.8
		M114	25	4	16.0	4.5	36.1	4	16.0	4.5	36.1	9.7	4.0	23.3
		M126	21	5	23.8	8.2	47.2	5	23.8	8.2	47.2	14.0	4.8	41.2
rSBA-MenY	ACWY<2	M78	54	21	38.9	25.9	53.1	18	33.3	21.1	47.5	21.5	11.5	40.1
		M90	60	21	35.0	23.1	48.4	20	33.3	21.7	46.7	19.9	11.0	36.1
		M102	65	26	40.0	28.0	52.9	25	38.5	26.7	51.4	26.1	14.4	47.5
		M114	64	27	42.2	29.9	55.2	22	34.4	22.9	47.3	23.1	13.0	41.2
		M126	64	28	43.8	31.4	56.7	23	35.9	24.3	48.9	25.8	14.0	47.3
	MenCCRM	M78	16	6	37.5	15.2	64.6	5	31.3	11.0	58.7	21.7	5.9	79.0
		M90	21	6	28.6	11.3	52.2	6	28.6	11.3	52.2	18.3	5.8	57.6
		M102	22	9	40.9	20.7	63.6	9	40.9	20.7	63.6	33.0	9.8	111.0
		M114	21	10	47.6	25.7	70.2	8	38.1	18.1	61.6	32.0	10.6	96.3
		M126	17	6	35.3	14.2	61.7	5	29.4	10.3	56.0	22.2	5.8	84.2
	ACWY≥2	M78	98	70	71.4	61.4	80.1	64	65.3	55.0	74.6	136.4	82.6	225.3
		M90	102	77	75.5	66.0	83.5	71	69.6	59.7	78.3	152.7	96.1	242.6
		M102	100	79	79.0	69.7	86.5	73	73.0	63.2	81.4	181.0	115.0	284.9
		M114	93	62	66.7	56.1	76.1	54	58.1	47.4	68.2	106.2	61.5	183.4
		M126	82	54	65.9	54.6	76.0	49	59.8	48.3	70.4	90.5	51.5	159.2
	MenPS	M78	24	5	20.8	7.1	42.2	5	20.8	7.1	42.2	11.6	4.7	28.7
		M90	27	4	14.8	4.2	33.7	4	14.8	4.2	33.7	8.2	4.1	16.5
		M102	25	6	24.0	9.4	45.1	5	20.0	6.8	40.7	10.9	4.8	24.6
		M114	25	5	20.0	6.8	40.7	4	16.0	4.5	36.1	10.0	4.4	22.9
		M126	21	5	23.8	8.2	47.2	4	19.0	5.4	41.9	12.7	4.2	38.1

Note: Subjects were randomized and the primary vaccinations were administered at 1 to 10 years of age in primary study MenACWY-TT-027; all subjects who were given the booster vaccination in Study MenACWY-TT-100 (C0921004) received MenACWY-TT at Month 126.

a. Exact 2-sided CI based upon the observed proportion of subjects, using the Clopper and Pearson method.

b. CIs are back transformations of confidence levels based on the Student t distribution for the mean logarithm of the concentrations, or the mean of the ratio.

c. M78 = Month 78, 6 years after the primary vaccination; M90 = Month 90, 7 years after the primary vaccination; M102 = Month 102, 8 years after the primary vaccination; M114 = Month 114, 9 years after the primary vaccination; M126 = Month 126, 10 years after the primary vaccination and before booster vaccination.

Table 10. ***Number (%) of Subjects With rSBA-MenA, rSBA-MenC, rSBA-MenW-135, or rSBA-MenY Titres ≥ 1:8 and ≥1:128 and GMTs Before and 1 Month After Booster Vaccination Visit***

				≥1:8				≥1:128				GMT		
					95% CI[a]				95% CI[a]			95% CI[b]		
Antibody	Vaccine Group	Visit[c]	N	n	%	LL	UL	n	%	LL	UL	Value	LL	UL
rSBA-MenA	ACWY<2	M126	62	41	66.1	53.0	77.7	16	25.8	15.5	38.5	28.9	16.4	51.0
		M127	62	61	98.4	91.3	100.0	61	98.4	91.3	100.0	5122.3	3725.6	7042.6
	MenCCRM	M126	16	3	18.8	4.0	45.6	1	6.3	0.2	30.2	5.9	3.1	11.3
		M127	16	16	100.0	79.4	100.0	16	100.0	79.4	100.0	4871.0	2465.1	9624.9
	ACWY≥2	M126	73	65	89.0	79.5	95.1	35	47.9	36.1	60.0	96.3	57.1	162.5
		M127	74	71	95.9	88.6	99.2	71	95.9	88.6	99.2	4626.4	3040.6	7039.4
	MenPS	M126	17	4	23.5	6.8	49.9	2	11.8	1.5	36.4	8.0	3.3	19.3
		M127	17	17	100.0	80.5	100.0	17	100.0	80.5	100.0	6414.2	3878.5	10607.8
rSBA-MenC	ACWY<2	M126	62	51	82.3	70.5	90.8	39	62.9	49.7	74.8	128.0	71.1	230.6
		M127	62	62	100.0	94.2	100.0	62	100.0	94.2	100.0	7163.5	5478.0	9367.7
	MenCCRM	M126	16	14	87.5	61.7	98.4	10	62.5	35.4	84.8	86.7	29.0	259.2
		M127	16	16	100.0	79.4	100.0	16	100.0	79.4	100.0	5792.6	3630.6	9242.2
	ACWY≥2	M126	74	63	85.1	75.0	92.3	49	66.2	54.3	76.8	181.0	105.6	310.3
		M127	74	74	100.0	95.1	100.0	74	100.0	95.1	100.0	4020.0	3319.0	4869.1
	MenPS	M126	17	13	76.5	50.1	93.2	11	64.7	38.3	85.8	96.2	28.9	320.2
		M127	17	17	100.0	80.5	100.0	17	100.0	80.5	100.0	15101.0	7099.3	32121.5
rSBA-MenW-135	ACWY<2	M126	62	19	30.6	19.6	43.7	17	27.4	16.9	40.2	15.8	9.1	27.6
		M127	62	62	100.0	94.2	100.0	62	100.0	94.2	100.0	25911.2	19119.7	35115.2
	MenCCRM	M126	16	0	0.0	0.0	20.6	0	0.0	0.0	20.6	4.0	NE	NE
		M127	15	15	100.0	78.2	100.0	15	100.0	78.2	100.0	17970.4	11666.4	27680.7
	ACWY≥2	M126	74	51	68.9	57.1	79.2	50	67.6	55.7	78.0	206.4	108.6	392.1
		M127	74	74	100.0	95.1	100.0	74	100.0	95.1	100.0	27944.4	22213.8	35153.3
	MenPS	M126	17	4	23.5	6.8	49.9	4	23.5	6.8	49.9	15.4	4.2	56.4
		M127	17	16	94.1	71.3	99.9	16	94.1	71.3	99.9	10462.5	3253.5	33645.5
rSBA-MenY	ACWY<2	M126	62	28	45.2	32.5	58.3	23	37.1	25.2	50.3	27.4	14.7	51.0
		M127	62	61	98.4	91.3	100.0	61	98.4	91.3	100.0	7660.5	5262.9	11150.3
	MenCCRM	M126	16	6	37.5	15.2	64.6	5	31.3	11.0	58.7	24.7	6.0	100.8
		M127	16	16	100.0	79.4	100.0	16	100.0	79.4	100.0	6316.9	3223.8	12377.5
	ACWY≥2	M126	74	50	67.6	55.7	78.0	45	60.8	48.8	72.0	98.5	54.3	178.7
		M127	74	74	100.0	95.1	100.0	74	100.0	95.1	100.0	7529.7	5827.5	9729.2
	MenPS	M126	17	3	17.6	3.8	43.4	3	17.6	3.8	43.4	10.2	3.5	30.2
		M127	17	17	100.0	80.5	100.0	17	100.0	80.5	100.0	6959.2	3636.7	13317.1

Note: Subjects were randomized and the primary vaccinations were administered at 1 to 10 years of age in primary study MenACWY-TT-027; all subjects who were given the booster vaccination in Study MenACWY-TT-100 (C0921004) received MenACWY-TT at Month 126.
a. Exact 2-sided CI based upon the observed proportion of subjects, using the Clopper and Pearson method.
b. CIs are back transformations of confidence levels based on the Student t distribution for the mean logarithm of the concentrations, or the mean of the ratio.
c. M126 = Month 126, 10 years after the primary vaccination and before booster vaccination; M127 = Month 127, 1 month after the booster vaccination.

Conclusion TT-100

Primary dose of Nimenrix and comparator vaccine (Meningitec or Mencevax) as toddlers 1- <2 years and children 2-10 years.

The percentage of subjects with rSBA or hSBA titres ≥1:8 and GMTs at time points 6,5 years through to 10 years after the primary vaccination are quite stable. For Men-A differences are seen and while around 60% of subjects have a rSBA titre ≥1:8 at the 10,5 year time point, the percentage for hSBA ≥ 1:8 is the half, around 30%. For both Men-W and Men-Y the percentage of subjects with rSBA or hSBA titres ≥1:8 is quite low at the last time points, around 30-40%.

Study TT-100 shows that a booster dose of Nimenrix administered 10 years after primary vaccination elicited 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.

Study TT-099 (primary vaccination at 11-55 years)

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.

The primary endpoint was the percentage of subjects with rSBA titres of serogroups A, C, W and Y measured ≥ 1:8 or ≥ 1:128 and GMT. Secondary endpoint was to measure the response to a booster dose.

Table 11. ***Number (%) of Subjects With rSBA-MenA, rSBA-MenC, rSBA-MenW-135, or rSBA-MenY Titres ≥1:8 and ≥1:128 and GMTs at Each Visit After Primary Vaccination (Adapted ATP Cohort) (Study 099)***

				≥1:8				≥1:128				GMT		
					95% CI[a]				95% CI[a]			95% CI[b]		
Antibody	**Vaccine**	**Visit[c]**	**N**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**Value**	**LL**	**UL**
rSBA-MenA	ACWY-TT	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	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	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	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-	ACWY-TT	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	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	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	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

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.

a. Exact 2-sided CI based upon the observed proportion of subjects, using the Clopper and Pearson method.

b. CIs are back transformations of confidence levels based on the Student t distribution for the mean logarithm of the concentrations, or the mean of the ratio.

c. M84 = Month 84, 7 years after the primary vaccination; M96 = Month 96, 8 years after the primary vaccination; M108 = Month 108, 9 years after the primary vaccination; M120 = Month 120, 10 years after the primary vaccination and before the booster vaccination.

Table 12. ***Number (%) of Subjects With rSBA-MenA, rSBA-MenC, rSBA-MenW-135 and rSBA-MenY Titres ≥1:8 and ≥1:128 and GMTs Before and 1 Month After Booster Vaccination Visit (Booster ATP Cohort for Immunogenicity) (Study 099)***

				≥1:8				≥1:128				GMT		
						95% CI[a]				95% CI[a]			95% CI[b]	
Antibody	Vaccine Group	Visit[c]	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

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.

a. Exact 2-sided CI based upon the observed proportion of subjects, using the Clopper and Pearson method.

b. CIs are back transformations of confidence levels based on the Student t distribution for the mean logarithm of the concentrations, or the mean of the ratio.

c. M120 = Month 120, 10 years after the primary vaccination and before the booster vaccination; M121 = Month 121, 1 month after the booster vaccination.

Conclusion study TT-099

The percentage of subjects with rSBA titres ≥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 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.

Study TT-102 (Subjects Vaccinated at 12 to 23 Months of Age)

The objectives of Study 102 were to evaluate the persistence of serum bactericidal antibodies for each of the 4 serogroups at 2, 3, 4, 5, and 6 years **after booster vaccination of children** with MenACWY-TT or MenCCRM (Meningitec) in terms of rSBA responses (primary objective) and hSBA responses (secondary objective). For rSBA, the endpoints were the percentage of subjects with rSBA antibody titres ≥1:8 and ≥1:128, and geometric mean titres (GMTs) for each of the 4 serogroups. For hSBA, the endpoints were the percentage of subjects with hSBA antibody titres titres ≥1:4, ≥1:8, and GMTs for each of the 4 serogroups.

Table 13. ***Study Population (Total Enrolled Cohort) (Study 102)***

	Vaccine Group		
	ACWY-TT	**MenCCRM**	**Total**
Enrolled, N (total enrolled cohort)	159	25	184
Completed Year 2 (Month 24), n (%)	144 (90.6)	23 (92.0)	167 (90.8)
Completed Year 3 (Month 36), n (%	147 (92.5)	24 (96.0)	171 (92.9)
Completed Year 4 (Month 48), n (%)	150 (94.3)	24 (96.0)	174 (94.6)
Completed Year 5 (Month 60), n (%)	146 (91.8)	24 (96.0)	170 (92.4)
Completed Year 6 (Month 72), n (%)	150 (94.3)	24 (96.0)	174 (94.6)
Females:males	74:85	10:15	84:100
Mean age at enrollment, months (SD)	90.2 (6.06)	89.6 (5.56)	90.1 (5.99)
Median age, months (minimum, maximum)	89.0 (85, 125)	88.0 (85, 112)	89.0 (85, 125)
Race			
White - Caucasian/European heritage, n (%)	158 (99.4)	24 (96.0)	182 (98.9)
Other race, n (%)	1 (0.6)	1 (4.0)	2 (1.1)
Ethnicity			
Not American Hispanic or Latino, n (%)	159 (100.0)	24 (96.0)	183 (99.5)
American Hispanic or Latino, n (%)	0 (0.0)	1 (4.0)	1 (0.5)

Table 14. ***Number and Percentage of Subjects With rSBA-MenA, rSBA-MenC, rSBAMenW- 135, or rSBA-MenY Titres ≥1:8 and ≥1:128 and GMTs (Adapted ATP Cohort) (Study 102)***

				≥1:8				≥1:128				GMT		
						95% CI				95% CI			95% CI	
Antibody	Vaccine Group	Visit[a]	N	n	%	LL	UL	n	%	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

Note: Vaccines were administered at 12 to 23 months of age in primary study MenACWY-TT-039; booster vaccine was administered at 5 years of age in Study MenACWY-TT-048.

Note: ACWY-TT = pooled Co-ad and ACWY-TT groups from primary study MenACWY-TT-039 who were primed and boosted with MenACWY-TT (Co-ad group = MenACWY-TT + MMRV vaccine followed by the second dose of MMRV vaccine 84 days later; ACWY-TT group = MenACWY-TT followed by 2 doses of MMRV vaccine 42 and 84 days later).

Note: MenCCRM = pooled MMRV and MenCCRM groups from primary study MenACWY-TT-039 who were primed and boosted with Meningitec (MMRV group = MMRV vaccine followed by Meningitec 42 days later and the second dose

of MMRV vaccine 84 days later; MenCCRM group = Meningitec followed by 2 doses of MMRV vaccine 42 and 84 days later).

a. M24 = Month 24 (Visit 1), 24 months after the booster vaccination; M36 = Month 36 (Visit 2), 36 months after the booster vaccination; M48 = Month 48 (Visit 3), 48 months after the booster vaccination; M60 = Month 60 (Visit 4), 60 months after the booster vaccination; M72 = Month 72 (Visit 5), 72 months after the booster vaccination.

Number and Percentage of Subjects With hSBA-MenC Titres ≥1:4 and ≥1:8 and GMTs (Adapted ATP Cohort) (Study 102)

					≥1:4			≥1:8				GMT		
					95% CI			95% CI				95% CI		
Antibody	Vaccine Group	Visit[a]	N	n	%	LL	UL	n	%	LL	UL	Value	LL	UL
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	2 3	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

The hSBA data on serogroup C show that the percentage of subjects with hSBA ≥ 1:8 is high and stable (≥ 97.7%) during the 6 years post booster. The corresponding data on rSBA show a larger decrease in percentage of subjects with rSBA ≥1:8 or 1:128 during the 6 years.

Conclusion study TT-102

The results from Study TT-102 demonstrate the persistence of serum bactericidal antibodies against all 4 meningococcal serogroups up to 6 years after a booster vaccination of MenACWY-TT or MenCCRM administered 4 years after primary vaccination with the same vaccine in subjects 12 to 23 months of age. The persistence of serum bactericidal antibody against MenC was similar in the ACWY-TT and MenCCRM (Meningitec) groups.

6.5. Discussion

No changes to the SmPC regarding posology or undesirable effects have been proposed based on the persistence and booster data. The data are not considered to change the benefit-risk profile of Nimenrix, but they add knowledge to the persistence of antibodies in different age categories, the response to a booster dose and the persistence of the response to a booster dose. Changes to the section 5.1 of the SmPC are therefore proposed where the new results on antibody persistence and booster are presented. That relates to the following studies and age categories (the number of subjects and results may vary slightly from the SmPC tables because of different cohorts: booster versus persistence cohort, ATP versus all completed a time point):

- *Antibody persistence up to 10 years after vaccination at 12-23 month of age and 2-10 years of age ; Response to a booster dose administered 10 years after primary vaccination (Studies 027, 032, and 100).*

  Number of subjects completing the 10 year persistence time point: Nimenrix < 2 years old 68, 2-10 years old 84, Meningitec 17, Mencevax 22.

  The percentage of subjects with rSBA ≥ 1:8 at the 10 year time point: Serogroup A: Nimenrix < 2 years 65%, Nimenrix ≥ 2 years 88%, serogroup C: Nimenrix < 2 years 82%, Nimenrix ≥ 2 years 84%, serogroup W: Nimenrix < 2 years 31%, Nimenrix ≥ 2 years 67%, serogroup Y: Nimenrix < 2 years 43%, Nimenrix ≥ 2 years 65%.

  The percentages of subjects with rSBA titres or hSBA ≥1:8 for serogroup C at the 10 year time point were high and similar for all vaccines and age groups (1-10 years). For serogroups W and Y the response is higher for the Nimenrix ≥ 2 year compared to the < 2 year group, for serogroup C it was equally good. Results for the percentages of subjects with rSBA titres ≥ 1:128 and results for rSBA GMTs followed similar trend. The hSBA against serogroup A at the 10 year time point was rather low, 31-34% of subjects with titres ≥ 1:4 for Nimenrix. Study TT-100 shows that a booster dose of Nimenrix administered 10 years after primary vaccination elicited robust immune responses against each of the 4 serogroups.

- *Antibody persistence up to 10 years after vaccination at 11-17 years of age; Response to a booster dose administered 10 years after primary vaccination (Studies 036, 043, and 101).*

  Number of subjects completing the 10 year persistence time point: Nimenrix 170, Mencevax 59.

  The percentage of subjects with rSBA ≥ 1:8 at the 10 year time point for Nimenrix: Serogroup A: 85%, serogroup C: 90%, serogroup W: 71%, serogroup Y: 90%. Nimenrix has higher levels of protective antibodies against all serogroups compared to Mencevax at the 10 year time point, the range of percentage of subjects with rSBA ≥ 1:128 was 64.8 – 85.2% for Nimenrix and 25.5 – 76.5% for Mencevax for all serogroups.

  High antibody levels were observed after the booster dose of Nimenrix given 10 years after primary vaccination with a single dose of Nimenrix or Mencevax. The booster response varied from 82-96% in subjects previously vaccinated with Nimenrix and 67-94% in subjects previously vaccinated with Mecevax. All subjects in the Nimenrix arm and nearly all subjects in the Mencevax arm had rSBA ≥1: 128 after the booster dose.

- *Antibody persistence up to 10 years after vaccination at 11-55 years of age; Response to a booster dose administered 10 years after primary vaccination (Studies 015, 020, and 099).*

  Number of subjects completing the 10 year persistence time point: Nimenrix 173, Mencevax 58.

  The percentage of subjects with rSBA ≥ 1:8 at the 10 year time point for Nimenrix: Serogroup A: 76%, serogroup C: 90%, serogroup W: 70%, serogroup Y: 87%.

  The percentage of subjects with rSBA titres ≥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.

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 robust immune responses against each of the 4 serogroups. All subjects in the Nimenrix groups had rSBA ≥ 1:128, and 99-100% of the Mencevax group.

- *Antibody persistence up to 4 years after vaccination at 12-23 months of age; Response to a booster dose administered 4 years after primary vaccination, and Antibody persistence up to 6 years after the booster dose (studies 039, 048, and 102).*

  Number of subjects completing the 6 year persistence time point after booster: Nimenrix 150, Meningitec 24.

  The percentage of subjects with rSBA ≥ 1:8 at the 6 year time point after booster for Nimenrix: Serogroup A: 92%, serogroup C: 71%, serogroup W: 85%, serogroup Y: 94%.

  The persistence of rSBA against serogroup C was similar in the Nimenrix and Meningitec groups. For subjects in the Nimenrix group, the percentages of subjects with hSBA titres ≥1:8 remained very high (≥97.0%) across all time points for serogroups C, W and Y. For serogroup A the percentage of subjects with hSBA ≥ 1:8 was 58% at the 6 year time point.

It is a strength that both rSBA and hSBA have been measured in most studies. For serogroup C rSBA and hSBA gives consistent results, while especially for serogroup A there are in many studies differences in the levels of antibodies measured by rSBA or hSBA. Variation is also due to the pool of subjects measured at each time point varied as the protocol allowed subjects to skip a time point. Also, change in the laboratory performing rSBA analysis has caused some variation. However, the total data on persistence and booster is extensive and makes a good platform for evaluating the need for a booster in different age categories.

The use of Nimenrix for booster vaccination is mentioned in section 4.2 Posology and in section 4.4 Special warnings and precautions for use of the SmPC. No changes to these sections other than orthographic are proposed. Section 4.4 mentions the potential need for a booster dose linked to waning serogroup A titres as measured with hSBA in some studies. Also, because of a general decline of antibody titres over time for all serogroups a booster may be beneficial for subjects with a high risk of exposure (see SmPC section 4.4):

> "*Following administration of Nimenrix there is a waning of serum bactericidal antibody titres against group A when using hSBA (see section 5.1). The clinical relevance of this observation is unknown. However, if an individual is expected to be at particular risk of exposure to group A and received a dose of Nimenrix more than approximately one year previously, consideration may be given to administering a booster dose.*
>
> *A decline in antibody titres over time has been observed for groups A, C, W-135 and Y. The clinical relevance of this observation is unknown. A booster dose might be considered in individuals vaccinated at toddler age remaining at high risk of exposure to meningococcal disease caused by groups A, C, W-135 or Y (see section 5.1).*"

It is agreed that the present recommendations in the SmPC regarding the need for a booster vaccine are sufficient for the time being.

7. Clinical Safety aspects

The results of the 4 clinical studies summarized above demonstrate that MenACWY-TT is well tolerated when administered as a booster vaccination 4 years or 10 years after administration of MenACWY-TT, MenPS, or MenCCRM to individuals 1 to 55 years of age.

The results are consistent with the safety profile that has been established for primary vaccination with Nimenrix, and no new adverse reactions for Nimenrix were identified.

Nimenrix may be given as a booster dose to individuals who have previously received primary vaccination with Nimenrix or with other conjugated or plain polysaccharide meningococcal vaccines.

As there are no new safety signals and that the studies main objectives were on antibody persistence and the immune response to a booster dose, no detailed safety data are reported here.

8. Changes to the Product Information

As a result of this variation, section 5.1 of the SmPC are being updated to include the new data and revise the tables illustrating persistence of antibodies and the effect of a booster dose.

Some of the aspects of the wording initially proposed by the MAH were not acceptable. The MAH therefore agreed to include terms recommended by CHMP, and provided updated SmPC and PL with changes made as requested.

The use of Nimenrix for booster vaccination is mentioned in SmPC section 4.2 Posology and in section 4.4 Special warnings and precautions for use. No changes to these sections other than minor editing of the wording are proposed. Section 4.4 mentions the potential need for a booster dose linked to waning serogroup A titres as measured with hSBA in some studies. Also, because of a general decline of antibody titres over time for all serogroups a booster may be beneficial for subjects with a high risk of exposure (see SmPC section 4.4). It is agreed that the current SmPC recommendations regarding the need for a booster vaccine are sufficient for the time being.

Changes are also made to the PI to bring it in line with the current QRD template and some minor editorial changes throughout the PI improved its consistency, clarity and accuracy.

The Package Leaflet (PL) is updated to include the sentence: "*In infants, Nimenrix can be given concomitantly with combined DTaP-HBV-IPV/Hib vaccines and with 10-valent pneumococcal conjugate vaccine.*" This information for infant coadministration was missing in the PL, which was therefore not consistent with the SmPC.

For full details of the changes approved with this variation, see attachment 1.

9. Appendix 1

1. CHMP assessment report for MenACWY-TT-100 (procedure EMEA/H/C/2226/P46/053), dated 25 July 2019.

25 July 2019
EMA/49111/2020
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/P46/053

Note

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

Introduction

On 11 April 2019, the MAH submitted a completed paediatric study for Nimenrix, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

1. Scientific discussion

1.1. Information on the development program

The MAH stated that study title and number is a stand alone study.

1.2. 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.

1.3. Clinical aspects

1.3.1. Introduction

The MAH submitted a final report for:

- Protocol MenACWY-TT-100 (C0921004); formerly GlaxoSmithKline 200171;

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 the Meningococcal Conjugate Vaccine MenACWY-TT Versus One Dose of Meningitec® Vaccine or One Dose of the 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 1-10 Year Old Subjects With MenACWY-TT, Meningitec or Mencevax ACWY.

In Study MenACWY-TT-027 (108658), 613 healthy subjects between 1 and 10 years of age were randomized using a 3:1 ratio to receive either a single dose of MenACWY-TT, or a meningococcal C conjugate vaccine (Meningitec) or a quadrivalent meningococcal polysaccharide vaccine (Mencevax ACWY). The subjects were followed for antibody persistence over 5 years after vaccination in studies MenACWY-TT-028 through -032.

The main purpose of the present study (MenACWY-TT-100 [C0921004]) was to continue to evaluate the antibody persistence 6, 7, 8, 9, and 10 years after administration of MenACWY-TT as compared to Meningitec or Mencevax ACWY when given to healthy subjects 1 to 10 years of age. In addition, the safety and immunogenicity of a booster dose of MenACWY-TT administered to all eligible subjects 10 years after the primary vaccination was evaluated.

1.3.2. Clinical study

Study MenACWY-TT-100

Description

Methods

Objective(s)

Primary Objectives:

Long-term persistence phase: 6, 7, 8, 9, and 10 years after primary vaccination with meningococcal polysaccharide groups A, C, W-135, Y tetanus toxoid conjugate vaccine (MenACWY-TT), Meningitec, or Mencevax ACWY, in Study MenACWY-TT-027

- To evaluate the long-term persistence of the serum bactericidal (antibody) titers induced by MenACWY-TT as compared to Meningitec when administered to individuals 1 to <2 years of age in terms of the percentage of subjects with *Neisseria meningitides* serogroup A (MenA), serogroup C (MenC), serogroup W-135 (MenW-135), and serogroup Y (MenY) titers ≥1:8, ≥1:128 and geometric mean titers (GMTs) as measured by a serum bactericidal assay using rabbit complement (rSBA) in those subjects who received MenACWY-TT, and serogroup C (MenC) rSBA titers ≥1:8, ≥1:128, and GMTs in those subjects who received Meningitec.
- 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 2 to 10 years of age in terms of the percentage of subjects with rSBA MenA, MenC, MenW-135, and MenY titers ≥1:8, ≥ 1:128 and GMTs as measured by rSBA.

Secondary Objectives:

Persistence phase

Long–term persistence phase: 6, 7, 8, 9, and 10 years after primary vaccination with MenACWY-TT, Meningitec, or Mencevax ACWY, in Study MenACWY-TT-027

- To evaluate the long-term persistence induced by MenACWY-TT as compared to Meningitec when administered to individuals 1 to <2 years of age in terms of percentage of subjects with serum bactericidal assay using human complement (hSBA) titers ≥1:4, ≥1:8, and GMTs for all 4 serogroups in those subjects who received MenACWY-TT, and MenC hSBA titers ≥1:4, ≥1:8, and GMTs in those subjects who received Meningitec.
- To evaluate the long-term persistence induced by MenACWY-TT as compared to Mencevax ACWY when administered to individuals 2 to 10 years of age in terms of percentage of subjects with hSBA titers ≥1:4, ≥1:8, and GMTs for all 4 serogroups.

Booster phase One (1) month after booster vaccination with MenACWY-TT 10 years after primary vaccination:

- To evaluate the immunogenicity of a booster dose of MenACWY-TT with respect to the percentage of subjects with rSBA-MenA, rSBA-MenC, rSBA-MenW-135, and rSBA-MenY antibody titers ≥1:8, 1:128, and GMTs.
- To evaluate the immunogenicity of a booster dose of MenACWY-TT with respect to the percentage of subjects with hSBA-MenA, hSBA-MenC, hSBA-MenW-135, and hSBA-MenY antibody titers ≥1:4, ≥1:8, and GMTs.
- To evaluate the immunogenicity of a booster dose of MenACWY-TT conjugate vaccine in terms of the percentage of subjects with an rSBA-MenA, rSBA-MenC, rSBA-MenW-135, rSBA-MenY booster response*.

*rSBA and hSBA booster responses to meningococcal antigens (A, C, W-135, and Y) are defined as:

For initially seronegative subjects (pre-vaccination rSBA titer below 1:8): rSBA titer ≥1:32 one month after vaccination, and for initially seropositive subjects (pre-vaccination rSBA titer ≥1:8): at least 4-fold increase in rSBA titers from pre-vaccination to 1 month after vaccination.

For initially seronegative subjects (pre-vaccination hSBA titer below 1:4): hSBA titers ≥1:8 one month after vaccination, and for initially seropositive subjects (pre-vaccination hSBA titer ≥1:4): a 4-fold increase in hSBA titers 1 month after vaccination.

Study design

This was a Phase 3b, open-label, multi-center, study with 4 parallel groups to evaluate the persistence of meningococcal antibodies 6, 7, 8, 9, and 10 years after primary vaccination with MenACWY-TT, Meningitec, or Mencevax ACWY in children who participated in Study MenACWY-TT-027 (108658). The immunogenicity, safety, and reactogentics of a booster dose of MenACWY-TT in subjects who had received primary vaccination with MenACWY-TT, Meningitec, or Mencevax ACWY was also evaluated.

There were 4 parallel groups with the subjects being allocated to the same groups as the previous study (MenACWY-TT-027 [108658]):

- ACWY<2 group: vaccinated with MenACWY-TT in Study MenACWY-TT-027 (108658) and aged <2 years at the time of primary vaccination,
- MenCCRM group: vaccinated with Meningitec in Study MenACWY-TT-027 (108658) and aged <2 years at the time of primary vaccination,
- ACWY≥2 group: vaccinated with MenACWY-TT in Study MenACWY-TT-027 (108658) and aged ≥2 years at the time of primary vaccination,
- MenPS group: vaccinated with Mencevax ACWY in Study MenACWY-TT-027 (108658) and aged ≥2 years at the time of primary vaccination.

<u>Booster phase</u>

Booster phase starting at Visit 5 (Month 126 [Year 10] after primary vaccination) and ending at the phone contact (Month 132 or 6 months after booster vaccination).

Study population /Sample size

All subjects who were vaccinated in Study MenACWY-TT-027 were invited to participate in this study. Approximately, 488 subjects were expected to participate in the study.

Subjects were ineligible to participate in this study if they met any of the following exclusion criteria:

- Child in care
- Previous vaccination with meningococcal polysaccharide or conjugate vaccine outside of Study MenACWY-TT-027.
- History of meningococcal disease due to serogroup A, C, W-135, or Y.
- Previous vaccination with meningococcal B vaccine.
- Any confirmed or suspected immunosuppressive or immunodeficient condition (congenital or secondary), including human immunodeficiency virus (HIV) infection, based on medical history and physical examination (no laboratory testing required).
- Family history of congenital or hereditary immunodeficiency.
- Major congenital defects or serious chronic illness.
- History of chronic alcohol consumption and/or drug abuse.

Treatments

Investigational Product Name	Manufacturer	Vaccine/ Component Name	Formulation	Presentation	Volume to Be Administered	Lot Number
Primary vaccine (1 through 10 years; Study MenACWY-TT-027 [108658])						
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	Lyophilized pellet to be reconstituted with saline diluent	0.5 mL	DMECA007A Diluent: AD02B118A
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	AMENB045BZ Diluent: AD02B118A
Meningococcal C conjugate vaccine	Wyeth Lederle	Meningitec	10 µg of capsular polysaccharide of meningococcal group C conjugated to 15 µg of *Corynebacterium diphtheriae* CRM_{197} protein Aluminum as salts	Whitish liquid in vial	0.5 mL	14838
Year 10 booster dose (present study)						
MenACWY-TT	GlaxoSmithKline (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	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: CRM_{197} = cross-reactive material 197; PSA, PSC, PSW-135, and PSY = polysaccharide *Neisseria meningitidis* groups A, C, W-135, and Y; TT = tetanus toxoid.

Outcomes/endpoints

Primary Endpoints

Immunogenicity with respect to the components of the investigational vaccine 6, 7, 8, 9, and 10 years after primary vaccination in Study MenACWY-TT-027:

- Percentage of subjects with rSBA titers ≥1:8, ≥1:128, and GMTs for all 4 serogroups.

Secondary Endpoints

Persistence phase:

Immunogenicity with respect to the components of the investigational vaccine 6, 7, 8, 9, and 10 years after primary vaccination in Study MenACWY-TT-027 (108658):

- Percentage of subjects with hSBA titers ≥1:4, ≥1:8, and GMTs for all 4 serogroups.

Booster phase:

Immunogenicity with respect to the components of the investigational vaccine 1 month after booster vaccination at 10 years after primary vaccination:

- Percentage of subjects with rSBA titers ≥1:8, ≥1:128, and GMTs for all 4 serogroups and rSBA booster response.
- Percentage of subjects with hSBA titers ≥1:4, ≥1:8, and GMTs for all 4 serogroups and hSBA booster response.

Statistical Methods

Analysis of Persistence

For each Month X: The analysis of antibody persistence for MenC was based on the ATP cohort for persistence - MenC - adapted for each time point. The analysis of antibody persistence for MenA, MenW-135, and MenY was based on the ATP cohort for persistence -MenAWY - adapted for each time point. If there were no differences between these cohorts, they may have been combined.

If, for any vaccine group, the percentage of subjects who came back for the Month X follow-up with serological results excluded from the ATP cohort was higher than 10%, a second analysis based on the total vaccinated cohort Month X was to be performed to complement the ATP analysis.

Within Group Analysis

For each vaccine group, at each blood sampling time point, for each antigen assessed:

- GMTs with 95% confidence intervals (CIs) were tabulated.
- Percentages of subjects with titers above the proposed cutoffs with exact 95% CIs were calculated.
- The distribution of antibody titers was tabulated and also presented using reverse cumulative distribution curves (RCDCs).

Between Group Analysis

An exploratory evaluation of the differences in the immune response at approximately 78, 90, 102, 114, and 126 months after the primary vaccination was performed in terms of:

- Differences in the percentage of subjects with rSBA titers ≥1:8 and ≥1:128 and hSBA titers ≥1:4 and ≥1:8 between the ACWY≥2 and MenPS groups, with their standardized asymptotic 95% CIs for the 4 serogroups and the differences in the percentage of subjects with rSBA-MenC titers ≥1:8 and ≥1:128 and hSBA-MenC titers ≥1:4 and ≥1:8 between the ACWY<2 and MenCCRM groups with their standardized asymptotic 95% CIs.
- Ratio of GMTs for comparing the ACWY≥2 and MenPS groups for the 4 serogroups and the ratio of MenC GMTs for comparing the ACWY<2 and MenCCRM groups, with their standardized asymptotic 95% CIs. This was performed using an analysis of variance (ANOVA) model on the logarithm10 transformation of the titers using the vaccine group and age stratum as covariates.

Modeling 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 was performed at the last persistence time point (month 126) before booster vaccination for rSBA-MenA, C, W-135, and Y and/or hSBA-MenA, C, W-135, and Y.

Except as noted below, these longitudinal analyses will include all titers from:

- Pre- and post-primary analyses (Month 0 and Month 1 in Study MenACWY-TT-027) for subjects belonging in the ATP cohort for immunogenicity,
- Months 12, 24, 36, 48, and 60 (in Studies MenACWY-TT-028, 029 , 030, 031, and 032 respectively) for subjects belonging in the ATP cohort for persistence in corresponding studies and
- Months 78, 90, 102, 114, and 126 (in Study MenACWY-TT-100) for subjects belonging in the ATP cohort for persistence at Month 78 up to Month 126, respectively.

Immunogenicity Measurements - MenACWY-TT Antibody Response

Bactericidal antibodies specific for meningococcal antigens are recognized as surrogate markers of protection against meningococcal disease. An rSBA titer cutoff 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 cutoff for rSBA-MenC was extended for rSBA-MenA, rSBA-MenW-135, and rSBA-MenY.

The established correlate of protection for hSBA-MenC is titer equal to or greater than 1:4, and this cutoff has been extended for hSBA-MenA, hSBA-MenW-135, and hSBA-MenY.

Approximately 7 mL (10 mL at Visits 4, 5, and 6) of whole blood was drawn from all subjects for each analysis of humoral immune response at each predefined time point. After centrifugation, serum samples were kept at -20° C or below until shipment.

Table 15. Humoral Immunity (Antibody Determination)

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

Different laboratories performed the rSBAs and hSBAs at different time points. rSBAs were performed either by GSK or Public Health England (PHE). hSBAs were performed either by GSK or Neomed (Neomed was a GSK facility until it was spun off as an independent company). Furthermore, GSK did not perform hSBAs for 2-<6 year subjects.

Table 16. Description of Laboratories Performing rSBAs by Time Point

		GSK		PHE	
Study MenACWY-	Time Point	1-<2 years	2-<11 years	1-<2 years	2-<11 years
TT-027	Baseline (Month 0)	✓	✓		
	Month 1	✓	✓		
TT-028	Year 1	✓	✓		
TT-029	Year 2	✓	✓		
TT-030	Year 3	✓	✓		
TT-031	Year 4	✓	✓	✓	✓
TT-032	Year 5			✓	✓
TT-100	Month 78 (Year 6)			✓	✓
	Month 90 (Year 7)			✓	✓
	Month 102 (Year 8)			✓	✓
	Month 114 (Year 9)			✓	✓
	Month 126 (Year 10)			✓	✓
	Month 127			✓	✓

Abbreviations: rSBA = serum bactericidal assay against *Neisseria meningitidis* using rabbit complement.

Table 17. Description of Laboratories Performing hSBAs by Time Point

		GSK		Neomed	
Study MenACWY-	Time Point	1-<2 years	6-<11 years	1-<2 years	2-<11 years
TT-027	Baseline (Month 0)	✓	✓		
	Month 1	✓	✓		
TT-028	Year 1	✓	✓		
TT-029	Year 2	✓			
TT-030	Year 3	✓			
TT-031	Year 4	✓			
TT-032	Year 5	✓			
TT-100	Month 78 (Year 6)			✓	✓
	Month 90 (Year 7)			✓	✓
	Month 102 (Year 8)			✓	✓
	Month 114 (Year 9)			✓	✓
	Month 126 (Year 10)			✓	✓
	Month 127			✓	✓

Abbreviations: hSBA = serum bactericidal assay against *Neisseria meningitidis* using human complement.

Results

Recruitment/ Number analysed

Baseline data

Table 18. Study Population - Persistence Phase (Total Cohort at Months 78, 90, 102, 114, and 126)

	Vaccine Group				
	ACWY<2[a]	MenCCRM[b]	ACWY≥2[c]	MenPS[d]	Total
Planned[e], N	183	61	183	61	488
Enrolled N[f] (total enrolled cohort)	76	23	115	29	243
Completed Month 78 (Visit 1), n[g] (%)[h]	56 (73.7)	16 (69.6)	100 (87.0)	25 (86.2)	197 (81.1)
Completed Month 90 (Visit 2), n[g] (%)[h]	64 (84.2)	21 (91.3)	107 (93.0)	28 (96.6)	220 (90.5)
Completed Month 102 (Visit 3), n[g] (%)[h]	68 (89.5)	23 (100.0)	104 (90.4)	26 (89.7)	221 (90.9)
Completed Month 114 (Visit 4), n[g] (%)[h]	67 (88.2)	21 (91.3)	94 (81.7)	26 (89.7)	208 (85.6)
Completed Month 126 (Visit 5), n[g] (%)[h]	68 (89.5)	17 (73.9)	84 (73.0)	22 (75.9)	191 (78.6)
Demographic information					
Females:males	40:36	12:11	56:59	14:15	122:121
Mean age at enrollment, years (SD)	8.2 (0.7)	8.2 (0.7)	12.5 (2.6)	12.1 (2.9)	10.7 (3.0)
Median age, years (minimum, maximum)	8.0 (7, 10)	8.0 (7, 10)	13.0 (8, 18)	12.0 (8, 16)	9.0 (7, 18)
Race					
White - Caucasian/European heritage, n[g] (%)[h]	75 (98.7)	22 (95.7)	113 (98.3)	28 (96.6)	238 (97.9)
White - Arabic/North African heritage, n[g] (%)[h]	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	1 (0.4)
Other race, n[g] (%)[h]	1 (1.3)	1 (4.3)	1 (0.9)	1 (3.4)	4 (1.6)
Ethnicity					
Not American Hispanic or Latino, n[g] (%)[h]	76 (100.0)	23 (100.0)	115 (100.0)	29 (100.0)	243 (100.0)

Note: Date of birth, sex, race, and ethnicity were collected in primary study MenACWY-TT-027.
Note: The total enrolled cohort includes all subjects enrolled in the study irrespective of the visit at which they were enrolled.
Note: Subjects were randomized and the primary vaccinations were administered at 1 to 10 years of age in primary study MenACWY-TT-027; all subjects who were given the booster vaccination in Study MenACWY-TT-100 (C0921004) received MenACWY-TT at Month 126.
Note: The age was computed based on the date of first enrollment visit in Study MenACW-TT-100 (C0921004).
a. ACWY<2 = vaccinated with MenACWY-TT in Study MenACWY-TT-027 and aged <2 years at the time of primary vaccination.
b. MenCCRM = vaccinated with Meningitec in Study MenACWY-TT-027.
c. ACWY≥2 = vaccinated with MenACWY-TT in Study MenACWY-TT-027 and aged ≥2 years at the time of primary vaccination.
d. MenPS = vaccinated with Mencevax ACWY in Study MenACWY-TT-027.
e. Planned number of subjects was based on an assumption that approximately 10% of the potential subjects would not participate at Month 78 (Visit 1).
f. N = number of subjects.
g. n = Number of subjects within each category.
h. % = Percentage of subjects within each category was calculated based on total enrolled cohort in persistence phase.

Booster phase.

A total of 181 subjects (67 from the ACWY<2 group, 16 from the MenCCRM group, 77 from the ACWY ≥ 2 group, and 21 from the MenPS group) were enrolled in the booster phase to receive MenACWY TT at Month 126.

Table 19. Disposition of Subjects - Persistence Phase (Total Cohort for Months 78, 90, 102, 114, and 126)

	Vaccine Group									
	ACWY<2[a]		MenCCRM[b]		ACWY≥2[c]		MenPS[d]		Total	
	n[e]	%[f]	n[e]	%[f]	n[e]	%[f]	n[e]	%[f]	n[e]	%[f]
Enrolled[g] (total enrolled cohort)	76	N/A	23	N/A	115	N/A	29	N/A	243	N/A
Completed persistence phase in the study										
Completed all persistence visits	47	61.8	10	43.5	71	61.7	17	58.6	145	59.7
Missed at least 1 persistence visit	21	27.6	7	30.4	13	11.3	5	17.2	46	18.9
Number of subjects withdrawn in persistence phase	8	10.5	6	26.1	31	27.0	7	24.1	52	21.4
Reason for withdrawal in persistence phase										
Serious adverse event	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Nonserious adverse event	0	0.0	0	0.0	1	0.9	0	0.0	1	0.4
Eligibility criteria not fulfilled (inclusion or exclusion criteria)	0	0.0	0	0.0	3	2.6	1	3.4	4	1.6
Protocol violation	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Consent withdrawal/not due to an (S)AE	4	5.3	5	21.7	18	15.7	4	13.8	31	12.8
Migrated/moved from study area	2	2.6	0	0.0	4	3.5	0	0.0	6	2.5
Lost to follow-up	2	2.6	1	4.3	5	4.3	2	6.9	10	4.1
Subject died	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Sponsor study termination	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Other reason	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0

Abbreviation: N/A = not applicable.

Note: Subjects were randomized and the primary vaccinations were administered at 1 to 10 years of age in primary study MenACWY-TT-027; all subjects who were given the booster vaccination in Study MenACWY-TT-100 (C0921004) received MenACWY-TT at Month 126.

a. ACWY<2 = vaccinated with MenACWY-TT in Study MenACWY-TT-027 and aged <2 years at the time of primary vaccination.

b. MenCCRM = vaccinated with Meningitec in Study MenACWY-TT-027.

c. ACWY≥2 = vaccinated with MenACWY-TT in Study MenACWY-TT-027 and aged ≥2 years at the time of primary vaccination.

d. MenPS = vaccinated with Mencevax ACWY in Study MenACWY-TT-027.

e. n = Number of subjects in a given category.

f. % = Percentage of subjects in a given category.

g. Enrolled = The total enrolled cohort includes all the subjects who were vaccinated in primary study MenACWY-TT-027 and enrolled in Study MenACWY-TT-100 (C0921004) irrespective of the visit at which they were enrolled.

Program ID: Study MenACWY-TT-100(C0921004)/CP CS_DISP.SAS. Date of Reporting Dataset Creation: 04OCT2018. Runtime ID: 06NOV2018 09:13. File ID: 4_CS_DISP_TEC.HTM.

Efficacy results

<u>rSBA titers.</u>

Figure 5. Reverse Cumulative Distribution Curves (RCDCs) for rSBA-MenA Titers - Vaccine Group ACWY<2

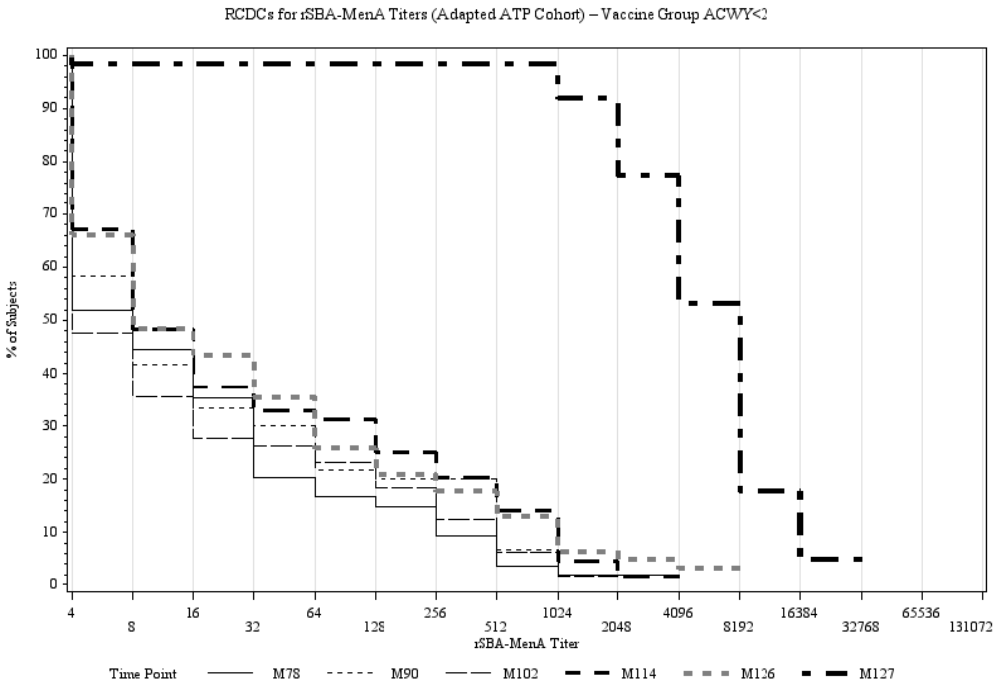


Figure 6. Reverse Cumulative Distribution Curves (RCDCs) for rSBA-MenC Titers - Vaccine Group ACWY<2

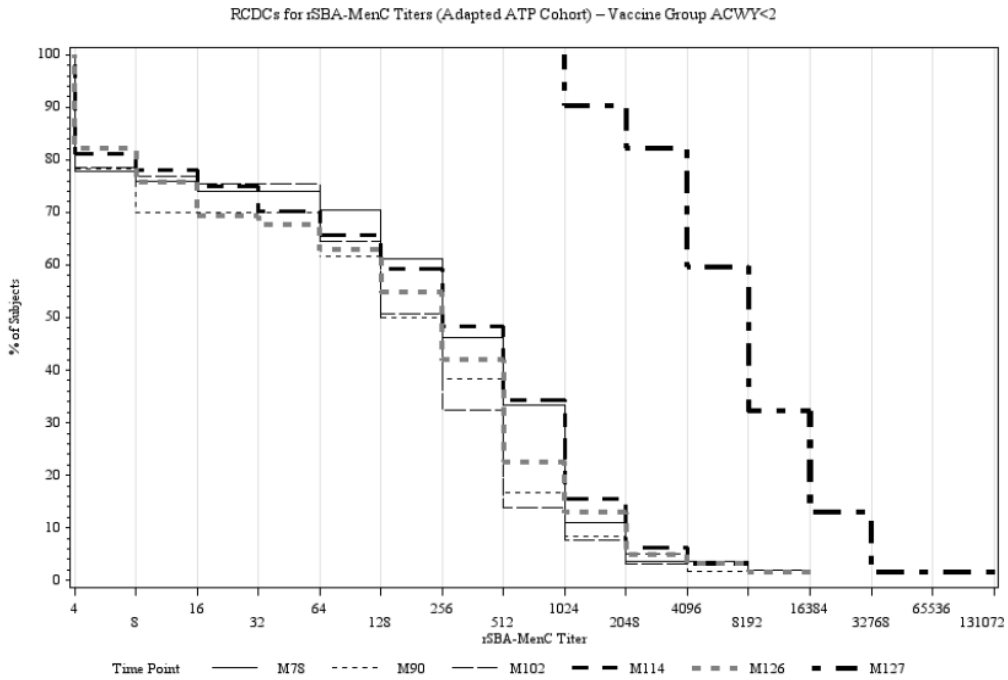


Figure 7. Reverse Cumulative Distribution Curves (RCDCs) for rSBA-MenW-135 Titers - Vaccine Group ACWY<2

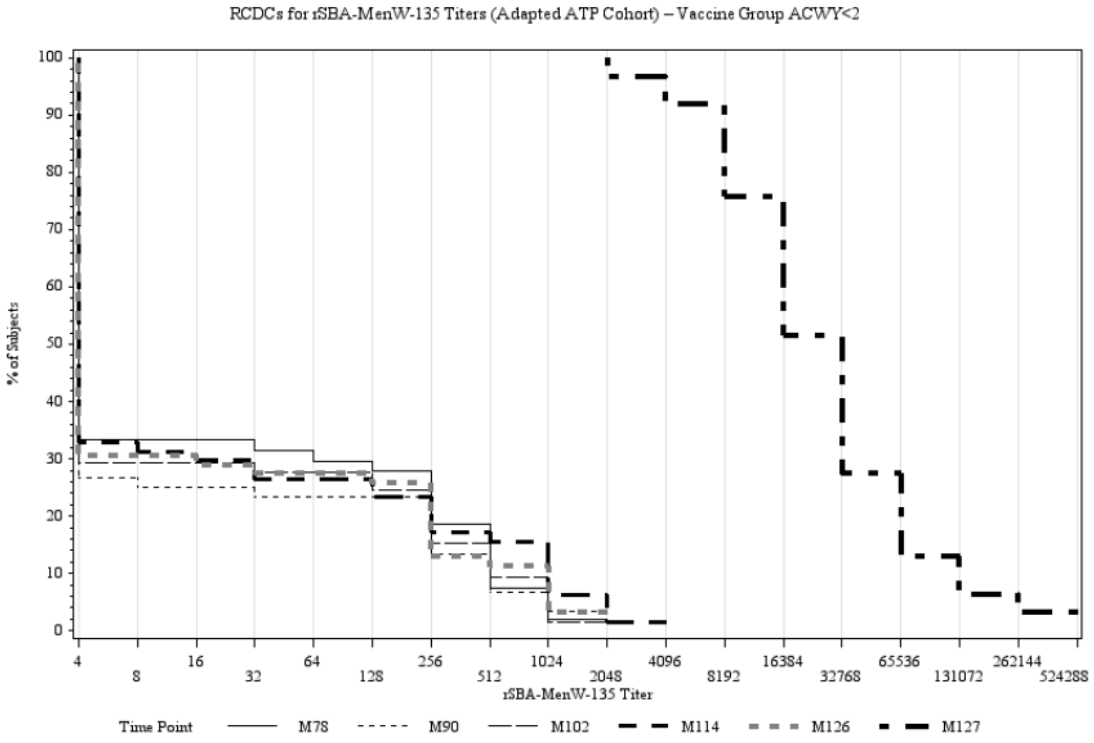
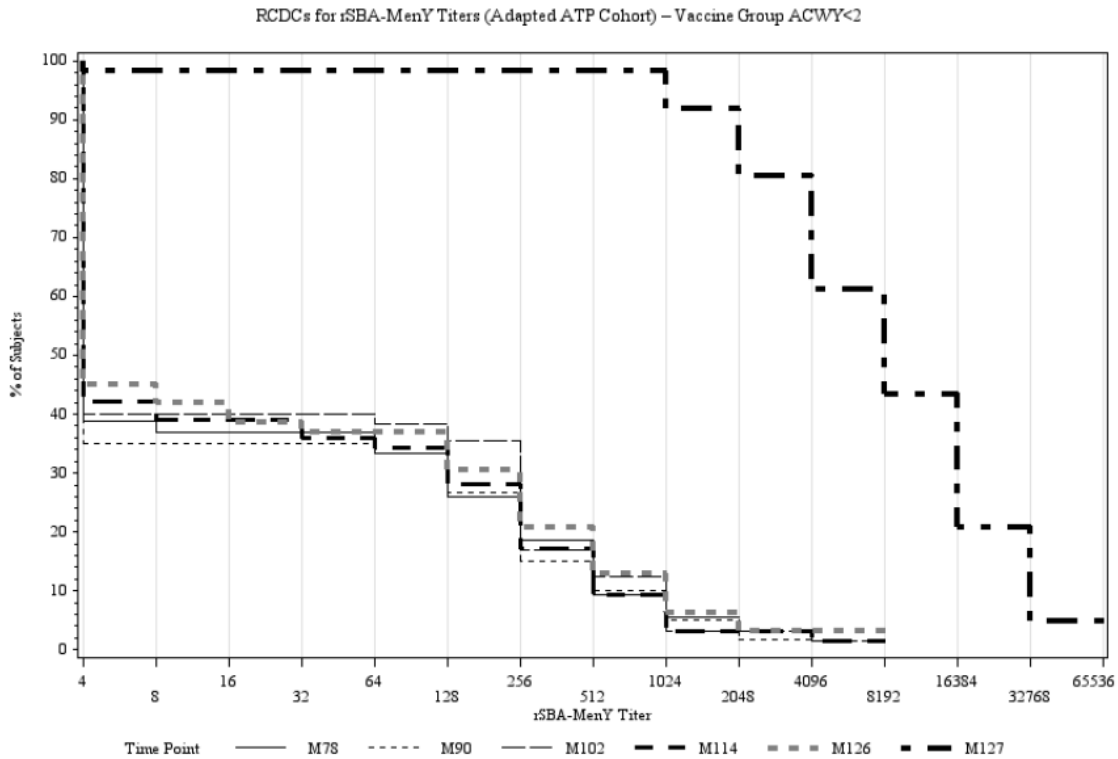


Figure 8. Reverse Cumulative Distribution Curves (RCDCs) for rSBA-MenY Titers - Vaccine Group ACWY<2



hSBA titers.

Figure 9. Reverse Cumulative Distribution Curves (RCDCs) for hSBA-MenA Titers - Vaccine Group ACWY<2

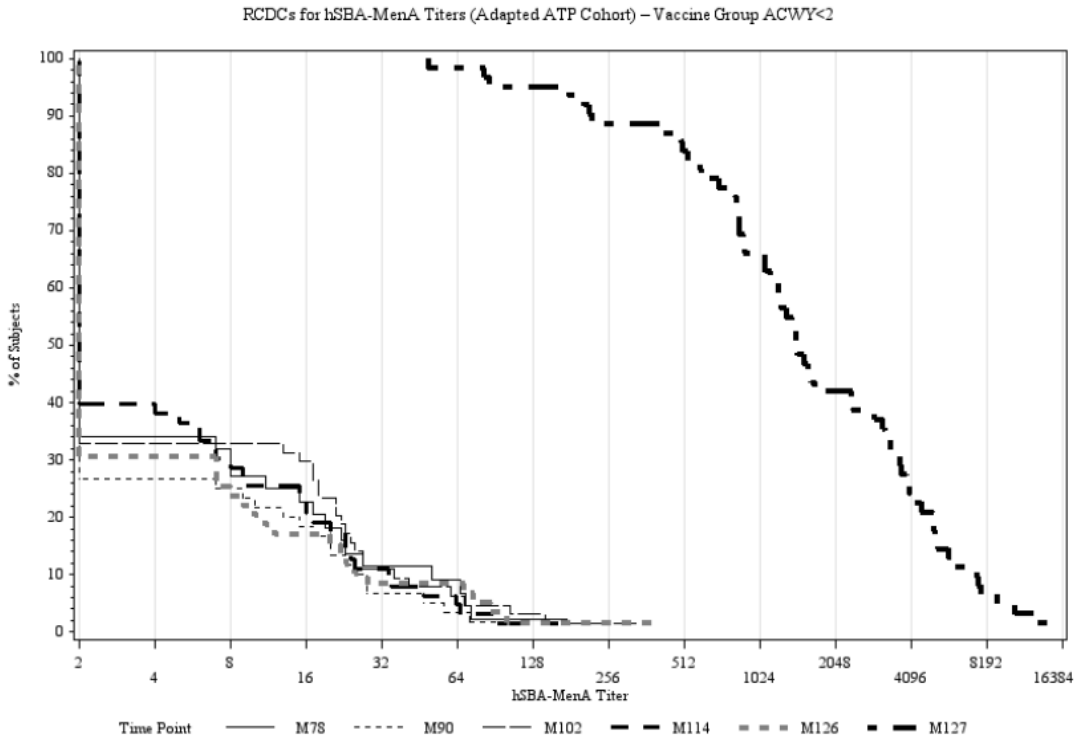


Figure 10. Reverse Cumulative Distribution Curves (RCDCs) for hSBA-MenC Titers - Vaccine Group ACWY<2

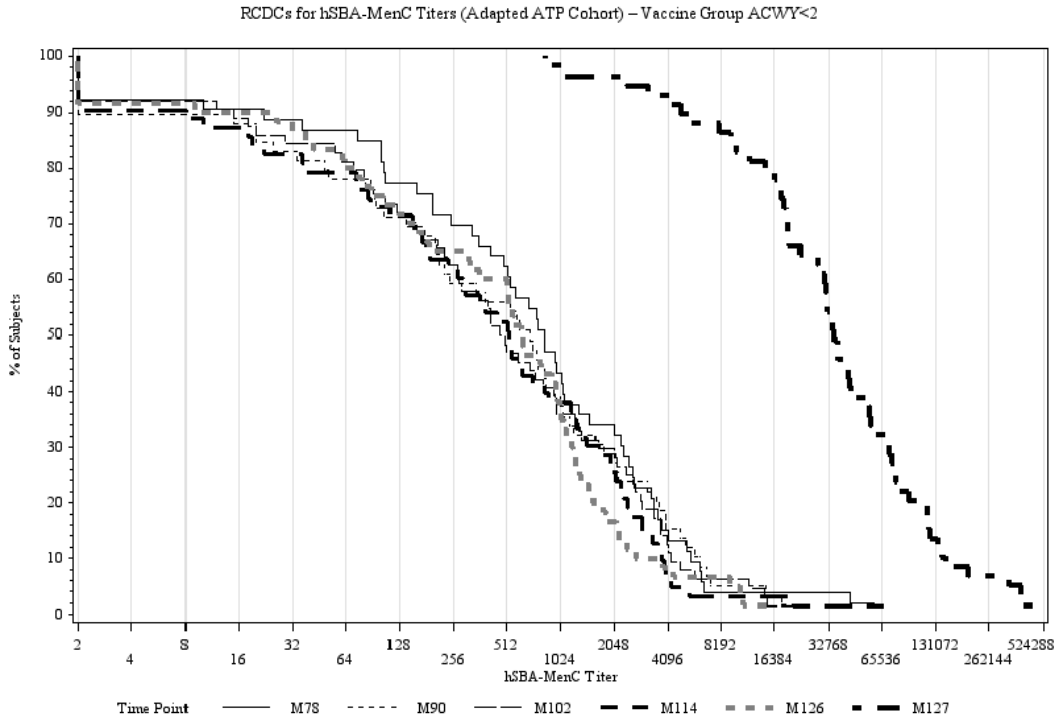


Figure 11. Reverse Cumulative Distribution Curves (RCDCs) for hSBA-MenW-135 Titers - Vaccine Group ACWY<2

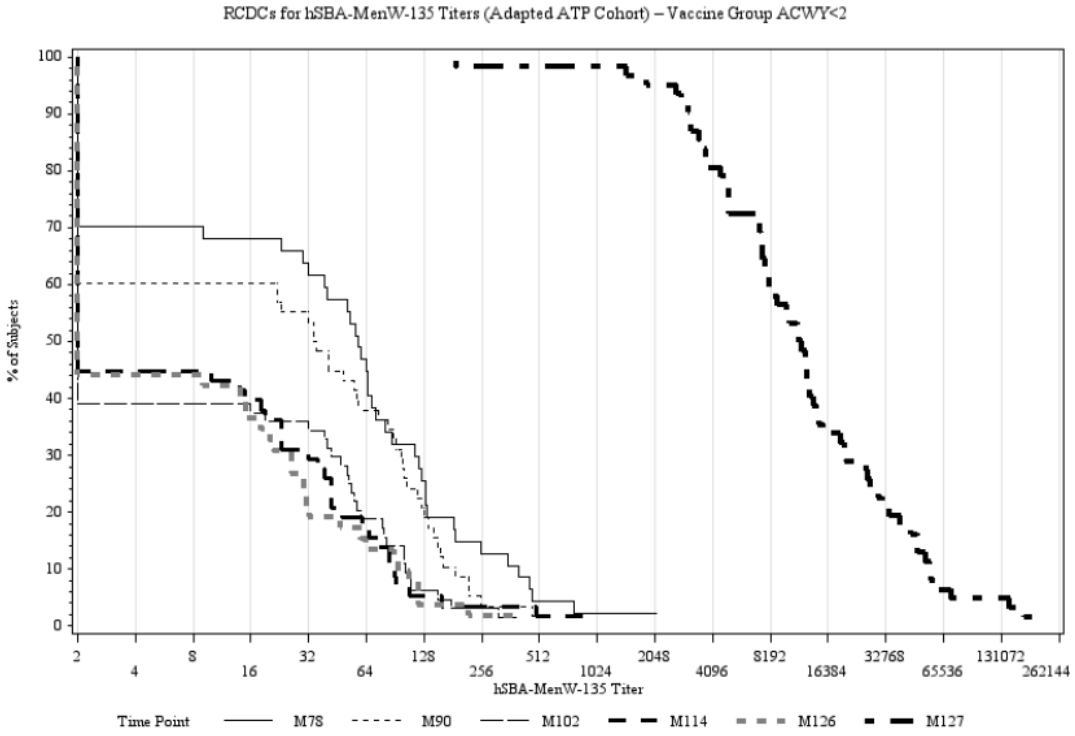


Figure 12. Reverse Cumulative Distribution Curves (RCDCs) for hSBA-MenY Titers - Vaccine Group ACWY<2

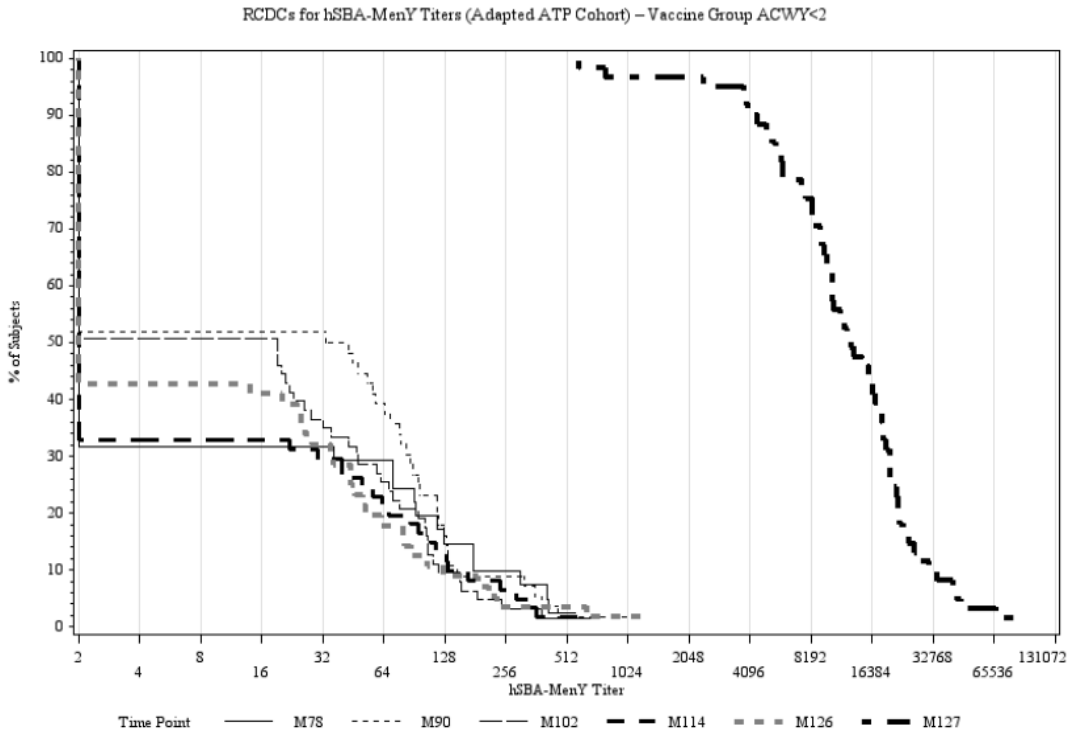


Table 20. Number (%) of Subjects With rSBA-MenA, rSBA-MenC, rSBA-MenW-135, or rSBA-MenY Titers ≥1:8 and ≥1:128 and GMTs at Each Visit After Primary Vaccination (Adapted ATP Cohort)

				≥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<2[g]	M78	54	28	51.9	37.8	65.7	9	16.7	7.9	29.3	16.0	9.8	26.1
		M90	60	35	58.3	44.9	70.9	13	21.7	12.1	34.2	20.4	12.1	34.4
		M102	65	31	47.7	35.1	60.5	15	23.1	13.5	35.2	15.8	9.8	25.6
		M114	64	43	67.2	54.3	78.4	20	31.3	20.2	44.1	28.4	16.5	48.9
		M126	64	42	65.6	52.7	77.1	17	26.6	16.3	39.1	29.3	16.8	51.3
	MenCCRM[h]	M78	16	3	18.8	4.0	45.6	1	6.3	0.2	30.2	5.9	3.1	11.3
		M90	21	2	9.5	1.2	30.4	2	9.5	1.2	30.4	6.1	3.3	11.4
		M102	22	1	4.5	0.1	22.8	1	4.5	0.1	22.8	4.8	3.3	7.2
		M114	21	1	4.8	0.1	23.8	1	4.8	0.1	23.8	5.2	3.0	9.0
		M126	17	3	17.6	3.8	43.4	1	5.9	0.1	28.7	5.8	3.2	10.6
	ACWY≥2[i]	M78	98	78	79.6	70.3	87.1	54	55.1	44.7	65.2	107.3	66.0	174.3
		M90	104	77	74.0	64.5	82.1	46	44.2	34.5	54.3	65.3	40.5	105.4
		M102	100	70	70.0	60.0	78.8	45	45.0	35.0	55.3	51.3	31.5	83.4
		M114	93	74	79.6	69.9	87.2	53	57.0	46.3	67.2	118.8	71.1	198.6
		M126	81	72	88.9	80.0	94.8	40	49.4	38.1	60.7	106.0	63.7	176.4
	MenPS[j]	M78	24	3	12.5	2.7	32.4	2	8.3	1.0	27.0	5.8	3.5	9.6
		M90	27	5	18.5	6.3	38.1	3	11.1	2.4	29.2	7.4	4.0	13.8
		M102	25	6	24.0	9.4	45.1	3	12.0	2.5	31.2	7.8	4.2	14.3
		M114	25	6	24.0	9.4	45.1	4	16.0	4.5	36.1	10.9	4.5	26.2
		M126	21	6	28.6	11.3	52.2	3	14.3	3.0	36.3	9.1	4.0	20.7
rSBA-MenC	ACWY<2[g]	M78	54	42	77.8	64.4	88.0	38	70.4	56.4	82.0	161.3	84.7	307.1
		M90	60	47	78.3	65.8	87.9	37	61.7	48.2	73.9	104.0	58.0	186.3
		M102	65	51	78.5	66.5	87.7	42	64.6	51.8	76.1	110.2	65.9	184.3
		M114	64	52	81.3	69.5	89.9	42	65.6	52.7	77.1	166.0	92.3	298.7
		M126	64	53	82.8	71.3	91.1	41	64.1	51.1	75.7	132.2	74.5	234.6
	MenCCRM[h]	M78	16	12	75.0	47.6	92.7	9	56.3	29.9	80.2	103.1	31.9	333.3
		M90	21	15	71.4	47.8	88.7	11	52.4	29.8	74.3	54.3	18.5	158.9
		M102	22	17	77.3	54.6	92.2	11	50.0	28.2	71.8	64.0	26.0	157.4
		M114	21	18	85.7	63.7	97.0	12	57.1	34.0	78.2	92.0	32.7	259.1
		M126	17	15	88.2	63.6	98.5	10	58.8	32.9	81.6	81.7	29.2	229.2
	ACWY≥2[i]	M78	98	81	82.7	73.7	89.6	67	68.4	58.2	77.4	192.9	121.0	307.5
		M90	101	85	84.2	75.6	90.7	62	61.4	51.2	70.9	139.0	87.8	220.0
		M102	100	85	85.0	76.5	91.4	61	61.0	50.7	70.6	140.1	91.3	214.9
		M114	93	80	86.0	77.3	92.3	60	64.5	53.9	74.2	176.4	106.8	291.3
		M126	82	69	84.1	74.4	91.3	54	65.9	54.6	76.0	175.0	104.7	292.4
	MenPS[j]	M78	24	19	79.2	57.8	92.9	15	62.5	40.6	81.2	98.7	42.2	230.7
		M90	27	22	81.5	61.9	93.7	18	66.7	46.0	83.5	101.6	42.1	245.0
		M102	25	22	88.0	68.8	97.5	16	64.0	42.5	82.0	121.1	52.2	281.1
		M114	25	21	84.0	63.9	95.5	17	68.0	46.5	85.1	164.3	66.5	405.8
		M126	21	17	81.0	58.1	94.6	14	66.7	43.0	85.4	105.0	37.2	296.4
rSBA-MenW-135	ACWY<2[g]	M78	54	18	33.3	21.1	47.5	16	29.6	18.0	43.6	18.0	9.8	32.9
		M90	60	16	26.7	16.1	39.7	14	23.3	13.4	36.0	13.0	7.6	22.3
		M102	65	19	29.2	18.6	41.8	18	27.7	17.3	40.2	15.3	9.0	26.3
		M114	64	21	32.8	21.6	45.7	17	26.6	16.3	39.1	17.3	9.7	30.8
		M126	64	20	31.3	20.2	44.1	18	28.1	17.6	40.8	16.7	9.5	29.3
	MenCCRM[h]	M78	16	2	12.5	1.6	38.3	1	6.3	0.2	30.2	6.2	3.1	12.3
		M90	21	2	9.5	1.2	30.4	2	9.5	1.2	30.4	6.8	3.0	15.3

				≥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
		M102	22	3	13.6	2.9	34.9	2	9.1	1.1	29.2	6.4	3.3	12.4
		M114	21	2	9.5	1.2	30.4	2	9.5	1.2	30.4	6.6	3.2	13.6
		M126	17	0	0.0	0.0	19.5	0	0.0	0.0	19.5	4.0	NE	NE
	ACWY≥2[i]	M78	98	72	73.5	63.6	81.9	72	73.5	63.6	81.9	265.2	154.9	454.1
		M90	102	75	73.5	63.9	81.8	71	69.6	59.7	78.3	206.0	120.9	350.9
		M102	100	76	76.0	66.4	84.0	76	76.0	66.4	84.0	252.5	154.3	413.2
		M114	92	70	76.1	66.1	84.4	66	71.7	61.4	80.6	274.0	155.8	481.7
		M126	82	55	67.1	55.8	77.1	54	65.9	54.6	76.0	187.2	101.0	347.1
	MenPS[j]	M78	24	3	12.5	2.7	32.4	3	12.5	2.7	32.4	7.6	3.7	15.6
		M90	27	3	11.1	2.4	29.2	2	7.4	0.9	24.3	6.3	3.7	10.9
		M102	25	5	20.0	6.8	40.7	5	20.0	6.8	40.7	11.8	4.7	29.8
		M114	25	4	16.0	4.5	36.1	4	16.0	4.5	36.1	9.7	4.0	23.3
		M126	21	5	23.8	8.2	47.2	5	23.8	8.2	47.2	14.0	4.8	41.2
rSBA-MenY	ACWY<2[g]	M78	54	21	38.9	25.9	53.1	18	33.3	21.1	47.5	21.5	11.5	40.1
		M90	60	21	35.0	23.1	48.4	20	33.3	21.7	46.7	19.9	11.0	36.1
		M102	65	26	40.0	28.0	52.9	25	38.5	26.7	51.4	26.1	14.4	47.5
		M114	64	27	42.2	29.9	55.2	22	34.4	22.9	47.3	23.1	13.0	41.2
		M126	64	28	43.8	31.4	56.7	23	35.9	24.3	48.9	25.8	14.0	47.3
	MenCCRM[h]	M78	16	6	37.5	15.2	64.6	5	31.3	11.0	58.7	21.7	5.9	79.0
		M90	21	6	28.6	11.3	52.2	6	28.6	11.3	52.2	18.3	5.8	57.6
		M102	22	9	40.9	20.7	63.6	9	40.9	20.7	63.6	33.0	9.8	111.0
		M114	21	10	47.6	25.7	70.2	8	38.1	18.1	61.6	32.0	10.6	96.3
		M126	17	6	35.3	14.2	61.7	5	29.4	10.3	56.0	22.2	5.8	84.2
	ACWY≥2[i]	M78	98	70	71.4	61.4	80.1	64	65.3	55.0	74.6	136.4	82.6	225.3
		M90	102	77	75.5	66.0	83.5	71	69.6	59.7	78.3	152.7	96.1	242.6
		M102	100	79	79.0	69.7	86.5	73	73.0	63.2	81.4	181.0	115.0	284.9
		M114	93	62	66.7	56.1	76.1	54	58.1	47.4	68.2	106.2	61.5	183.4
		M126	82	54	65.9	54.6	76.0	49	59.8	48.3	70.4	90.5	51.5	159.2
	MenPS[j]	M78	24	5	20.8	7.1	42.2	5	20.8	7.1	42.2	11.6	4.7	28.7
		M90	27	4	14.8	4.2	33.7	4	14.8	4.2	33.7	8.2	4.1	16.5
		M102	25	6	24.0	9.4	45.1	5	20.0	6.8	40.7	10.9	4.8	24.6
		M114	25	5	20.0	6.8	40.7	4	16.0	4.5	36.1	10.0	4.4	22.9
		M126	21	5	23.8	8.2	47.2	4	19.0	5.4	41.9	12.7	4.2	38.1

Abbreviations: ATP = according-to-protocol; GMT = geometric mean titer; LL = lower limit; rSBA-MenA, rSBA-MenC, rSBA-MenW-135, and rSBA-MenY = serum bactericidal assay using rabbit complement to measure activity against *Neisseria meningitidis* group A, group C, group W-135, and group Y; UL = upper limit.
Note: Subjects were randomized and the primary vaccinations were administered at 1 to 10 years of age in primary study MenACWY-TT-027; all subjects who were given the booster vaccination in Study MenACWY-TT-100 (C0921004) received MenACWY-TT at Month 126.

a. Exact 2-sided CI based upon the observed proportion of subjects, using the Clopper and Pearson method.
b. CIs are back transformations of confidence levels based on the Student t distribution for the mean logarithm of the concentrations, or the mean of the ratio.
c. M78 = Month 78, 6 years after the primary vaccination; M90 = Month 90, 7 years after the primary vaccination; M102 = Month 102, 8 years after the primary vaccination; M114 = Month 114, 9 years after the primary vaccination; M126 = Month 126, 10 years after the primary vaccination and before booster vaccination.
d. N = number of subjects with available results.
e. n = Number of subjects within each category.
f. % = Percentage of subjects within each category.

Table 21. Number (%) of Subjects With hSBA-MenA, hSBA-MenC, hSBA-MenW-135, or hSBA-MenY Titers ≥1:4 and ≥1:8 and GMTs at Each Visit After Primary Vaccination (Adapted ATP Cohort)

				≥1:4		95% CI[a]		≥1:8		95% CI[a]		GMT	95% CI[b]	
Antibody	Vaccine Group	Visit[c]	N[d]	n[e]	%[f]	LL	UL	n[e]	%[f]	LL	UL	Value	LL	UL
hSBA-MenA	ACWY<2[g]	M78	44	15	34.1	20.5	49.9	14	31.8	18.6	47.6	4.7	3.2	7.1
		M90	60	16	26.7	16.1	39.7	15	25.0	14.7	37.9	3.8	2.9	5.2
		M102	64	21	32.8	21.6	45.7	21	32.8	21.6	45.7	5.0	3.5	7.1
		M114	63	25	39.7	27.6	52.8	19	30.2	19.2	43.0	4.8	3.5	6.6
		M126	61	19	31.1	19.9	44.3	16	26.2	15.8	39.1	4.2	3.1	5.9
	MenCCRM[h]	M78	14	4	28.6	8.4	58.1	4	28.6	8.4	58.1	3.5	2.1	5.8
		M90	21	3	14.3	3.0	36.3	3	14.3	3.0	36.3	2.8	1.8	4.2
		M102	22	6	27.3	10.7	50.2	6	27.3	10.7	50.2	3.7	2.2	6.1
		M114	20	6	30.0	11.9	54.3	4	20.0	5.7	43.7	3.4	2.2	5.2
		M126	16	4	25.0	7.3	52.4	3	18.8	4.0	45.6	3.1	2.0	4.8
	ACWY≥2[i]	M78	90	38	42.2	31.9	53.1	37	41.1	30.8	52.0	6.5	4.8	8.8
		M90	99	26	26.3	17.9	36.1	26	26.3	17.9	36.1	4.5	3.4	6.0
		M102	97	28	28.9	20.1	39.0	28	28.9	20.1	39.0	4.6	3.4	6.0
		M114	86	37	43.0	32.4	54.2	37	43.0	32.4	54.2	6.6	4.8	9.0
		M126	69	24	34.8	23.7	47.2	23	33.3	22.4	45.7	4.6	3.4	6.2
	MenPS[j]	M78	21	9	42.9	21.8	66.0	7	33.3	14.6	57.0	5.9	3.0	11.7
		M90	26	7	26.9	11.6	47.8	6	23.1	9.0	43.6	4.7	2.4	9.0
		M102	25	10	40.0	21.1	61.3	9	36.0	18.0	57.5	6.7	3.2	14.0
		M114	23	7	30.4	13.2	52.9	6	26.1	10.2	48.4	4.5	2.4	8.8
		M126	21	7	33.3	14.6	57.0	6	28.6	11.3	52.2	5.4	2.5	11.7
hSBA-MenC	ACWY<2[g]	M78	53	49	92.5	81.8	97.9	49	92.5	81.8	97.9	542.5	284.8	1033.5
		M90	59	53	89.8	79.2	96.2	53	89.8	79.2	96.2	368.1	191.9	706.0
		M102	64	59	92.2	82.7	97.4	59	92.2	82.7	97.4	378.2	210.7	679.0
		M114	63	57	90.5	80.4	96.4	57	90.5	80.4	96.4	319.0	172.7	589.0
		M126	62	57	91.9	82.2	97.3	57	91.9	82.2	97.3	362.2	207.2	633.4
	MenCCRM[h]	M78	16	15	93.8	69.8	99.8	15	93.8	69.8	99.8	230.0	84.3	628.1
		M90	20	20	100.0	83.2	100.0	20	100.0	83.2	100.0	223.6	105.8	472.7
		M102	22	21	95.5	77.2	99.9	21	95.5	77.2	99.9	203.4	73.8	560.9
		M114	20	19	95.0	75.1	99.9	19	95.0	75.1	99.9	217.2	82.8	569.9
		M126	16	15	93.8	69.8	99.8	15	93.8	69.8	99.8	112.4	41.2	307.0
	ACWY≥2[i]	M78	97	91	93.8	87.0	97.7	91	93.8	87.0	97.7	427.2	260.7	700.0
		M90	96	85	88.5	80.4	94.1	85	88.5	80.4	94.1	342.7	200.7	585.4
		M102	96	86	89.6	81.7	94.9	86	89.6	81.7	94.9	365.5	214.1	624.1
		M114	90	78	86.7	77.9	92.9	77	85.6	76.6	92.1	190.4	112.1	323.4
		M126	79	72	91.1	82.6	96.4	72	91.1	82.6	96.4	199.3	118.4	335.7
	MenPS[j]	M78	24	24	100.0	85.8	100.0	24	100.0	85.8	100.0	234.8	122.2	451.1
		M90	26	24	92.3	74.9	99.1	24	92.3	74.9	99.1	169.2	67.3	425.2
		M102	25	24	96.0	79.6	99.9	24	96.0	79.6	99.9	273.8	103.8	722.1
		M114	24	22	91.7	73.0	99.0	22	91.7	73.0	99.0	125.7	51.2	308.8
		M126	21	21	100.0	83.9	100.0	21	100.0	83.9	100.0	119.1	50.2	282.5
hSBA-MenW-135	ACWY<2[g]	M78	47	33	70.2	55.1	82.7	33	70.2	55.1	82.7	31.8	17.5	57.8
		M90	58	35	60.3	46.6	73.0	35	60.3	46.6	73.0	19.5	11.6	32.7
		M102	64	25	39.1	27.1	52.1	25	39.1	27.1	52.1	8.0	5.1	12.6
		M114	58	26	44.8	31.7	58.5	26	44.8	31.7	58.5	8.5	5.3	13.5
		M126	54	24	44.4	30.9	58.6	24	44.4	30.9	58.6	7.6	4.8	11.8
	MenCCRM[h]	M78	15	2	13.3	1.7	40.5	2	13.3	1.7	40.5	3.3	1.6	6.8
		M90	20	4	20.0	5.7	43.7	4	20.0	5.7	43.7	4.9	1.9	12.5
		M102	21	4	19.0	5.4	41.9	4	19.0	5.4	41.9	4.1	1.9	8.6
		M114	16	3	18.8	4.0	45.6	3	18.8	4.0	45.6	3.7	1.6	8.4
		M126	14	3	21.4	4.7	50.8	3	21.4	4.7	50.8	3.8	1.7	8.2
	ACWY≥2[i]	M78	92	75	81.5	72.1	88.9	75	81.5	72.1	88.9	62.5	42.0	93.1
		M90	98	78	79.6	70.3	87.1	78	79.6	70.3	87.1	50.5	34.5	74.1
		M102	94	53	56.4	45.8	66.6	53	56.4	45.8	66.6	20.4	13.0	32.2
		M114	79	54	68.4	56.9	78.4	53	67.1	55.6	77.3	23.1	14.7	36.1
		M126	67	41	61.2	48.5	72.9	41	61.2	48.5	72.9	17.4	10.8	28.0
	MenPS[j]	M78	23	7	30.4	13.2	52.9	7	30.4	13.2	52.9	7.0	2.9	16.9
		M90	27	5	18.5	6.3	38.1	5	18.5	6.3	38.1	4.0	2.1	7.3
		M102	25	3	12.0	2.5	31.2	3	12.0	2.5	31.2	3.3	1.8	6.0
		M114	21	2	9.5	1.2	30.4	2	9.5	1.2	30.4	2.8	1.7	4.4
		M126	19	5	26.3	9.1	51.2	5	26.3	9.1	51.2	4.2	2.2	8.0

				≥1:4				≥1:8				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
hSBA-MenY	ACWY<2[g]	M78	41	13	31.7	18.1	48.1	13	31.7	18.1	48.1	7.9	4.1	15.2
		M90	56	29	51.8	38.0	65.3	29	51.8	38.0	65.3	15.8	9.0	27.7
		M102	63	32	50.8	37.9	63.6	32	50.8	37.9	63.6	11.6	7.3	18.6
		M114	61	20	32.8	21.3	46.0	20	32.8	21.3	46.0	7.3	4.4	11.9
		M126	58	24	41.4	28.6	55.1	24	41.4	28.6	55.1	8.6	5.3	14.2
	MenCCRM[h]	M78	14	1	7.1	0.2	33.9	1	7.1	0.2	33.9	3.1	1.2	7.6
		M90	21	7	33.3	14.6	57.0	7	33.3	14.6	57.0	6.9	2.9	16.6
		M102	21	8	38.1	18.1	61.6	8	38.1	18.1	61.6	8.7	3.5	21.5
		M114	19	5	26.3	9.1	51.2	5	26.3	9.1	51.2	5.8	2.3	15.0
		M126	15	6	40.0	16.3	67.7	6	40.0	16.3	67.7	8.5	2.8	25.7
	ACWY≥2[i]	M78	89	58	65.2	54.3	75.0	58	65.2	54.3	75.0	40.3	23.9	68.1
		M90	100	75	75.0	65.3	83.1	75	75.0	65.3	83.1	54.4	35.0	84.4
		M102	93	67	72.0	61.8	80.9	67	72.0	61.8	80.9	43.7	27.5	69.5
		M114	84	57	67.9	56.8	77.6	57	67.9	56.8	77.6	35.5	21.5	58.8
		M126	73	53	72.6	60.9	82.4	53	72.6	60.9	82.4	36.8	22.4	60.7
	MenPS[j]	M78	24	6	25.0	9.8	46.7	6	25.0	9.8	46.7	7.3	2.7	19.8
		M90	27	11	40.7	22.4	61.2	11	40.7	22.4	61.2	10.5	4.4	25.0
		M102	23	8	34.8	16.4	57.3	8	34.8	16.4	57.3	8.8	3.4	22.5
		M114	22	6	27.3	10.7	50.2	6	27.3	10.7	50.2	6.2	2.5	15.3
		M126	18	8	44.4	21.5	69.2	8	44.4	21.5	69.2	13.9	4.2	46.0

Abbreviations: ATP = according-to-protocol; GMT = geometric mean titer; hSBA-MenA, hSBA-MenC, hSBA-MenW-135, and hSBA-MenY = serum bactericidal assay using human complement to measure activity against *Neisseria meningitidis* group A, group C, group W-135, and group Y.

Note: Subjects were randomized and the primary vaccinations were administered at 1 to 10 years of age in primary study MenACWY-TT-027; all subjects who were given the booster vaccination in Study MenACWY-TT-100 (C0921004) received MenACWY-TT at Month 126.

a. Exact 2-sided CI based upon the observed proportion of subjects, using the Clopper and Pearson method.

b. CIs are back transformations of confidence levels based on the Student t distribution for the mean logarithm of the concentrations, or the mean of the ratio.

c. M78 = Month 78, 6 years after the primary vaccination; M90 = Month 90, 7 years after the primary vaccination; M102 = Month 102, 8 years after the primary vaccination; M114 = Month 114, 9 years after the primary vaccination; M126 = Month 126, 10 years after the primary vaccination and before booster vaccination.

d. N = number of subjects with available results.

e. n = Number of subjects within each category.

f. % = Percentage of subjects within each category.

g. ACWY<2 = vaccinated with MenACWY-TT in Study MenACWY-TT-027 and aged <2 years at the time of primary vaccination.

h. MenCCRM = vaccinated with Meningitec in Study MenACWY-TT-027.

i. ACWY≥2 = vaccinated with MenACWY-TT in Study MenACWY-TT-027 and aged ≥2 years at the time of primary vaccination.

j. MenPS = vaccinated with Mencevax ACWY in Study MenACWY-TT-027.

Analysis of Additional Dose of MenC Conjugate Vaccine Administration

In Study MenACWY-TT-027 (108658), subjects with antibody responses below the cutoff threshold for rSBA MenC at a measured postvaccination time point were allowed to receive an additional dose of MenC conjugate vaccine at a post vaccination time point (1 month and 1, 2, 3, 4, or 5 years after vaccination).

Overall, the percentage of subjects with rSBA-MenC titers ≥1:8 was higher for subjects receiving an additional dose of MenC conjugate vaccine across all vaccine groups, in comparison to subjects who did not receive an additional dose of MenC conjugate vaccine. The percentage of subjects with rSBA-MenA, rSBA-MenW-135, and rSBA-MenY titers ≥1:8 was lower for subjects receiving an additional dose of MenC conjugate vaccine across all vaccine groups, in comparison to subjects who did not receive an additional dose of MenC conjugate vaccine.

In all vaccine groups the percentage of subjects with hSBA-MenA, hSBA-MenC, hSBA-MenW-135, and hSBA-MenY titers ≥1:4 increased irrespective of prior receipt of an additional dose of MenC conjugate vaccine. No clinically relevant differences were observed in vaccine response between subjects who received an additional dose of MenC conjugate vaccine versus those who did not.

Estimated rSBA and hSBA GMTs

In order to complement the descriptive analyses of observed antibody persistence per time point and evaluate the bias that may have occurred due to the loss to follow-up after the vaccination, longitudinal analysis was performed for the rSBA and hSBA in all study groups. rSBA and hSBA GMTs were predicted by modeling for prevaccination and postvaccination (1 month) time points (from Study MenACWY-TT-027) and Months 78, 90, 102, 114, and 126 after primary vaccination. In all vaccine groups the estimated GMTs at Months 78 to 126 were generally similar to the observed values, with no indication of bias caused by subjects lost to follow-up during the persistence phase.

Inspection of the observed rSBA geometric means from Month 0 to Year 5 in TT-032 suggests that PHE (Public Health England) titers are about 1 order of magnitude lower than GSK titers. In spite of the apparent change in titers all time points will be retained in the modelling prediction. The modeling prediction method specifies that time point is a categorical variable, so the abrupt change starting Year 4 will be captured in the model. Interpretation of the model's predicted values should keep the change in laboratories in mind.

Different laboratories performed the rSBAs and hSBAs at different time points (see Table 2 and 3). rSBAs were performed either by GSK or Public Health England (PHE). hSBAs were performed either by GSK or Neomed (Neomed was a GSK facility until it was spun off as an independent company).

Table 22. Estimated rSBA-MenC GMTs as Predicted by Modeling for ACWY <2 and MenCCRM Vaccine Groups (Adapted ATP Cohort)

Antibody	Vaccine Group	Visit[b]	GMT	95% CI[a]	
			Value	LL	UL
rSBA-MenC	ACWY<2[c]	PRE	13.8	11.03	17.37
		POST	865.9	694.31	1079.84
		M12	190.0	151.45	238.43
		M24	114.4	90.81	144.07
		M36	111.1	87.16	141.67
		M48	9.2	7.11	11.84
		M60	28.6	18.69	43.79
		M78	188.6	125.09	284.38
		M90	126.4	85.46	186.98
		M102	126.9	86.97	185.04
		M114	190.3	130.12	278.33
		M126	151.5	103.56	221.56
	MenCCRM[d]	PRE	9.3	6.18	13.87
		POST	412.1	277.10	612.95
		M12	73.2	48.59	110.32
		M24	46.1	29.56	72.00
		M36	120.0	71.61	200.92
		M48	7.1	4.14	12.07
		M60	12.8	5.42	30.28
		M78	77.9	36.62	165.52
		M90	42.2	21.64	82.11
		M102	45.3	23.60	87.06
		M114	68.3	35.04	132.95
		M126	64.6	31.01	134.62

Abbreviations: ATP = according-to-protocol; GMT = geometric mean titer; LL = lower limit; rSBA-MenC = serum bactericidal assay using rabbit complement to measure activity against *Neisseria meningitidis* group C; UL = upper limit.

Note: Subjects were randomized and the primary vaccinations were administered at 1 to 10 years of age in primary study MenACWY-TT-027; all subjects who were given the booster vaccination in Study MenACWY-TT-100 (C0921004) received MenACWY-TT at Month 126.

Note: Estimated values from longitudinal model on log-transformed titer with categorical factors of vaccine group and time point. Titers below cutoff reset to 0.5 × cutoff.

a. Exact 2-sided CI based upon the observed proportion of subjects, using the Clopper and Pearson method.

b. PRE = before the primary vaccination (Study MenACWY-TT-027); POST = 1 month after the primary vaccination (Study MenACWY-TT-027); M12 = Month 12, 1 year after the primary vaccination (Study MenACWY-TT-028); M24 = Month 24, 2 years after the primary vaccination (Study MenACWY-TT-029); M36 = Month 36, 3 years after the primary vaccination (Study MenACWY-TT-030); M48 = Month 48, 4 years after the primary vaccination (Study MenACWY-TT-031); M60 = Month 60, 5 years after the primary vaccination (Study MenACWY-TT-032); M78 = Month 78, 6 years after the primary vaccination; M90 = Month 90, 7 years after the primary vaccination; M102 = Month 102, 8 years after the primary vaccination; M114 = Month 114, 9 years after the primary vaccination; M126 = Month 126, 10 years after the primary vaccination and before booster vaccination.

c. ACWY<2 = vaccinated with MenACWY-TT in Study MenACWY-TT-027 and aged <2 years at the time of primary vaccination.

d. MenCCRM = vaccinated with Meningitec in Study MenACWY-TT-027.

Table 23. Estimated hSBA-MenC GMTs as Predicted by Modeling for ACWY<2 and MenCCRM Vaccine Groups (Adapted ATP Cohort)

Antibody	Vaccine Group	Visit[b]	GMT	95% CI[a]	
			Value	LL	UL
hSBA-MenC	ACWY<2[c]	PRE	2.1	1.70	2.63
		POST	190.1	153.09	236.14
		M12	87.9	70.17	110.20
		M24	56.4	44.85	70.90
		M36	60.5	47.48	77.04
		M48	43.4	33.75	55.87
		M60	116.0	76.69	175.32
		M78	683.3	458.62	1017.91
		M90	490.3	335.30	717.08
		M102	462.7	320.64	667.60
		M114	396.4	274.02	573.42
		M126	440.4	303.63	638.80
	MenCCRM[d]	PRE	2.2	1.49	3.21
		POST	21.1	14.31	31.21
		M12	11.6	7.80	17.33
		M24	10.9	7.02	16.86
		M36	23.0	13.57	38.83
		M48	20.0	11.88	33.58
		M60	75.1	32.88	171.65
		M78	233.3	112.86	482.21
		M90	184.6	95.66	356.28
		M102	168.2	89.56	315.93
		M114	175.3	90.88	337.99
		M126	100.9	48.85	208.58

Abbreviations: ATP = according-to-protocol; GMT = geometric mean titer; hSBA-MenC = serum bactericidal assay using human complement to measure activity against *Neisseria meningitidis* group C; LL = lower limit; UL = upper limit.

Assessors comment

The GMT data from before the primary vaccination as toddlers 12-23 months through 10 years after demonstrates that the titer values vary due to other factors than a response to vaccination (a peak) followed by a decrease with time. External factors such as analysis in separate study numbers and analysis in different laboratories seems to play a role. At year 4 visit a large number of subjects did not participate, about half of them because of suboptimal MenC response leading to an extra dose of MenC vaccine. In addition there are obvious differences between data generated using rabbit complement compared to human complement.

For rSBA the shift upwards in GMT (see Table 8) from M60 to M78 (> 6 times increase in GMT) is not explained by a change in laboratory from GSK to PHE as this change occurred earlier (Year 4). The MAH should discuss reasons for this increase in GMTs and a critical discussion of the variation in rSBA and hSBA GMTs for all serotypes covering the whole time series**.**

Table 24. Number (%) of Subjects With rSBA-MenA, rSBA-MenC, rSBA-MenW-135, or rSBA-MenY Titers ≥ 1:8 and ≥1:128 and GMTs Before and 1 Month After Booster Vaccination Visit

					≥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<2[g]	M126	62	41	66.1	53.0	77.7	16	25.8	15.5	38.5	28.9	16.4	51.0
		M127	62	61	98.4	91.3	100.0	61	98.4	91.3	100.0	5122.3	3725.6	7042.6
	MenCCRM[h]	M126	16	3	18.8	4.0	45.6	1	6.3	0.2	30.2	5.9	3.1	11.3
		M127	16	16	100.0	79.4	100.0	16	100.0	79.4	100.0	4871.0	2465.1	9624.9
	ACWY≥2[i]	M126	73	65	89.0	79.5	95.1	35	47.9	36.1	60.0	96.3	57.1	162.5
		M127	74	71	95.9	88.6	99.2	71	95.9	88.6	99.2	4626.4	3040.6	7039.4
	MenPS[j]	M126	17	4	23.5	6.8	49.9	2	11.8	1.5	36.4	8.0	3.3	19.3
		M127	17	17	100.0	80.5	100.0	17	100.0	80.5	100.0	6414.2	3878.5	10607.8
rSBA-MenC	ACWY<2[g]	M126	62	51	82.3	70.5	90.8	39	62.9	49.7	74.8	128.0	71.1	230.6
		M127	62	62	100.0	94.2	100.0	62	100.0	94.2	100.0	7163.5	5478.0	9367.7
	MenCCRM[h]	M126	16	14	87.5	61.7	98.4	10	62.5	35.4	84.8	86.7	29.0	259.2
		M127	16	16	100.0	79.4	100.0	16	100.0	79.4	100.0	5792.6	3630.6	9242.2
	ACWY≥2[i]	M126	74	63	85.1	75.0	92.3	49	66.2	54.3	76.8	181.0	105.6	310.3
		M127	74	74	100.0	95.1	100.0	74	100.0	95.1	100.0	4020.0	3319.0	4869.1
	MenPS[j]	M126	17	13	76.5	50.1	93.2	11	64.7	38.3	85.8	96.2	28.9	320.2
		M127	17	17	100.0	80.5	100.0	17	100.0	80.5	100.0	15101.0	7099.3	32121.5
rSBA-MenW-135	ACWY<2[g]	M126	62	19	30.6	19.6	43.7	17	27.4	16.9	40.2	15.8	9.1	27.6
		M127	62	62	100.0	94.2	100.0	62	100.0	94.2	100.0	25911.2	19119.7	35115.2
	MenCCRM[h]	M126	16	0	0.0	0.0	20.6	0	0.0	0.0	20.6	4.0	NE	NE
		M127	15	15	100.0	78.2	100.0	15	100.0	78.2	100.0	17970.4	11666.4	27680.7
	ACWY≥2[i]	M126	74	51	68.9	57.1	79.2	50	67.6	55.7	78.0	206.4	108.6	392.1
		M127	74	74	100.0	95.1	100.0	74	100.0	95.1	100.0	27944.4	22213.8	35153.3
	MenPS[j]	M126	17	4	23.5	6.8	49.9	4	23.5	6.8	49.9	15.4	4.2	56.4
		M127	17	16	94.1	71.3	99.9	16	94.1	71.3	99.9	10462.5	3253.5	33645.5
rSBA-MenY	ACWY<2[g]	M126	62	28	45.2	32.5	58.3	23	37.1	25.2	50.3	27.4	14.7	51.0
		M127	62	61	98.4	91.3	100.0	61	98.4	91.3	100.0	7660.5	5262.9	11150.3
	MenCCRM[h]	M126	16	6	37.5	15.2	64.6	5	31.3	11.0	58.7	24.7	6.0	100.8
		M127	16	16	100.0	79.4	100.0	16	100.0	79.4	100.0	6316.9	3223.8	12377.5
	ACWY≥2[i]	M126	74	50	67.6	55.7	78.0	45	60.8	48.8	72.0	98.5	54.3	178.7
		M127	74	74	100.0	95.1	100.0	74	100.0	95.1	100.0	7529.7	5827.5	9729.2
	MenPS[j]	M126	17	3	17.6	3.8	43.4	3	17.6	3.8	43.4	10.2	3.5	30.2
		M127	17	17	100.0	80.5	100.0	17	100.0	80.5	100.0	6959.2	3636.7	13317.1

Abbreviations: ATP = according-to-protocol; GMT = geometric mean titer; LL = lower limit; rSBA-MenA, rSBA-MenC, rSBA-MenW-135, and rSBA-MenY = serum bactericidal assay using rabbit complement to measure activity against *Neisseria meningitidis* group A, group C, group W-135, and group Y; UL = upper limit.
Note: Subjects were randomized and the primary vaccinations were administered at 1 to 10 years of age in primary study MenACWY-TT-027; all subjects who were given the booster vaccination in Study MenACWY-TT-100 (C0921004) received MenACWY-TT at Month 126.

a. Exact 2-sided CI based upon the observed proportion of subjects, using the Clopper and Pearson method.
b. CIs are back transformations of confidence levels based on the Student t distribution for the mean logarithm of the concentrations, or the mean of the ratio.
c. M126 = Month 126, 10 years after the primary vaccination and before booster vaccination; M127 = Month 127, 1 month after the booster vaccination.
d. N = number of subjects with available results.
e. n = Number of subjects within each category.
f. % = Percentage of subjects within each category.
g. ACWY<2 = vaccinated with MenACWY-TT in Study MenACWY-TT-027 and aged <2 years at the tim of primary vaccination.
h. MenCCRM = vaccinated with Meningitec in Study MenACWY-TT-027.
i. ACWY≥2 = vaccinated with MenACWY-TT in Study MenACWY-TT-027 and aged ≥2 years at the tim of primary vaccination.
j. MenPS = vaccinated with Mencevax ACWY in Study MenACWY-TT-027.

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

Table 25. Exploratory Comparison of the ACWY≥2 and MenPS Vaccine Groups in Terms of rSBA-MenA, rSBA-MenC, rSBA-MenW-135, and rSBA-MenY GMTs Before and 1 Month After Booster Vaccination Visit (Booster ATP Cohort for Immunogenicity)

		Vaccine Group				GMT Ratio (ACWY≥2/MenPS)		
		ACWY≥2[a]		MenPS[b]			95% CI[c]	
Antibody	Visit[d]	N[e]	Adjusted GMT[f]	N[e]	Adjusted GMT[f]	Value	LL	UL
rSBA-MenA	M126	73	96.1	17	8.1	11.9	3.72	38.32
	M127	74	4633.7	17	6370.4	0.7	0.29	1.81
rSBA-MenC	M126	74	182.7	17	92.5	2.0	0.56	6.90
	M127	74	4052.3	17	14583.0	0.3	0.17	0.47
rSBA-MenW-135	M126	74	202.5	17	16.7	12.1	2.84	51.93
	M127	74	28419.9	17	9721.5	2.9	1.48	5.76
rSBA-MenY	M126	74	96.1	17	11.3	8.5	2.28	31.48
	M127	74	7542.7	17	6907.1	1.1	0.59	2.02

Abbreviations: ANOVA = Analysis of variance; ATP = according-to-protocol; hSBA-MenA, hSBA-MenC, hSBA-MenW-135, and hSBA-MenY = serum bactericidal assay using human complement to measure activity against *Neisseria meningitidis* group A, group C, group W-135, and group Y; LL = lower limit; UL = upper limit.

Note: Subjects were randomized and the primary vaccinations were administered at 1 to 10 years of age in primary study MenACWY-TT-027; all subjects who were given the booster vaccination in Study MenACWY-TT-100 (C0921004) received MenACWY-TT at Month 126.

a. ACWY≥2 = vaccinated with MenACWY-TT in Study MenACWY-TT-027 and aged ≥2 years at the time of primary vaccination.

b. MenPS = vaccinated with Mencevax ACWY in Study MenACWY-TT-027.

c. CIs are back transformations of confidence levels based on the mean logarithm of the titers, or the mean of the ratio from an ANOVA model with vaccine group and age stratum (2-<6 and 6-<11 years of age at primary vaccination) as covariates in the model.

d. M126 = Month 126, 10 years after the primary vaccination and before booster vaccination; M127 = Month 127, 1 month after the booster vaccination.

e. N = number of subjects with available results.

f. Adjusted GMT is from the ANOVA model with vaccine group and age stratum as covariates.

Program ID: Study MenACWY-TT-100(C0921004)/CP IMM_EXP_GMT2.SAS. Date of Reporting Dataset Creation: 04OCT2018. Runtime ID: 22JAN2019 11:42. File ID: 67_IMM_EXP_GMT2_R_BATPI.HTM.

Table 26. Exploratory Comparison of the ACWY≥2 and MenPS Vaccine Groups in Terms of Vaccine Response for hSBA-MenA, hSBA-MenC, hSBA-MenW-135, or hSBA-MenY Titers 1 Month After Booster Vaccination Visit

		Vaccine Response[a]						Difference in Vaccine Response (ACWY≥2 Minus MenPS)		
		ACWY≥2[b]			MenPS[c]				95%CI[d]	
Antibody	Prevaccination Status[e]	N[f]	n[g]	%[h]	N[f]	n[g]	%[h]	%	LL	UL
hSBA-MenA	S-	39	39	100.0	11	11	100.0	0.0	-9.13	26.27
	S+	22	22	100.0	6	4	66.7	33.3	9.47	70.50
	Total	61	61	100.0	17	15	88.2	11.8	3.26	34.51
hSBA-MenC	S-	6	6	100.0	0	0	NE	NE	NE	NE
	S+	64	54	84.4	17	16	94.1	-9.7	-22.39	12.58
	Total	70	60	85.7	17	16	94.1	-8.4	-20.33	13.76
hSBA-MenW-135	S-	23	23	100.0	10	10	100.0	0.0	-14.69	28.37
	S+	36	34	94.4	4	4	100.0	-5.6	-18.36	44.54
	Total	59	57	96.6	14	14	100.0	-3.4	-11.63	18.54
hSBA-MenY	S-	18	18	100.0	9	9	100.0	0.0	-18.14	30.71
	S+	47	46	97.9	5	2	40.0	57.9	20.32	86.60
	Total	65	64	98.5	14	11	78.6	19.9	5.24	46.36

Abbreviations: ATP = according-to-protocol; hSBA-MenA, hSBA-MenC, hSBA-MenW-135, and hSBA-MenY = serum bactericidal assay using human complement to measure activity against *Neisseria meningitidis* group A, group C, group W-135, and group Y; LL = lower limit; NE = not estimable; UL = upper limit.

Note: Subjects were randomized and the primary vaccinations were administered at 1 to 10 years of age in primary study MenACWY-TT-027; all subjects who were given the booster vaccination in Study MenACWY-TT-100 (C0921004) received MenACWY-TT at Month 126.

a. Vaccine response defined as: for initially seronegative subjects (S-): antibody titer ≥1:8 1 month after the booster vaccination; for initially seropositive subjects (S+): antibody titer at least 4 times the pre-booster vaccination antibody titer, 1 month after vaccination.

b. ACWY≥2 = vaccinated with MenACWY-TT in Study MenACWY-TT-027 and aged ≥2 years at the time of primary vaccination.

c. MenPS = vaccinated with Mencevax ACWY in Study MenACWY-TT-027.

d. 2-Sided 95% CI of the difference using the Miettinen-Nurminen method.

e. S- = initially seronegative subjects (antibody titer <1:4) prior to booster vaccination; S+ = initially seropositive subjects (antibody titer ≥1:4) prior to booster vaccination.

f. N = number of subjects with before and after booster vaccination results available.

g. n = Number of subjects with a vaccine response.

h. % = Percentage of subjects with a vaccine response.

Immunogenicity Conclusions

In general, for the all vaccine groups, vaccine meningococcal antibodies persisted from Months 78 to 126 after vaccination with MenACWY-TT, Mencevax ACWY, or Meningitec.

The percentage of subjects with rSBA and hSBA titers greater than or equal to the cutoff values (1:8 and 1:128 for rSBA and 1:4 and 1:8 for hSBA) and GMTs for the adapted ATP cohort remained generally stable across all time points. The persistence of the rSBA-MenC and hSBA-MenC immune response over time was similar in the ACWY<2, ACWY≥2, MenPS, and MenCCRM groups and was higher among subjects who had received an additional dose of MenC conjugate vaccine during Study MenACWY-TT-027.

The number of subjects with rSBA and hSBA results in the MenCCRM and MenPS groups was much smaller than that of the ACWY-TT groups for rSBAs for MenA, MenW-135, and MenY, limiting the accuracy of comparison between the groups.

For subjects who received a booster vaccination 10 years after the primary vaccination, a robust booster vaccination response was observed. In all vaccine groups the percentage of subjects with rSBA-MenA, rSBA-MenC, rSBA-MenW-135, and rSBA-MenY titers ≥1:8 increased from 0% to 89.0% (range) at Month 126 to 94.1% to 100% at Month 127 (1 month after booster vaccination) and the percentage of subjects with hSBA-MenA, hSBA-MenC, hSBA-MenW-135, and hSBA-MenY titers ≥1:4 increased from 20.0% to 100.0% at Month 126 to 87.5% to 100% at Month 127 (1 month after booster vaccination).

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

Safety results

Safety Conclusions

In the total enrolled cohort, 2 AEs leading to study withdrawal were reported by 2 subjects in the ACWY≥2 group. One (1) subject withdrew because of an AE of juvenile idiopathic arthritis (moderate severity) and 1 subject withdrew because of an AE of depression (severe); both AEs were considered to be unrelated to the investigational vaccine by the investigator.

Following the booster vaccination, 23.9% of subjects in the ACWY<2 group, 31.3% of subjects in the MenCCRM group, 35.1% of subjects in the ACWY≥2 group, and 52.4% of subjects in the MenPS group reported at least 1 AE during the 31-day postbooster vaccination period. AEs occurring in ≥5% of subjects and >1 subject in any given vaccine group included: pyrexia (12.5% [2 subjects] of the MenCCRM group), upper respiratory tract infection (9.1% [7 subjects] of the ACWY≥2 group; 9.5% [2 subjects] of the MenPS group), and headache (6% [4 subjects] of the ACWY<2 group). The proportion of subjects with at least 1 AE considered to be related to the investigational vaccine by the investigator was <10% for all vaccine groups except in the ACWY≥2 group (15.6%). For the ACWY ≥2 group, the only related AE reported in more than 1 subject was upper respiratory tract infection (4 subjects [5.2%]). After booster vaccination, 1 SAE of abdominal pain was reported in the ACWY≥2 group and was considered to be unrelated to the investigational vaccine by the investigator. No subjects were withdrawn from the study for safety-related reasons following booster vaccination. Most solicited local and general events were mild to moderate in severity and none led to study withdrawal.

1.3.3. Discussion on clinical aspects

In the initial Study TT-027 the immune response after a single primary dose of Nimenrix was investigated and 613 subjects between 1 and 10 years were randomised. All subjects from the TT-027 study were invited to participate in the extension studies, each year up to 10 years after the primary dose. In the extension TT-100 where the antibody titers were measured at time points 6.5, 7.5, 8.5, 9.5 and 10.5 years, 488 subjects were planned to be enrolled. The actual number was 243 subjects enrolled, representing around 40% of the pool of primary vaccinated children.

The number of subjects that completed the visits at different time points varied. For the MenCCRM and MenPS groups the range was 16 - 28 subjects that completed the visits, for the ACWY<2 group the range was 56 to 68 subjects and for ACWY≥2 group the range was 84-107 subjects.

The GMT data from before the primary vaccination as toddlers 12-23 months through 10 years after demonstrates that the titer values vary due to other factors than a response to vaccination (a peak) followed by a decrease with time. External factors such as analysis in separate study numbers and analysis in different laboratories seems to play a role. Also, at year 4 visit a large number of subjects did not participate, about half of them because of suboptimal MenC response leading to an extra dose of MenC conjugate vaccine. This is mentioned in SmPC section 5.1, footnote to Table 8 (TT-032, extension study 027 with year 4 and 5 data):

> "A selection bias mainly due to revaccination of subjects with group C rSBA titres <8 and their exclusion from subsequent time-point(s) may have led to an overestimation of the titres."

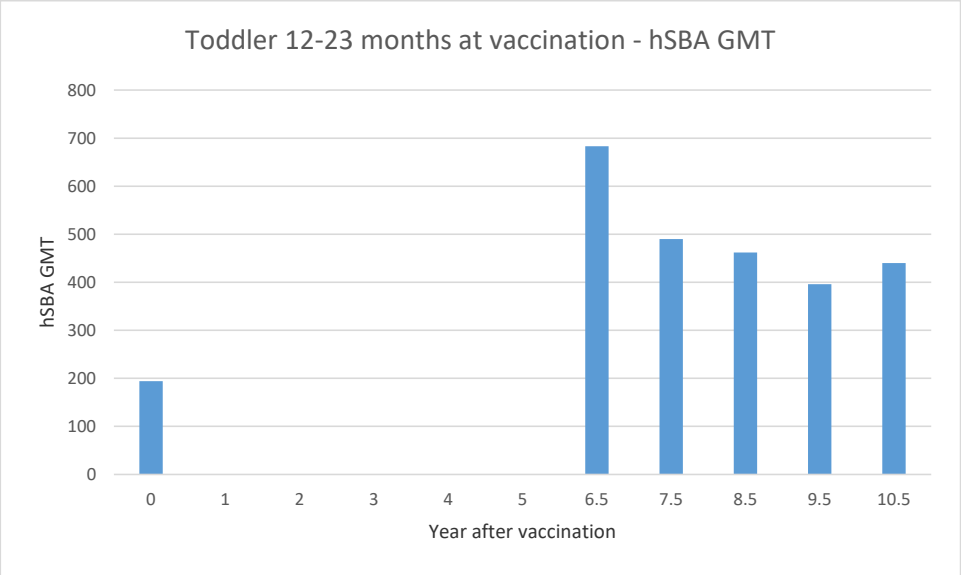
There are obvious differences between data generated using rabbit complement compared to human complement.

Even though the study TT-100 is reported as a stand-alone study, a longitudinal analysis of predicted GMTs for all time point after the primary vaccination has been performed. As shown in Table 9 (above), an upward jump in hSBA GMT between Year 5 and 6 may be explained by a change in the laboratory doing the hSBA analysis. However, the shift upwards rSBA GMT (see Table 8) from M60 to M78 (> 6 times increase in GMT) is not explained by a change in laboratory from GSK to PHE as this change occurred earlier (Year 4). The MAH should discuss reasons for this increase in GMTs**.**

The large variation in the rSBA and hSBA GMT data measured at different time points due to factors like change in the analytical laboratory used, bias due to selection of subjects at different time points, the complement source etc., makes an assessment of the whole time span uncertain and of less value.

Figure 9 below illustrates hSBA GMT data for MenC and the age group ACWY< 2. Data from years 1-5 are not shown due to variability.

Figure 13. hSBA GMT at different time points ACWY<2. (Data from TT-100 study and TT-031 EXT (year 0). Year 0 is 1 month post vaccination.



When looking at all serogroups and both rSBA and hSBA measurements, the general picture is that GMTs are quite stable from month-78 to month-126 with a weak tendency of decrease. That means there is no dramatic drop in bactericidal antibodies during the time period of study TT-100. It is strength of the study that both rSBA and hSBA are measured in parallel, although the clinical significance of differences in the measurements are not clear.

While GMT as a primary endpoint is sensitive for changes due to change in analytical laboratory or other external factors, the percentage of subjects with rSBA or hSBA titers ≥1:8, which are also part of the primary endpoint, seem to be less sensitive (see Figure 10 and 11).

Figure 14. The percentage of subjects with rSBA titers ≥1:8 at different time points.

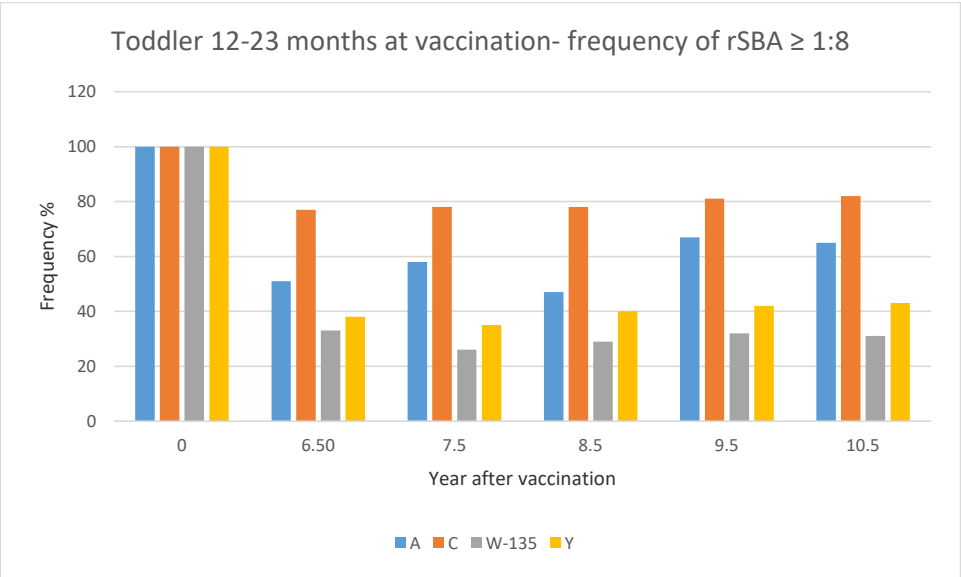
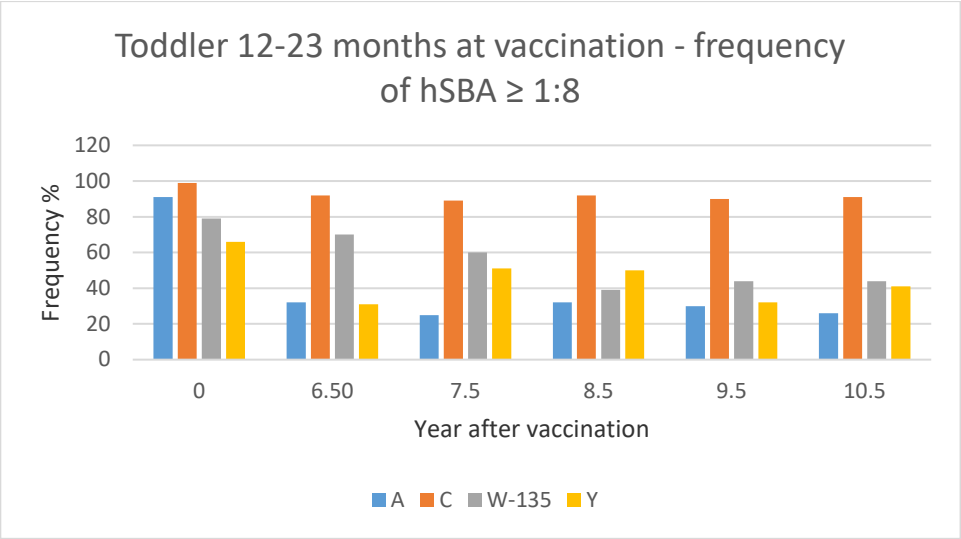


Figure 15. The percentage of subjects with hSBA titers ≥1:8 at different time points.



We agree with the MAH that the percentage of subjects with rSBA or hSBA titers ≥1:8 and GMTs at time points 6,5 years through to 10 years after the primary vaccination are quite stable. For Men-A differences are seen and while around 60% of subjects have a rSBA titre≥1:8 at the 10,5 year time point, the percentage for hSBA ≥1:8 is the half, around 30%. For both Men-W and Men-Y the percentage of subjects with rSBA or hSBA titers ≥1:8 is quite low at the last time points, around 30-40%.

Both the decrease in Men-A hSBA and the lower titers against Men-W and Men-Y in toddlers are mentioned in the SmPC and an additional dose 2 is recommended if the risk for invasive disease is high (section 4.4 SmPC).

Study TT-100 shows that a booster dose of Nimenrix administered 10 years after primary vaccination 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.

A clinical study is ongoing (TT-104) testing immunogenicity and persistence of 1 and 2 doses of Nimenrix in toddlers.

The clinical overview document for this study did not include a critical overall discussion of the results from the initial study TT-027 with measurements of SBA each year up to 10 years and including the booster at that time point. The variation and uncertainties linked to changes in the SBA assays (different laboratories, different runs), the effect of the additional MenC dose after the primary vaccination and potential bias caused by the large number of dropouts from the initial study TT-027, have not been sufficiently reviewed. MAH should discuss the reasons for not including these long-term data in the SmPC. Regarding the present SmPC we do not see the value of Table 8 in section 5.1 showing data for 5 year persistence in toddlers 12-23 months at vaccination with a footnote saying that the data may be biased. We would prefer to delete Table 8 and instead present the 10 year data from the present study TT-100 including the booster response.

We agree that the data from Study MenACWY-TT-100 do not change the benefit-risk profile of Nimenrix. However, we suggest some changes to the SmPC**:**

- In section 5.1, Table 8 should be deleted and alternatively be replaced with data from this study TT-100 showing the serum bactericidal antibodies up to 10 years after a single primary dose to toddlers 12-23 months of age.
- Present information that a very good response was observed to a booster dose 10 years after a single primary dose.

2. Rapporteur's overall conclusion and recommendation

The percentage of subjects with rSBA or hSBA titers ≥1:8 and GMTs at time points 6,5 years through to 10 years after the primary vaccination are quite stable. For Men-A differences are seen and while around 60% of subjects have a rSBA titre≥1:8 at the 10,5 year time point, the percentage for hSBA ≥ 1:8 is the half, around 30%. For both Men-W and Men-Y the percentage of subjects with rSBA or hSBA titers ≥1:8 is quite low at the last time points, around 30-40%.

Study TT-100 shows that a booster dose of Nimenrix administered 10 years after primary vaccination 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.

We agree that the data from Study MenACWY-TT-100 do not change the benefit-risk profile of Nimenrix. However, we suggest some changes to the SmPC which the MAH should consider**:**

a. In section 5.1, Table 8 could be replaced with data from this study TT-100 showing the serum bactericidal antibodies up to 10 years after a single primary dose to toddlers 12-23 months of age.

b. Present information that a very good response was observed after a booster dose administered 10 years after a single primary dose.

☐ **Fulfilled:**

☒ **Not fulfilled:**

Based on the data submitted, the MAH should provide additional clarifications requested as part of this procedure. (see section "Additional clarification requested")

3. Additional clarification requested

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

1. The MAH should consider changes to the SmPC**:**

   a. In section 5.1, Table 8 should be replaced with data from this study TT-100 showing the serum bactericidal antibodies up to 10 years after a single primary dose to toddlers 12-23 months of age. If the MAH is awaiting more data from other studies which are considered more important and relevant, this should be stated.

b. Present information that a very good response was observed after a booster dose administered 10 years after a single primary dose.

2. Regarding the time-series data of GMT, the shift upwards in rSBA GMT (see Table 8) from M60 to M78 (> 6 times increase in GMT) is not explained by a change in laboratory from GSK to PHE as this change occurred earlier (Year 4). The MAH should discuss reasons for this increase in GMTs and a critical discussion of the variation in rSBA and hSBA GMTs for all serotypes covering the whole time series**.**

The timetable is a 30 day response timetable without clock stop.

4. MAH responses to Request for supplementary information

Question 1

The MAH should consider changes to the SmPC:

a) In section 5.1, Table 8 should be replaced with data from this study TT-100 showing the serum bactericidal antibodies up to 10 years after a single primary dose to toddlers 12-23 months of age. If the MAH is awaiting more data from other studies which are considered more important and relevant, this should be stated.

b) Present information that a very good response was observed after a booster dose administered 10 years after a single primary dose.

Response

Three studies have recently been completed that assessed the long-term antibody persistence up to 10 years after vaccination with meningococcal polysaccharide groups A, C, W-135, and Y tetanus toxoid conjugate vaccine (MenACWY-TT) or comparator vaccine and the immunogenicity and safety of a booster dose of MenACWY-TT administered 10 years after primary vaccination. These studies were:

Study MenACWY-TT-099 (C0921002), which evaluated antibody persistence after administration of Nimenrix® or Mencevax® ACWY (meningococcal groups A, C, W-135, and Y polysaccharide vaccine) to subjects 11-55 years of age (Extension of Studies MenACWY-TT-015, 016, 017, 018, 019, and 020);

Study MenACWY-TT-100 (C0921004), which evaluated antibody persistence after administration of Nimenrix versus Mencevax ACWY or Meningitec (meningococcal group C oligosaccharide conjugate vaccine) in subjects 1-10 years of age (Extension of Studies MenACWY-TT-027, 028, 029, 030, 031, and 032); and

Study MenACWY-TT-101 (C0921005), which evaluated antibody persistence after administration of Nimenrix or Mencevax ACWY to subjects 11-17 years of age (Extension of Studies MenACWY-TT-036 and 043).

After complete data from all 3 of the studies have been reviewed, Pfizer proposes to submit a variation to update the Summary of Product Characteristics (SmPC) with long term antibody persistence and booster data based on the complete dataset from these studies. Pfizer anticipates submitting the variation in either September or October this year.

Assessor's comment

The MAH plans to submit a variation this year to update the SmPC based on three completed long-term studies including a booster.

Issue resolved.

Question 2

Regarding the time-series data of GMT, the shift upwards in rSBA GMT (see Table 8) from M60 to M78 (>6 times increase in GMT) is not explained by a change in laboratory from GSK to PHE as this change occurred earlier (Year 4). The MAH should discuss reasons for this increase in GMTs and a critical discussion of the variation in rSBA and hSBA GMTs for all serotypes covering the whole time series.

Response

The design of the series of extension studies, as well as the multiple visits within Study MenACWY-TT-100 itself, was such that subjects could enter the series at any visit before the year 10 visit and could also miss one or more visits but then re-enter the series of visits at any point. This resulted in cohorts differing from one year to the next, which made the analysis of trends through the years more difficult, and likely contributed to the variability in rSBA and hSBA data for all 4 serogroups.

Furthermore, subjects who received MenACWY-TT, Meningitec, or Mencevax ACWY in Study MenACWY-TT-027 and had suboptimal levels of bactericidal activity against MenC at a post vaccination time point (1 month and 1, 2, 3, 4, or 5 years after vaccination) were to be administered an additional dose of meningococcal group C (MenC) conjugate vaccine.

In the parent study (MenACWY-TT-027) and the extension studies preceding Study MenACWY-TT-100 (MenACWY-TT-028, 029, 030, 031, 032), subjects who received an extra dose of MenC vaccine did not enter the long-term follow-up of that particular year, nor were they included in the years that followed.

In contrast, subjects who had received an additional MenC vaccination in any of the preceding studies were included in the analyses in Study MenACWY-TT-100, and sensitivity analyses were performed to compare those subjects who had received an additional dose of MenC vaccine versus those who had not. Across all vaccine groups, the percentages of subjects with rSBA-MenC titers ≥1:8 and ≥1:128, as well as rSBA-MenC GMTs, were higher for subjects who had received an additional dose of MenC conjugate vaccine, as compared with subjects who did not receive an additional dose of MenC conjugate vaccine. Similar trends were seen for hSBA responses among subjects who had received an additional dose of MenC vaccine versus those who had not.

The tables below summarize rSBA data (Table 1) and hSBA data (Table 2) for all serogroups at Month 48 (Study MenACWY-TT-031) and Month 60 (Study MenACWY-TT-032), which do not include data for subjects who had received an additional dose of MenC vaccine, and data for Month 78 and Month 90 in Study MenACWY-TT-100, which include data for all subjects in the according-to-protocol (ATP) cohort, regardless of their having received additional MenC vaccination or not. [Note that hSBA results for Month 48 and Month 60 are available only for subjects <2 years of age, and therefore hSBA data are shown only for the ACWY<2 group and the MenCCRM group.]

As can be seen from the tables, the substantial shifts upwards in GMTs are seen for rSBA-MenC and hSBA-MenC only, while GMTs for the other 3 serogroups generally remain within the same range across these 4 time points. Since the sensitivity analyses showed that rSBA-MenC and hSBA-MenC GMTs were higher in those subjects who received an additional dose of MenC vaccine, the shift upwards in the estimated GMTs from Month 60 to Month 78 can be explained by the inclusion of these subjects in the analyses for Study MenACWY-TT-100 (Month 78) but not in the Month 60 analyses.

Table 27. 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 (ATP Cohort)

				≥1:8		95% CI[a]		≥1:128		95% CI[a]		GMT	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<2[g]	M48	152	93	61.2	53.0	69.0	48	31.6	24.3	39.6	25.7	19.1	34.7
		M60	49	36	73.5	58.9	85.1	18	36.7	23.4	51.7	37.4	22.1	63.2
		M78	54	28	51.9	37.8	65.7	9	16.7	7.9	29.3	16.0	9.8	26.1
		M90	60	35	58.3	44.9	70.9	13	21.7	12.1	34.2	20.4	12.1	34.4
	MenCCRM[h]	M48	31	0	0.0	0.0	11.2	0	0.0	0.0	11.2	4.0	4.0	4.0
		M60	11	0	0.0	0.0	28.5	0	0.0	0.0	28.5	4.0	4.0	4.0
		M78	16	3	18.8	4.0	45.6	1	6.3	0.2	30.2	5.9	3.1	11.3
		M90	21	2	9.5	1.2	30.4	2	9.5	1.2	30.4	6.1	3.3	11.4
	ACWY≥2[i]	M48	188	157	83.5	77.4	88.5	102	54.3	46.8	61.5	77.5	59.3	101.3
		M60	98	89	90.8	83.3	95.7	66	67.3	57.1	76.5	141.3	98.2	203.4
		M78	98	78	79.6	70.3	87.1	54	55.1	44.7	65.2	107.3	66.0	174.3
		M90	104	77	74.0	64.5	82.1	46	44.2	34.5	54.3	65.3	40.5	105.4
	MenPS[j]	M48	29	5	17.2	5.8	35.8	3	10.3	2.2	27.4	7.3	4.3	12.4
		M60	13	2	15.4	1.9	45.4	0	0.0	0.0	24.7	4.7	3.7	6.0
		M78	24	3	12.5	2.7	32.4	2	8.3	1.0	27.0	5.8	3.5	9.6
		M90	27	5	18.5	6.3	38.1	3	11.1	2.4	29.2	7.4	4.0	13.8
rSBA-MenC	ACWY<2[g]	M48	152	46	30.3	23.1	38.2	22	14.5	9.3	21.1	11.2	8.3	15.1
		M60	49	38	77.6	63.4	88.2	21	42.9	28.8	57.8	48.9	28.5	84.0
		M78	54	42	77.8	64.4	88.0	38	70.4	56.4	82.0	161.3	84.7	307.1
		M90	60	47	78.3	65.8	87.9	37	61.7	48.2	73.9	104.0	58.0	186.3
	MenCCRM[h]	M48	31	8	25.8	11.9	44.6	6	19.4	7.5	37.5	11.4	5.2	25.0
		M60	11	7	63.6	30.8	89.1	4	36.4	10.9	69.2	26.5	6.5	107.2
		M78	16	12	75.0	47.6	92.7	9	56.3	29.9	80.2	103.1	31.9	333.3
		M90	21	15	71.4	47.8	88.7	11	52.4	29.8	74.3	54.3	18.5	158.9
	ACWY≥2[i]	M48	188	94	50.0	42.6	57.4	52	27.7	21.4	34.6	21.7	16.2	29.1
		M60	98	89	90.8	83.3	95.7	45	45.9	35.8	56.3	79.7	56.0	113.3
		M78	98	81	82.7	73.7	89.6	67	68.4	58.2	77.4	192.9	121.0	307.5
		M90	101	85	84.2	75.6	90.7	62	61.4	51.2	70.9	139.0	87.8	220.0
	MenPS[j]	M48	29	12	41.4	23.5	61.1	9	31.0	15.3	50.8	23.5	9.8	56.3
		M60	13	13	100	75.3	100	9	69.2	38.6	90.9	128.0	56.4	290.7
		M78	24	19	79.2	57.8	92.9	15	62.5	40.6	81.2	98.7	42.2	230.7
		M90	27	22	81.5	61.9	93.7	18	66.7	46.0	83.5	101.6	42.1	245.0
rSBA-MenW-135	ACWY<2g	M48	152	78	51.3	43.1	59.5	60	39.5	31.6	47.7	31.3	21.4	45.6
		M60	49	17	34.7	21.7	49.6	12	24.5	13.3	38.9	18.2	9.3	35.3
		M78	54	18	33.3	21.1	47.5	16	29.6	18.0	43.6	18.0	9.8	32.9
		M90	60	16	26.7	16.1	39.7	14	23.3	13.4	36.0	13.0	7.6	22.3
	MenCCRMh	M48	31	0	0.0	0.0	11.2	0	0.0	0.0	11.2	4.0	4.0	4.0
		M60	11	2	18.2	2.3	51.8	1	9.1	0.2	41.3	7.1	2.6	19.1
		M78	16	2	12.5	1.6	38.3	1	6.3	0.2	30.2	6.2	3.1	12.3
		M90	21	2	9.5	1.2	30.4	2	9.5	1.2	30.4	6.8	3.0	15.3
	ACWY≥2i	M48	187	169	90.4	85.2	94.2	167	89.3	84.0	93.3	671.1	500.8	899.4

Table 27. 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 (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
		M60	98	77	78.6	69.1	86.2	68	69.4	59.3	78.3	208.5	127.9	340.0
		M78	98	72	73.5	63.6	81.9	72	73.5	63.6	81.9	265.2	154.9	454.1
		M90	102	75	73.5	63.9	81.8	71	69.6	59.7	78.3	206.0	120.9	350.9
	MenPSj	M48	29	4	13.8	3.9	31.7	4	13.8	3.9	31.7	7.6	4.0	14.4
		M60	13	0	0.0	0.0	24.7	0	0.0	0.0	24.7	4.0	4.0	4.0
		M78	24	3	12.5	2.7	32.4	3	12.5	2.7	32.4	7.6	3.7	15.6
		M90	27	3	11.1	2.4	29.2	2	7.4	0.9	24.3	6.3	3.7	10.9
rSBA-MenY	ACWY<2g	M48	152	84	55.3	47.0	63.3	54	35.5	27.9	43.7	29.9	21.5	41.6
		M60	49	21	42.9	28.8	57.8	15	30.6	18.3	45.4	20.6	10.9	39.2
		M78	54	21	38.9	25.9	53.1	18	33.3	21.1	47.5	21.5	11.5	40.1
		M90	60	21	35.0	23.1	48.4	20	33.3	21.7	46.7	19.9	11.0	36.1
	MenCCRMh	M48	31	9	29.0	14.2	48.0	8	25.8	11.9	44.6	12.5	6.0	26.1
		M60	11	2	18.2	2.3	51.8	2	18.2	2.3	51.8	11.7	2.3	59.7
		M78	16	6	37.5	15.2	64.6	5	31.3	11.0	58.7	21.7	5.9	79.0
		M90	21	6	28.6	11.3	52.2	6	28.6	11.3	52.2	18.3	5.8	57.6
	ACWY≥2i	M48	187	151	80.7	74.4	86.1	127	67.9	60.7	74.5	134.8	99.1	183.5
		M60	98	77	78.6	69.1	86.2	65	66.3	56.1	75.6	143.3	88.0	233.4
		M78	98	70	71.4	61.4	80.1	64	65.3	55.0	74.6	136.4	82.6	225.3
		M90	102	77	75.5	66.0	83.5	71	69.6	59.7	78.3	152.7	96.1	242.6
	MenPSj	M48	29	2	6.9	0.8	22.8	1	3.4	0.1	17.8	4.7	3.5	6.4
		M60	13	1	7.7	0.2	36.0	1	7.7	0.2	36.0	5.5	2.7	11.1
		M78	24	5	20.8	7.1	42.2	5	20.8	7.1	42.2	11.6	4.7	28.7
		M90	27	4	14.8	4.2	33.7	4	14.8	4.2	33.7	8.2	4.1	16.5

Table 28. Number (%) of Subjects With hSBA-MenA, hSBA-MenC, hSBA-MenW-135, or hSBA-MenY Titers ≥1:4 and ≥1:8 and GMTs at Each Visit After Primary Vaccination (ATP Cohort) – Subjects <2 Years of Age

				≥1:4				≥1:8				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
hSBA-MenA	ACWY<2[g]	M48	140	57	40.7	32.5	49.3	55	39.3	31.1	47.9	6.0	4.7	7.7
		M60	45	16	35.6	21.9	51.2	16	35.6	21.9	51.2	5.2	3.4	7.8
		M78	44	15	34.1	20.5	49.9	14	31.8	18.6	47.6	4.7	3.2	7.1
		M90	60	16	26.7	16.1	39.7	15	25.0	14.7	37.9	3.8	2.9	5.2
	MenCCRM[h]	M48	31	8	25.8	11.9	44.6	6	19.4	7.5	37.5	3.1	2.3	4.0
		M60	11	3	27.3	6.0	61.0	3	27.3	6.0	61.0	3.6	1.8	7.2
		M78	14	4	28.6	8.4	58.1	4	28.6	8.4	58.1	3.5	2.1	5.8
		M90	21	3	14.3	3.0	36.3	3	14.3	3.0	36.3	2.8	1.8	4.2
hSBA-MenC	ACWY<2[g]	M48	147	126	85.7	79.0	90.9	126	85.7	79.0	90.9	51.4	36.9	71.7
		M60	48	45	93.8	82.8	98.7	44	91.7	80.0	97.7	216.5	123.6	379.1
		M78	53	49	92.5	81.8	97.9	49	92.5	81.8	97.9	542.5	284.8	1033.5
		M90	59	53	89.8	79.2	96.2	53	89.8	79.2	96.2	368.1	191.9	706.0
	MenCCRM[h]	M48	31	24	77.4	58.9	90.4	24	77.4	58.9	90.4	32.4	14.8	71.1
		M60	11	10	90.9	58.7	99.8	10	90.9	58.7	99.8	108.7	21.2	557.2
		M78	16	15	93.8	69.8	99.8	15	93.8	69.8	99.8	230.0	84.3	628.1
		M90	20	20	100.0	83.2	100.0	20	100.0	83.2	100.0	223.6	105.8	472.7
hSBA-MenW-135	ACWY<2[g]	M48	143	117	81.8	74.5	87.8	117	81.8	74.5	87.8	48.3	36.2	64.4
		M60	46	38	82.6	68.6	92.2	38	82.6	68.6	92.2	59.7	35.1	101.4
		M78	47	33	70.2	55.1	82.7	33	70.2	55.1	82.7	31.8	17.5	57.8
		M90	58	35	60.3	46.6	73.0	35	60.3	46.6	73.0	19.5	11.6	32.7
	MenCCRM[h]	M48	31	3	9.7	2.0	25.8	3	9.7	2.0	25.8	2.8	1.9	4.2
		M60	9	2	22.2	2.8	60.0	2	22.2	2.8	60.0	5.1	1.2	20.9
		M78	15	2	13.3	1.7	40.5	2	13.3	1.7	40.5	3.3	1.6	6.8
		M90	20	4	20.0	5.7	43.7	4	20.0	5.7	43.7	4.9	1.9	12.5
hSBA-MenY	ACWY<2[g]	M48	129	100	77.5	69.3	84.4	100	77.5	69.3	84.4	42.1	30.6	58.1
		M60	45	36	80.0	65.4	90.4	36	80.0	65.4	90.4	70.6	38.7	128.8
		M78	41	13	31.7	18.1	48.1	13	31.7	18.1	48.1	7.9	4.1	15.2
		M90	56	29	51.8	38.0	65.3	29	51.8	38.0	65.3	15.8	9.0	27.7
	MenCCRM[h]	M48	26	12	46.2	26.6	66.6	12	46.2	26.6	66.6	13.5	5.6	32.3
		M60	10	4	40.0	12.2	73.8	4	40.0	12.2	73.8	11.6	2.2	59.4
		M78	14	1	7.1	0.2	33.9	1	7.1	0.2	33.9	3.1	1.2	7.6
		M90	21	7	33.3	14.6	57.0	7	33.3	14.6	57.0	6.9	2.9	16.6

Assessor's comment

The main reason for the large increase in MenC from month 60 to month 78 is that data from subjects who received an extra dose of MenC because of low antibody levels the first 5 years were not included in the month 60 data (study TT-032), but included in month 78 data (study TT-100). Therefore, the large increase is only seen with MenC and not the other serogroups. In addition, variability in the time

series is due to differences in the cohorts from year to year as the subjects that showed up for samples varied.

Issue resolved

5. Rapporteur's final overall conclusion and recommendation

The percentage of subjects with rSBA or hSBA titers ≥1:8 and GMTs at time points 6,5 years through to 10 years after the primary vaccination are quite stable. For Men-A differences are seen and while

around 60% of subjects have a rSBA titre≥1:8 at the 10,5 year time point, the percentage for hSBA ≥ 1:8 is the half, around 30%. For both Men-W and Men-Y the percentage of subjects with rSBA or hSBA titers ≥1:8 is quite low at the last time points, around 30-40%.

Study TT-100 shows that a booster dose of Nimenrix administered 10 years after primary vaccination 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.

We agree that the data from Study MenACWY-TT-100 do not change the benefit-risk profile of Nimenrix. The MAH plans to submit an application for a variation where data from three long term studies including booster will be described.

This procedure (053) is concluded and there is no further request for supplementary information. The final Variation application, however, is awaited.

☐ **Fulfilled:**

☒ **Not fulfilled:**

The MAH should submit an application for a variation to update the SmPC with a description of the results from three long-term studies including booster.