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Committee for Medicinal Products for Human Use (CHMP)

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

Menveo

Meningococcal Group A, C, W-135 and Y Conjugate vaccine

Procedure No: EMEA/H/C/001095

P46 029

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

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I. Introduction

On 04-07-2014, the MAH submitted 6 completed paediatric studies for Menveo, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

II. Scientific discussion

Information on the development program

The MAH stated that study titles and numbers are stand alone studies.

Information on the pharmaceutical formulation used in the studies

The MAH declared that only the licensed vaccine formulation was used in these studies.

Clinical aspects

Introduction

The purpose of this addendum is to provide a summary of the safety and immunogenicity data from 6 recently completed studies involving the use of Menveo, from now on referred to as MenACWY, in the paediatric population, as per Article 46 of the European Paediatric Regulation (EC N0 1901/2006).

Of these 6 paediatric studies, 4 were in children 2 years of age and above (studies V59_39, V59_40, V59_49, and V59_50) and 2 in children < 2 years of age (studies V59_33 and V59P14E1). The MAH submitted final reports for V59_39, V59_40, V59_49, V59_50, V59_33 and V59P14E1. An overview of these studies is provided in the following table:

Study	Location	Age at enrollment	Design (study title)	Test Product(s); Dosage Regimen ACWY Antigen Content (µg)	Number of Subjects Enrolled	Study Status
Subjects ≥ 2 years of age						
V59_39	Korea	Adolescents and Adults (11-55 years)	A phase 3, multi-center, observer-blind, placebo-controlled, randomized study to evaluate the immunogenicity and safety of MenACWY in healthy subjects from 11-55 years of age in Korea	MenACWY: 10-5-5-5 µg Placebo (saline)	297 153	Completed
V59_40	US, Italy	Adolescents (11-18 years)	A phase 4, Placebo-Controlled, Randomized Study to Evaluate the Immunogenicity and Safety of a Combined Tetanus, Reduced Diphtheria Toxoid, Acellular Pertussis Vaccine (Tdap, Boostrix®) and Quadrivalent Human Papillomavirus [Types 6, 11, 16, 18] Recombinant Vaccine (Gardasil®) in Healthy Adolescents when Administered with MenACWY	MenACWY: 10-5-5-5 µg Placebo (saline)	402 399	Completed
V59_49	Taiwan	Children, Adolescents (11-18 years)	A phase 3, multi-center, open-label study to evaluate immunogenicity and safety of MenACWY in healthy subjects from 2-18 years in Taiwan	MenACWY: 10-5-5-5 µg	173 (2-10) 168 (11-18)	Completed
V59_50	Russia	Children (2-10 years) Adolescents (11-17 years) Adults ≥ 18 years	A phase 3, multi-center, open-label study to evaluate immunogenicity and safety of MenACWY in healthy children, adolescents, and adults in Russia.	MenACWY: 10-5-5-5 µg	65 (2-10) 66 (11-18) 66 (adults ≥ 18 years)	Completed
V59P14E1	US	Children	A phase 3b, open-label, controlled, multi-center study to evaluate the persistence of antibody	MenACWY: 10-5-5-5 µg	335	Completed

		(~3 and 5 years)	responses among children who previously received MenACWY	administered in V59P14 naïve subjects	~50 at each visit	
V59_33	US, Canada, Australia	Infants (2 months)	A phase 3, randomized, open-label, controlled multi-center study to evaluate the safety and immunogenicity of 4 doses of MenACWY, administered concomitantly with routine vaccines, among infants aged 2 months	MenACWY: 10-5-5-5 µg + Routine Vaccines Routine Vaccines Only	258 271	Completed

Clinical studies

Study V59_39

Description

This phase 3 study was designed to evaluate the immunogenicity and the safety of MenACWY in healthy subjects from 11 to 55 years of age in Korea.

Methods

Objectives

Primary:

To assess the immunogenicity of a single injection of MenACWY as measured by the percentage of subjects with hSBA seroresponse, directed against *N. meningitidis* serogroups A, C, W and Y.

Secondary:

To assess the immunogenicity of MenACWY as measured by hSBA geometric mean titers (GMTs) and by the percentage of subjects with hSBA .1:8 directed against *N. meningitidis* serogroups A, C, W and Y.

Safety objectives:

To assess the safety profile following MenACWY and saline placebo in terms of percentages and numbers of subjects with:

▫ Local and systemic reactions reported from day 1 (day of vaccination) through day 7 postvaccination.

▫ All other adverse events (AEs) reported from day 1 through day 7 postvaccination.

▫ Serious AEs (SAEs) and medically attended AEs from day 1 through day 29.

Study design

This study was designed as a phase 3, observer-blind, multi-center, randomized, placebo-controlled study in healthy subjects aged 11 to 55 years in Korea.

Study population /Sample size

The study enrolled (non-pregnant) healthy subjects aged 11 to 55 years who had not:

- had a previous or suspected disease caused by *N. meningitidis,*

- had household contact with and/or intimate exposure to an individual with culture-proven *N. meningitidis* infection within 60 days prior to enrolment, or
- had previously been immunized with a meningococcal vaccine

A total of approximately 450 healthy subjects (including a drop-out rate of 20%) were enrolled in this study.

Treatments

Subjects between the ages of 11 and 55 years old were randomized in a 2:1 ratio to receive either MenACWY or saline placebo.

Subjects who have been randomized to Group II, the control group, will be given the option to be vaccinated with MenACWY after successful registration of the vaccine.

Outcomes/endpoints

The measure of immunogenicity used in this study is a Serum Bactericidal Assay using human complement (hSBA). hSBA for MenA, MenC, MenW135, and MenY was performed at Novartis Vaccines, Klinische Serologie, Marburg (Germany). All subjects had a blood draw before the vaccination (day 1) and 28 days following the vaccination (day 29).

The immunogenicity endpoints are (all at day 29):

Primary: % subjects with hSBA seroresponse defined as:

- for subjects with a pre-vaccination hSBA titer < 1:4, a postvaccination hSBA titer ≥1:8
- for subjects with a pre-vaccination hSBA titer ≥1:4, an increase in hSBA titer of at least four times the pre-vaccination titer.

Secondary: hSBA GMTs and % subjects with hSBA ≥ 1:8

The immune response was considered sufficient (i.e., the primary objective is met) if for all four serogroups, the lower limit of the two-sided 95% confidence interval (CI) of the percentage of subjects with hSBA seroresponse is≥50%.

CHMP's comments

Note that the acceptance criteria for the immune response (i.e. hSBA seroresponse ≥50%) would not be acceptable in the European context – response would be expected to be ~70%.

Statistical Methods

Definition of analysis populations:

(a) All Enrolled Population included▫ all subjects who were randomized

(b) Full Analysis Set/Modified Intention-to-treat (MITT) population, Immunogenicity included▫ all subjects in the enrolled population who actually received a study vaccination, and - provided at least one evaluable serum sample both before and after baseline and whose assay result is available for at least one serogroup.

(c) Per Protocol Set/Per protocol (PP) population, Immunogenicity included all subjects in the MITT immunogenicity population who had correctly received the vaccine, and provided evaluable serum samples at the relevant time points, and had no major protocol violation as defined prior to unblinding. In case of randomization errors, subjects were excluded from the PP analysis and analyzed as randomized in the MITT population

(d) Exposed Population included all enrolled subjects who actually received a study vaccination

(e) Safety population included all subjects in the Exposed population who provided post-baseline safety data. In case of randomization errors, subjects were analyzed as treated in the safety analysis.

Statistical Hypothesis

The antibody response of MenACWY was planned to be considered sufficient if for all four serogroups the lower limit of the two-sided 95% CI (i.e., the lower limit of the onesided 97.5% CI) for the percentage of subjects with seroresponse, was at least 50%.

Analysis

Primary analysis: The primary analysis population for immunogenicity is the Per Protocol Immunogenicity Population. If the difference between the PP and MITT population was at least 10% then the immunogenicity analyses on the primary endpoints was also assessed on the MITT population

Descriptive statistics (mean, standard deviation, median, minimum and maximum) for age, height and weight at enrollment were calculated overall and by vaccine group. Distributions of subjects by sex and age were summarized overall and by vaccine group. The percentages of subjects with hSBA seroresponse and associated two-sided 95% Clopper-Pearson CIs were computed for each vaccine group and *N. meningitidis* serogroup, at each time point for which a blood sample was available. The hSBA titers at each visit were logarithmically transformed (base10) and summarized by serogroup and vaccine group. GMTs and associated two sided 95% CIs were calculated at each time point by exponentiating the corresponding log-transformed means (and mean differences from baseline in log-transformed titers) and 95% CIs for the log-transformed means obtained from a two-way Analysis of Variance (ANOVA) with a factor for vaccine group and study center. Titers below the limit of detection were set to half that limit for the purposes of analysis. The percentage of subjects with hSBA $\geq$1:8 to *N. meningitidis* serogroups A, C, W135 and Y was computed for each vaccine group, serogroup and time point including two-sided 95% Clopper-Pearson CIs.

Results

Recruitment / Number analysed

All 297 subjects enrolled in the MenACWY group and 153 subjects in the placebo group completed the study. Major protocol deviations were reported for 1 subject (<1%) in the MenACWY group and 1 subject (<1%) in the placebo group, while minor protocol deviations were reported for 5 subjects (2%) in the MenACWY group and 1 subject (<1%) in the placebo group. Protocol deviations were mostly “Developed Withdrawal Criteria but not Withdrawn” (2 in MenACWY group, 1 in control group) and no hSBA results at visit 2 (1 in MenACWY group).

Baseline data

The demographic and other baseline characteristics were balanced across the different vaccination groups. Age, sex ratios, height and weight were similar across the vaccination groups and all the enrolled subjects met the study entry criteria (Table).

	MenACWY N=297	Placebo N=153	Total N=450
Age (Years):	19.6±9.2	19.3±8.9	19.5±9.1
Sex:			
Male	158 (53%)	76 (50%)	234 (52%)
Female	139 (47%)	77 (50%)	216 (48%)
Race:			
Asian	297 (100%)	153 (100%)	450 (100%)
Weight (kg):	58.04±12.75	58.85±12.94	58.31±12.81
Height (cm):	163.98±10.04	163.94±8.92	163.97±9.66
Met Entry Criteria:			
Yes	297 (100%)	153 (100%)	450 (100%)

Source: Table 14.1.1.3; Categorical parameters: N (%), non-categorical parameters: Mean±Std.

Efficacy results

The overall seroresponse rates at day 29 were 76%, 86%, 28%, and 69% for the A, C, W and Y serogroups, respectively. Lower limits of the two-sided 95% Clopper-Pearson CI for these observed seroresponse rates were 71%, 82%, 23%, and 63% for the A, C, W and Y serogroups, respectively. The majority of subjects entered the study with hSBA ≥1:4 against W serogroup in both MenACWY and placebo groups (261 out of 293 subjects [89%] in the MenACWY group and 131 out of 151 subjects [87%] in the placebo group). Only 21% of the 261 MenACWY subjects who had baseline hSBA ≥1:4 against the W serogroup were seroresponders.

Table 11.4.1-1: Primary Immunogenicity Objective: Percentage (95% CI) [a] of Seroresponders at Day 29 in 11 to 55 Year Olds - Per Protocol Population

	MenA hSBA		MenC hSBA		MenW hSBA		MenY hSBA	
	MenACWY N=295	Placebo N=152	MenACWY N=293	Placebo N=150	MenACWY N=293	Placebo N=151	MenACWY N=294	Placebo N=152
Seroresponse - baseline < 4	187 (76%) (70-81) N=246	2 (2%) (0-6) N=120	107 (96%) (91-99) N=111	2 (3%) (0-10) N=67	27 (84%) (67-95) N=32	6 (30%) (12-54) N=20	106 (89%) (82-94) N=119	3 (5%) (1-13) N=62
Seroresponse - baseline ≥ 4	37 (76%) (61-87) N=49	0 (0%) (0-11) N=32	146 (80%) (74-86) N=182	0 (0%) (0-4) N=83	54 (21%) (16-26) N=261	0 (0%) (0-3) N=131	96 (55%) (47-62) N=175	0 (0%) (0-4) N=90
Overall Seroresponse	224 (76%) (71-81)	2 (1%) (0-5)	253 (86%) (82-90)	2 (1%) (0-5)	81 (28%) (23-33)	6 (4%) (1-8)	202 (69%) (63-74)	3 (2%) (0-6)

Source: Table 14.2.1.1; [a] Two-sided 95% Clopper-Pearson confidence interval.

The baseline GMT against the W serogroup for these 261 seropositive MenACWY subjects was 73 and the day 29 hSBA GMT was 171. The GMR to the baseline for these seropositive subjects was 2.34, with a two sided 95% CI that did not overlap 1.0 (2.09, 2.62).

Among the 32 MenACWY subjects who had baseline hSBA <1:4 against the W serogroup, 84% had a day 29 hSBA ≥1:8. The lower limit of the two-sided 95% Clopper-Pearson CI for this observed

seroresponse rate was 67%. The hSBA GMT against the W serogroup for these 32 initially seronegative MenACWY subjects was 40 on day 29. The GMR at day 29 was 20 (GMTday 29 /GMT day 1), with a two-sided 95% CI of (12, 34). Baseline GMTs were low for the A, C and Y serogroups (2.7, 7.82 and 9.01 in the MenACWY group and 2.86, 5.94 and 8.82 in the placebo group), whereas baseline GMTs were elevated for the W serogroup (51 in the MenACWY group and 48 in the placebo group).

The GMTs at 29 days after vaccination in the MenACWY group were 48, 231, 147 and 107 for the A, C, W and Y serogroups, respectively.

Table 11.4.1-2: Secondary Immunogenicity Objective: hSBA GMTs (95% CI) [a] at Day 1 and Day 29, Age 11 to 55 Years - Per Protocol Population

	MenA hSBA		MenC hSBA		MenW hSBA		MenY hSBA	
	MenACWY N=295	Placebo N=152	MenACWY N=293	Placebo N=150	MenACWY N=293	Placebo N=151	MenACWY N=294	Placebo N=152
Day 1	2.7 (2.47-2.95)	2.86 (2.53-3.24)	7.82 (6.76-9.05)	5.94 (4.85-7.27)	51 (44-61)	48 (38-60)	9.01 (7.64-11)	8.82 (7.02-11)
Day 29	48 (39-57)	3 (2.31-3.88)	231 (198-269)	6.04 (4.89-7.47)	147 (125-171)	47 (38-58)	107 (89-128)	8.4 (6.54-11)
Day 29 to Day 1	18 (15-21)	1.05 (0.82-1.33)	29 (25-34)	1.02 (0.82-1.26)	2.85 (2.49-3.25)	0.99 (0.82-1.19)	12 (9.92-14)	0.95 (0.74-1.22)

Source: Table 14.2.1.5;
[a] GMT and associated two-sided 95% CI obtained by exponentiating the least square mean and associated two-sided 95% CI from a two-way ANOVA of $\log_{10}$ hSBA having factors for group and center.

Table 11.4.1-3: hSBA GMTs (95% CI) [a] at Day 1 and Day 29, Age 11 to 55 Years, by Pre-Vaccination Titer - Per Protocol Population

	MenA hSBA		MenC hSBA		MenW hSBA		MenY hSBA	
	MenACWY	Placebo	MenACWY	Placebo	MenACWY	Placebo	MenACWY	Placebo
Baseline <4	N=246	N=120	N=111	N=67	N=32	N=20	N=119	N=62
Day 1 GMT	2 (2-2)	2 (2-2)	2 (2-2)	2 (2-2)	2 (2-2)	2 (2-2)	2 (2-2)	2 (2-2)
Day 29 GMT	37 (30-44)	2.13 (1.61-2.81)	157 (127-194)	2.25 (1.71-2.96)	40 (24-68)	3.83 (1.97-7.45)	67 (52-86)	2.31 (1.64-3.26)
Day 29 to Day 1 GMR	18 (15-22)	1.06 (0.81-1.4)	78 (63-97)	1.12 (0.85-1.48)	20 (12-34)	1.91 (0.98-3.73)	34 (26-43)	1.16 (0.82-1.63)
Baseline ≥4	N=49	N=32	N=182	N=83	N=261	N=131	N=175	N=90
Day 1 GMT	14 (11-17)	12 (9.29-15)	18 (16-21)	14 (12-18)	73 (66-82)	74 (63-86)	26 (22-30)	25 (21-31)
Day 29 GMT	172 (113-261)	10 (6.11-17)	269 (223-325)	12 (9.43-16)	171 (149-196)	69 (57-84)	157 (127-196)	22 (16-29)
Day 29 to Day 1 GMR	12 (8.35-19)	0.87 (0.53-1.43)	15 (12-18)	0.86 (0.66-1.12)	2.34 (2.09-2.62)	0.93 (0.79-1.09)	6.08 (4.95-7.48)	0.86 (0.65-1.15)

[a] GMT and associated two-sided 95% CI obtained by exponentiating the mean and associated two-sided 95% CI from a one-way ANOVA of $\log_{10}$ hSBA having a single factor for group;
Source: Table 14.2.1.13

The percentages of subjects with hSBA ≥1:8 were 79%, 99%, 98%, and 94% for the A, C, W and Y serogroups, respectively at 29 days after vaccination in the MenACWY group.

Table 11.4.1-4: Secondary Immunogenicity Objective: Percentage (95% CI) [a] of Subjects with hSBA Titer ≥ 1:8 at Day 1 and Day 29, Age 11 to 55 Years - Per Protocol Population

	MenA hSBA		MenC hSBA		MenW hSBA		MenY hSBA	
	MenACWY N=295	Placebo N=152	MenACWY N=293	Placebo N=150	MenACWY N=293	Placebo N=151	MenACWY N=294	Placebo N=152
Day 1	37 (13%) (9-17)	23 (15%) (10-22)	145 (49%) (44-55)	58 (39%) (31-47)	260 (89%) (85-92)	131 (87%) (80-92)	159 (54%) (48-60)	80 (53%) (44-61)
Day 29	234 (79%) (74-84)	24 (16%) (10-23)	289 (99%) (97-100)	56 (37%) (30-46)	288 (98%) (96-99)	133 (88%) (82-93)	277 (94%) (91-97)	77 (51%) (42-59)

Source: Table 14.2.1.3;
[a] Two-sided 95% Clopper-Pearson confidence interval.

The percentages of subjects with hSBA ≥1:8 at baseline were high for the C, W, and Y serogroups (49% and 39% for C, 89% and 87% for W and 54% and 53% for Y serogroups in MenACWY and placebo arms, respectively). However, the percentage of subjects with pre-existing titers was low for the A serogroup (13% in the MenACWY group and 15% in the placebo group).

CHMP's comments

These primary outcome of seroresponse at D29 is largely in line with the results seen from pivotal study V59P13 submitted in support of the licensing of Menveo in the EU. A high level of baseline immunity to MenW has also been seen in other studies, albeit not this high. The seroresponse in these subjects was however lower than would be expected based upon earlier studies (21% in this study compared to 47% in V59P13 for example). Importantly, there is a substantial increase in GMTs in subjects with baseline immunity against MenW in the present study (GMR 2.09 vs 0.93 in placebo group). Moreover, the % of subjects with hSBA ≥1:8 is acceptable.

Safety results

In total 450 persons were enrolled, of which 297 exposed to MenACWY and 153 exposed to placebo. All subjects were included in the safety population. Of these, 40% in the MenACWY group compared to 34% in the placebo group had at least one reported local or systemic reaction during the 7 days after vaccination. The percentage of subjects reporting local reactions was comparatively higher in the MenACWY group (28%) than the placebo group (9%), whereas the percentage of subjects reporting systemic reactions was similar in both groups (28%). Unsolicited AEs were reported by 12% of subjects receiving MenACWY vs 7% of those receiving placebo (up to D29). AEs considered related to study vaccine were reported for 4% (11 subjects) of the MenACWY group vs 1% (2 subjects) of the placebo group.

Solicited local and systemic reactogenicity.

The percentage of subjects reporting solicited local reactions was comparatively higher in the MenACWY group than the placebo group. The most commonly reported local reaction was pain (23% in the MenACWY group and 8% in the placebo group) and none of them were severe in intensity. Other local reactions were erythema and induration.

Table 12.2.3.1-1: Numbers (%) of Subjects with Local Reactions During 7-Days after Vaccination – Safety Population

		Number (%) of Subjects with Injection Site Reactions		
		MenACWY N=297	Placebo N=153	Total N=450
Pain	Any	69 (23%)	12 (8%)	81 (18%)
	Severe	0	0	0
Erythema (mm)	Any	30 (10%)	3 (2%)	33 (7%)
	>100 mm	8 (3%)	0	8 (2%)
Induration (mm)	Any	30 (10%)	0	30 (7%)
	>100 mm	4 (1%)	0	4 (1%)

Source: Table 14.3.1.1.2;
Note: The number (N) in the header is the total number of subjects at risk for local reactions.

The percentage of subjects with solicited systemic reactions was similar in both the MenACWY and placebo groups. The most commonly reported systemic reaction was myalgia (15% in the MenACWY group and 8% in the placebo group) and none of them was severe in intensity. Other systemic reactions were headache, nausea, chills, arthralgia, rash, and fever.

Table 12.2.3.1-2: Numbers (%) of Subjects with Systemic Reactions During 7-Days after Vaccination – Safety Population

		Number (%) of Subjects with Systemic Reactions		
		MenACWY N=297	Placebo N=153	Total N=450
Systemic				
Chills	Any	17 (6%)	7 (5%)	24 (5%)
	Severe	0	0	0
Nausea	Any	22 (7%)	10 (7%)	32 (7%)
	Severe	1 (<1%)	0	1 (<1%)
Myalgia	Any	45 (15%)	13 (8%)	58 (13%)
	Severe	0	0	0
Arthralgia	Any	6 (2%)	4 (3%)	10 (2%)
	Severe	0	0	0
Headache	Any	39 (13%)	25 (16%)	64 (14%)
	Severe	1 (<1%)	0	1 (<1%)
Rash	Any	1 (<1%)	0	1 (<1%)
	Other	0	0	0
Fever (≥38°C)	Yes	3 (1%)	1 (1%)	4 (1%)

Other AEs.

The most commonly experienced AEs by SOC were: infections and infestations (1-5% of subjects), gastrointestinal disorders and general disorders and administrative site conditions (1-3%). The most commonly experienced AEs by preferred term were: acute tonsillitis and nasopharyngitis (1% in the MenACWY group).

Table 12.2.3.1-4: Number (%) of Subjects Reporting AEs by Preferred Term (≥1%) after Vaccination - Safety Population

Preferred Term	Number (%) of Subjects with Adverse Events			
	All		At Least Possibly Related	
	MenACWY	Placebo	MenACWY	Placebo
	N=297	N=153	N=297	N=153
Acute Tonsillitis	4 (1%)	0	0	0
Nasopharyngitis	4 (1%)	0	0	0
Nasal Congestion	0	2 (1%)	0	0
Diarrhea	3 (1%)	0	1 (<1%)	0
Injection Site Pruritus	3 (1%)	0	3 (1%)	0
Upper Respiratory Tract Infection	3 (1%)	1 (1%)	0	0
Vomiting	3 (1%)	0	0	0

Source: Table 14.3.1.1.9, Table 14.3.1.1.12.

There were no deaths, serious adverse events or other significant adverse events reported during the study.

CHMP's comments

Safety findings are in line with the known safety profile of Menveo.

V59_40

Description

A Phase 4, Placebo-Controlled, Randomized Study to Evaluate the Immunogenicity and Safety of a Combined Tetanus, Reduced Diphtheria Toxoid, Acellular Pertussis Vaccine (Tdap, Boostrix®) and Quadrivalent Human Papillomavirus [Types 6, 11, 16, 18] Recombinant Vaccine (Gardasil®) in Healthy Adolescents when Administered with MenACWY Conjugate Vaccine

CHMP's comments

The possible interaction between Gardasil and Menveo and Tdap/Boostrix and Menveo has been studied in V59P18. V59P18 examined the effect of concomitant administration of MenACWY with Tdap and HPV on immunogenicity (to MenACWY, Tdap and HPV vaccine) and safety. This study provided no evidence to suggest that concomitant administration of MenACWY with Tdap & HPV vaccines has an effect on the immune response to MenACWY. There was some evidence to suggest that vaccination with Tdap one month prior to vaccination with MenACWY might interfere with the immune response to MenACWY, as non-inferiority could not be demonstrated for MenW. Secondly, there was some evidence to suggest a negative effect of concomitant vaccination with MenACWY and HPV on the response to pertussis antigens FHA and PRN, however the clinical relevance is unknown.

Methods

Objective(s)

Immunogenicity Objectives:

Coprimary:

1. To demonstrate that the immune response of Tdap given concomitantly with MenACWY and HPV is noninferior to the response of Tdap when given with placebo and HPV when measured at 1 month after 1 dose of Tdap.

2. To demonstrate that the immune response of HPV vaccine given concomitantly with MenACWY and Tdap is noninferior to the response when HPV is given with placebo and Tdap when measured at 1 month after the third dose of HPV vaccination.

Secondary:

To assess the immune response of MenACWY when administered with Tdap and HPV at 1 month after 1 dose of MenACWY vaccination.

Safety Objectives

To describe the safety profile of Men+Tdap+HPV vs. Placebo+Tdap+HPV.

The current clinical study report (CSR) presents only data for the first primary objective and the secondary immunogenicity and safety objectives. The immunogenicity analysis for the second primary objective (assessment of immune response against HPV antigens) will be performed as soon as serological results are available. The results will be presented in an addendum to the clinical study report.

Study design

This study was designed as a phase 4, placebo-controlled, randomized study to evaluate the immunogenicity and safety of a combined tetanus, reduced diphtheria toxoid, acellular pertussis vaccine and quadrivalent HPV (types 6, 11, 16, 18) recombinant vaccine in healthy adolescents when administered with MenACWY.

Study population /Sample size

The study included healthy male/ (non-pregnant) female subjects with no history of meningococcal infection and/or vaccination or HPV vaccination, and with an up-to-date vaccination record for DTP. Approximately 800 subjects, 400 in group 1 and 400 in group 2 were to be enrolled in this study. The expected dropout rate was 10%.

Treatments

Subjects were randomized in a 1:1 allocation ratio within each study center. Group 1 received Tdap, HPV and MenACWY concomitantly for the first vaccination. Group 2 received Tdap, HPV and placebo concomitantly for the first vaccination.

Outcomes/endpoints

Primary outcomes:

▫ Seroprotection rates for diphtheria and tetanus at 1 month after Tdap vaccination:

- Percentage of subjects with diphtheria antitoxin ≥1.0 IU/mL; and
- Percentage of subjects with tetanus antitoxin ≥1.0 IU/mL.

▫ GMCs for anti-PT, anti-FHA and anti-PRN at 1 month after Tdap vaccination

▫ Seroconversion rates for HPV types 6, 11, 16 and 18 at 1 month after 3 HPV vaccinations. Seroconversion was defined as a negative baseline sample for anti-HPV antibodies and anti-HPV antibody level greater than or equal to the HPV type-specific cutoff at 1 month after the third dose of HPV vaccine. The HPV type-specific seroconversion cutoffs were:

- Percentage of subjects with HPV 6 ≥ 20 mMU/mL;
- Percentage of subjects with HPV 11 ≥16 mMU/mL;
- Percentage of subjects with HPV 16 ≥20 mMU/mL; and
- Percentage of subjects with HPV 18 ≥24 mMU/mL.

General Endpoints and Statistics:

▫ GMT or GMC with associated 2-sided 95% CIs are displayed by visit and vaccine group. When baseline values were available, geometric mean ratios (GMRs) to baseline were also presented.

▫ Percentage of subjects meeting response criteria. For the routine vaccine antigens, the cut-off levels indicated seroprotection/seroconversion rates. The 2-sided 95% CIs for all response rates were displayed for all available immunogenicity data by visit and vaccine group.

▫ Anti-HPV seroconversion was defined as a negative baseline sample for anti-HPV and an anti-HPV greater than or equal to the HPV type-specific cutoff at 1 month after the third dose of the vaccine.

▫ All primary and secondary objectives are embedded within the display of GMT/GMC/percentage response according to the respective visit and vaccine group of interest.

Statistical Methods

Definition of populations analyzed:

All Enrolled Population: The enrolled population contained all subjects enrolled and randomized in the study.

Exposed Population: All subjects in the enrolled population who received a study vaccination.

MITT Population: The MITT population included all subjects in the enrolled population who received all the relevant doses of vaccine, and provided at least 1 evaluable serum sample after baseline.

Per Protocol (PP) Population: The PP population included all subjects in the MITT immunogenicity population who correctly received all the relevant doses of vaccine, provided evaluable serum samples at the relevant time points; and ▫ had no major protocol deviation as defined prior to study unblinding.

The PP populations were:

PP – Tdap Serology results at visit 2 within required windows for at least 1 Tdap antigen.

PP – HPV Serology results for at least 1 HPV type at both visit 1 and visit 5 within required window

PP – MenACWY Serology results for at least 1 serogroup at both visit 1 and visit 2 within the required window

Subjects were included in the PP population if they had no major deviations. A major deviation was defined as a protocol deviation that was considered to have a significant impact on the immunogenicity result of the subject.

Analysis for the primary immunogenicity objectives was based on the PP population as well as the MITT population. Analyses for secondary immunogenicity objectives and other immunogenicity endpoints were carried out in the PP population only.

Safety Population

All subjects who had received at least 1 study vaccine and had postbaseline safety data were included in the safety analysis. If an error in administration occurred where the actual vaccination that the subject received was different than the one to which they were randomly assigned (unless they received all doses in accordance with the incorrect schedule), the subject was included in the vaccination group for the vaccine they were randomized to receive. If the full series was provided incorrectly, the subject was analyzed as treated. Safety analyses were based on the safety population.

Subjects who only provided safety data at 30 minutes postvaccination were represented in summaries of safety at 30 minutes postvaccination and were excluded from all other summaries of safety.

Analysis of Immunogenicity criteria

The success criterion for this study was a composite based upon 2 coprimary objectives that involve 9 noninferiority hypotheses. The first coprimary objective was to demonstrate that the immune response of Tdap given concomitantly with MenACWY and HPV was noninferior to the response of Tdap when given with placebo and HPV when measured at 1 month after 1 dose of Tdap. The second coprimary objective was to demonstrate that the immune response of HPV vaccine given concomitantly with MenACWY and Tdap was noninferior to the response when HPV was given with placebo and Tdap when measured at 1 month after the third dose of HPV vaccination.

First Coprimary Objective: To demonstrate that the immune response of Tdap given concomitantly with MenACWY and HPV is noninferior to the response of Tdap when given with placebo and HPV when measured at 1 month after 1 dose of Tdap.

The group 1 immune response to Tdap was considered noninferior to the group 2 immune response to Tdap at 1 month after Tdap administration if the lower limit of the 2-sided 95% CI on the difference between the group 1 and group 2 diphtheria seroprotection rate and on the difference between the group 1 and group 2 tetanus seroprotection rate were each greater than -10%, and if the lower limit of the 2-sided 95% CI on the ratio of group 1 to group 2 GMCs for anti-PT, anti-FHA, and anti-PRN were each greater than 0.5.

The 2-sided 95% CIs for group 1 minus group 2 differences in diphtheria and tetanus response rates were constructed using the method of Miettinen and Nurminen. The group 1 versus group 2 GMC ratios for anti-PT, anti-FHA and anti-PRN and their associated 2-sided 95% CIs were computed by exponentiating (base10) the corresponding vaccine group difference in least square means of the log-transformed concentrations and the associated 95% CI for the difference obtained from an ANOVA model having factors for vaccine group and center. Concentrations below the limit of detection were set to half the limit for the purpose of analysis.

Second Coprimary Objective: To demonstrate that the immune response of HPV vaccine given concomitantly with MenACWY and Tdap is noninferior to the response when HPV was given with placebo and Tdap when measured at 1 month after the third dose of HPV.

The group 1 immune response to HPV will be considered noninferior to the group 2 immune response to HPV if the lower limit of the 2-sided 95% CI on the differences between the group 1 and group 2 HPV type 6, 11, 16, and 18 seroconversion rates are each greater than -5%. The 2-sided 95% CIs for the group 1 minus group 2 differences in HPV 6, HPV 11, HPV 16, and HPV 18 seroconversion rates will be constructed using the method of Miettinen and Nurminen. Titers below the limit of detection will be set to half the limit for the purpose of analysis.

Secondary Response Variables: To assess the immune response of MenACWY when administered with Tdap and HPV at 1 month after 1 dose of MenACWY vaccination. For a subject with baseline hSBA <1:4, seroresponse was defined as a postvaccination hSBA ≥ 1:8; for a subject with baseline hSBA ≥ 1:4, seroresponse was defined as a postvaccination hSBA of at least 4 times the baseline. The assessment of this objective was based upon descriptive statistics and the construction of 2-sided 95% Clopper-Pearson CIs on the seroresponse rates for each serogroup at 1 month after MenACWY vaccination in group 1.

Exploratory/Other Analyses

Other measures of immunogenicity included i) GMCs for diphtheria antitoxin and tetanus antitoxin at 1 month after Tdap vaccination, ii) seroresponse rates for anti-PT, anti-FHA and anti-PRN at 1 month after Tdap vaccination, iii) GMTs for human HPV types 6, 11, 16 and 18 at 1 month after 3 HPV vaccinations, iv) percentage of subjects with hSBA ≥1:8 for meningococcal serogroups A, C, W and Y, and v) hSBA GMTs for meningococcal serogroups A, C, W and Y. These additional endpoints were assessed using the same methods as for the analogous primary and secondary endpoints. However, there were no criteria for assessing vaccine group differences where group comparisons were made. For analyses showing GMCs/GMTs, GMRs to baseline were presented.

Results

Recruitment / Number analysed

A total of 801 subjects who signed informed consent forms were enrolled in the study and were randomized; 402 subjects were included in the Men+Tdap+HPV group and 399 subjects in the Placebo+Tdap+HPV group. In the enrolled population, 741 (93%) subjects completed the study and 60 (7%) subjects were prematurely withdrawn. The premature withdrawals were mostly due to withdrawal of consent (3%) and lost to follow up (3%). Less than 1% subjects were withdrawn due to protocol deviations (7 subjects), AEs (2 subjects), and administrative reasons (1 subject).

Out of a total of 801 enrolled subjects, 131 (16%) subjects (18% in the MenACWY+Tdap+HPV group and 15% in the Placebo+Tdap+HPV group) had major protocol deviations. The most common major deviations were due to noncompliance with study vaccination schedule (10% subjects in the MenACWY+Tdap+HPV group and 8% subjects in the Placebo+Tdap+HPV group), followed by receipt of concomitant vaccine(s) forbidden in the protocol (2% in the MenACWY+Tdap+HPV group and 3% in the Placebo+Tdap+HPV group) and noncompliance with blood draw schedules (2% in the MenACWY+Tdap+HPV and Placebo+Tdap+HPV groups).

Minor protocol deviations were reported for 297 (37%) subjects. These were most commonly due to procedural deviations (27%), unavailability of diary card or worksheet and/or solicited safety data (13%), and subject randomization out of sequence (2%).

Baseline data

The demographic parameters, such as age, sex and race, were generally similar across the study groups. The average age of the subjects at study entry was 11.9 (±1.6) years and the majority of the subjects were male (60%). The percentage of female subjects was 42% in the Men+Tdap+HPV group and 39% in the Placebo+Tdap+HPV group.

Table 11.2-1: Summary of Demography - Enrolled Population

	Men+Tdap+HPV N=402	Placebo+Tdap+HPV N=399	Total N=801
Age (Yrs):	11.9±1.7	11.8±1.5	11.9±1.6
Sex:			
Male	233 (58%)	244 (61%)	477 (60%)
Female	169 (42%)	155 (39%)	324 (40%)
Race:			
Asian	5 (1%)	7 (2%)	12 (1%)
Black, Non-Hispanic	39 (10%)	36 (9%)	75 (9%)
White, Non-Hispanic	319 (79%)	310 (78%)	629 (79%)
Native American/Alaskan	1 (<1%)	2 (<1%)	3 (<1%)
Pacific/Hawaii	0	2 (<1%)	2 (<1%)
Other	38 (9%)	42 (11%)	80 (10%)
Weight (kg):	50.37±15.69 (N=400)	50.56±15.26 (N=398)	50.47±15.46 (N=798)
Height (cm):	153.32±11.73 (N=400)	152.91±11.33 (N=398)	153.12±11.53 (N=798)
Body Mass Index:	21.13±4.72 (N=400)	21.36±4.95 (N=398)	21.24±4.84 (N=798)
Pregnancy Test:			
Negative	164 (97%)	150 (97%)	314 (97%)
Not Done	5 (3%)	5(3%)	10 (3%)
Child Bearing Potential[a]:			
No	91 (54%)	87 (56%)	178 (55%)
Yes	77 (46%)	66 (43%)	143 (44%)

Source: Table 14.1.1.3. Categorical parameters: N (%), noncategorical parameters: Mean±Std.
Abbreviations: HPV, human papilloma virus; MenACWY, meningococcal ACWY vaccine; Tdap, tetanus diphtheria acellular pertussis. [a]The percentages are based on denominator of female subjects.

Efficacy results

First Coprimary endpoint: The noninferiority criterion for diphtheria antigen was met, as the difference in seroprotection rates observed between the study groups was 13%, with the lower limit of the 2-sided 95% CI for the difference being 9%. The difference in seroprotection rates was 0%, with the lower limit of the 2-sided 95% CI for the difference being -2% (Table 11.4.1-1), satisfying the noninferiority criterion for tetanus antigen. The ratios of the GMCs of antibodies against pertussis antigens for the Men+Tdap+HPV group to the Placebo+Tdap+HPV group were 1.01 for anti-PT, 0.84 for anti-FHA, and 0.82 for anti-PRN with the lower limit of the 2-sided 95% CI for the vaccine group ratio being 0.89, 0.76, and, 0.72 respectively (each greater than 0.5). Therefore the noninferiority criteria for all pertussis antigens were met. In summary, the primary immunogenicity analysis showed that the immune responses to Tdap vaccine given concomitantly with MenACWY and HPV were

noninferior to that of Tdap vaccine given with placebo and HPV vaccine, for all 5 endpoints measured. Results were similar when analyses were repeated for the Tdap MITT population.

Table 11.4.1-1: Percentages (95% Confidence Intervals) of Subjects With Protective Anti-Diphtheria Toxin and Anti-Tetanus Toxin Antibody Levels, and GMCs of Anti-Pertussis Antibodies at 1 Month After Tdap Vaccination – Tdap PP Population

		Number (%) of Subjects (95% CI)		Vaccine Group Differences/ Ratios[a]
	≥1.0 IU/mL	Men+Tdap+HPV	Placebo+Tdap+HPV	Men+Tdap+HPV - Placebo+Tdap+HPV
Diphtheria		**N=376**	**N=382**	
	Day 1	5% (3%-8%) N=375	3% (2%-5%) N=380	2% (-1%-5%)
	Day 31	95% (93%-97%)	82% (78%-86%)	**13% (9%-17%)**
Tetanus		**N=376**	**N=382**	
	Day 1	28% (24%-33%) N=375	28% (23%-32%) N=380	1% (-6%-7%)
	Day 31	99% (97%-100%)	98% (97%-99%)	**0% (-2%-2%)**
Pertussis antigen	EU/mL			**Men+Tdap+HPV / Placebo+Tdap+HPV**
	GMC	**N=376**	**N=382**	
PT	Day 1	4.77 (4.11-5.53) N=375	4.16 (3.59-4.82) N=380	1.15 (0.95-1.39)
	Day 31	44 (40-48)	44 (40-48)	**1.01 (0.89-1.14)**
	Day 31 to Day1 GMR	9.23 (8.25-10) N=375	11 (9.42-12) N=380	0.88 (0.76-1.01)
		N=376	**N=382**	
FHA	Day 1	24 (21-27) N=375	21 (18-23) N=380	1.15 (0.98-1.34)
	Day 31	202 (187-218)	240 (222-259)	**0.84 (0.76-0.93)**
	Day 31 to Day1 GMR	8.42 (7.49-9.46) N=375	11 (10-13) N=380	0.73 (0.63-0.86)
		N=376	**N=382**	
PRN	Day 1	20 (18-23) N=375	21 (18-24) N=380	0.99 (0.83-1.18)
	Day 31	330 (300-363)	403 (367-443)	**0.82 (0.72-0.93)**
	Day 31 to Day1 GMR	16 (14-18) N=375	19 (17-22) N=380	0.83 (0.71-0.97)

Source: Table 14.2.1.1; Table 14.2.1.2. Abbreviations: HPV, human papilloma virus; MenACWY, meningococcal ACWY vaccine; Tdap, tetanus diphtheria acellular pertussis; FHA, filamentous hemagglutinin; PRN, pertactin; PT, pertussis toxin. Note: Bold values indicate that noninferiority criteria were met. [a]Noninferiority criteria: The lower limit of the 2-sided 95% CI on the inter-group difference for diphtheria and tetanus seroprotection rates was >-10%, and the lower limit of the 2- sided 95% CI on the inter-group ratio of GMCs for anti-pertussis antibodies were >0.5.

Second Coprimary endpoint: The immunogenicity analysis for the second primary objective (assessment of immune response against HPV antigens) are to be presented in an addendum to the clinical study report as soon as results are available.

CHMP's comments

The MAH should submit these results.

Table 11.4.1-2: Percentage (95% Confidence Interval) of Subjects With Seroresponse Against *N meningitidis* Serogroups A, C, W, and Y at 1 Month After MenACWY or Placebo Vaccination - MenACWY PP Population

Serogroup	Baseline	Men+Tdap+HPV	Placebo+Tdap+HPV
		N=371	N=99
A	hSBA <1:4	268 (76%) (71%-80%) N=354	0 (0%) (0%-4%) N=95
	hSBA ≥1:4	11 (65%) (38%-86%) N=17	1 (25%) (1%-81%) N=4
	Overall	279 (75%) (70%-80%)	1 (1%) (0.026%-5%)
		N=370	N=97
C	hSBA <1:4	165 (78%) (72%-84%) N=211	1 (2%) (0.048%-10%) N=53
	hSBA ≥1:4	92 (58%) (50%-66%) N=159	1 (2%) (0.058%-12%) N=44
	Overall	257 (69%) (64%-74%)	2 (2%) (0%-7%)
		N=369	N=96
W	hSBA <1:4	112 (89%) (82%-94%) N=126	3 (10%) (2%-26%) N=31
	hSBA ≥1:4	68 (28%) (22%-34%) N=243	2 (3%) (0%-11%) N=65
	Overall	180 (49%) (44%-54%)	5 (5%) (2%-12%)
		N=369	N=97
Y	hSBA <1:4	184 (81%) (75%-86%) N=227	3 (4%) (1%-12%) N=70
	hSBA ≥1:4	71 (50%) (42%-58%) N=142	0 (0%) (0%-13%) N=27
	Overall	255 (69%) (64%-74%)	3 (3%) (1%-9%)

Source: Table 14.2.1.9. Abbreviations: HPV, human papilloma virus; MenACWY, meningococcal ACWY vaccine; hSBA, human serum bactericidal assay; PP, per protocol; Tdap, tetanus diphtheria acellular pertussis. Note: For a subject with baseline hSBA <1:4, seroresponse is defined as a postvaccination hSBA ≥ 1:8; for a subject with baseline hSBA ≥1:4, seroresponse is defined as a postvaccination hSBA of at least 4 times the baseline.

Secondary Objectives: In the Men+Tdap+HPV group, at 1 month postvaccination, the overall seroresponse rate to a single dose of MenACWY was 75%, 69%, 49%, and 69% respectively for serogroups A, C, W, and Y. Among the subjects with baseline hSBA <1:4, the seroresponse rate at 1 month postvaccination was 76%, 78%, 89%, and 81% respectively for serogroups A, C,W and Y. For subjects with baseline hSBA ≥1:4, the seroresponse rate was 65%, 58%, 28% and 50% respectively for serogroups A, C, W, and Y. Approximately 1% to 5% of subjects in the Placebo+Tdap+HPV group showed seroresponse against any MenACWY serogroup.

At 1 month postvaccination, the GMTs in the Men+Tdap+HPV group versus the Placebo+Tdap+HPV group were 35 vs. 2.13 against serogroup A, 59 vs. 3.92 against serogroup C, 61 vs. 12 against

serogroup W and 48 vs. 3.54 against serogroup Y, respectively. In the Men+Tdap+HPV group, at 1 month postvaccination, the GMTs increased 16-fold (GMR) over the baseline against serogroup A, 13-fold against serogroup C, 5-fold against serogroup W and 12-fold against serogroup Y. The relative increase in GMTs for MenW was lower than the other serogroups, reflecting the higher baseline hSBA.

Assessor's comments

Results are in line with the known immunogenicity of MenACWY. Note that earlier studies (V59P18) provided some indication that there might be immune interference between Tdap and MenACWY: the effect of concomitant administration on the response to the MenW component can not be evaluated in the current study.

V59P18 also provided some evidence to suggest a negative effect of concomitant vaccination with MenACWY and HPV on the response to pertussis antigens FHA and PRN, in this study too the response to FHA and PRN is significantly lower (albeit non-inferiority was demonstrated) when Tdap is given concomitantly with MenACWY, confirming earlier findings.

Safety results

Among 801 subjects in the enrolled population, 793 (99%) subjects were exposed to the study vaccines, all of whom provided postvaccination safety data and were included in the safety set.

Solicited local and systemic reactogenicity.

The percentage of subjects with any solicited AE reported from day 1 (6 hours) through day 7 postvaccination was 72% in the Men+Tdap+HPV group and 64% in the Placebo+Tdap+HPV group

The rates of both local and systemic solicited AEs were higher in the Men+Tdap+HPV group than in the Placebo+Tdap+HPV group (local AEs: 54% vs. 43%; systemic AEs: 53% vs. 46%) after the first study vaccination. The most commonly reported local solicited AE was pain at the injection site (41% vs. 35% in Men+Tdap+HPV vs. Placebo+Tdap+HPV, respectively; p=0.095), followed by erythema (17% vs. 7%; p<0.001) and induration (16% vs. 10%;p=0.011). The most commonly reported systemic solicited AE from 6 hours through day 7 was myalgia (30% vs. 26% in Men+Tdap+HPV vs. Placebo+Tdap+HPV, respectively) followed by headache (29% vs. 25%), chills (15% vs. 13%) and malaise (15% vs. 11%).

Table 12.2.3.1-1: Percentages of Subjects With Local Solicited Adverse Events With Onset From 6 Hours Through Day 7 After the First Vaccination – Reactogenicity Set

Local Solicited AEs		Number (%) of Subjects		P-Value
		Men+Tdap+HPV	Placebo+Tdap+HPV	
		N=389	N=385	
Erythema	Any	65 (17%)	25 (7%)	<0.001[a]
	>100 mm	2 (1%)	0	
Induration	Any	61 (16%)	37 (10%)	0.011[b]
	>100 mm	2 (1%)	1 (<1%)	
Pain	Any	158 (41%)	134 (35%)	0.095
	Severe	2 (1%)	3 (1%)	

Source: Table 14.3.1.1.2. Note: P-value from Pearson's chi-square test for vaccine group differences; [a]p <0.001; [b]p <0.05; N refers to the number of subjects with data at a time point for that specific solicited adverse event. Abbreviations: AE, adverse event; HPV, human papilloma virus; MenACWY, Meningococcal ACWY vaccine; Tdap- tetanus, diphtheria, acellular pertussis.

Table 12.2.3.1-2: Number (Percentages) of Subjects with Systemic Solicited Adverse Events With Onset From 6 Hours Through Day 7 After the First study Vaccination-Reactogenicity Set

Systemic Solicited AEs		Number (%) of Subjects		
		Men+Tdap+HPV	Placebo+Tdap+HPV	P-Value
		N=389	N=385	
Chills	Any	60 (15%)	50 (13%)	0.34
	Severe	0	1 (<1%)	
Malaise	Any	57 (15%)	44 (11%)	0.19
	Severe	0	1 (<1%)	
Nausea	Any	54 (14%)	39 (10%)	0.11
	Severe	3 (1%)	2 (1%)	
Myalgia	Any	115 (30%)	101 (26%)	0.31
	Severe	2 (1%)	3 (1%)	
Arthralgia	Any	35 (9%)	43 (11%)	0.31
	Severe	2(1%)	2 (1%)	
Headache	Any	113 (29%)	95 (25%)	0.18
	Severe	4 (1%)	3 (1%)	
Rash	Any	4 (1%)	7 (2%)	0.35
	Urticarial	1 (<1%)	2 (1%)	
Fever (≥38°C)	Yes	9 (2%)	8 (2%) N=383	0.83
Other				
Temp. (C)	<38.0°C	380 (98%)	375 (98%) N=383	0.83
	38 - 38.9°C	7 (2%)	7 (2%) N=383	
	39 - 39.9°C	2 (1%)	1 (<1%) N=383	
	≥40.0°C	0	0	
Stayed Home Due To React.	Yes	25(6%)	33 (9%)	0.25
Analgesic Antipyretic used	Yes	74 (19%)	65 (17%)	0.45

Source: Table 14.3.1.1.2. Note: P-value from Pearson's chi-square test for vaccine group differences; N refers to the number of subjects with data at a time point for that specific solicited adverse event.
Abbreviations: AE, adverse event; HPV, human papilloma virus; MenACWY, Meningococcal ACWY vaccine; Tdap- tetanus, diphtheria, acellular pertussis.

Other AEs.

The proportion of subjects with each unsolicited AE was similar across the study groups; 51% in the Men+Tdap+HPV group and 50% in Placebo+Tdap+HPV group. The possibly related unsolicited AEs were reported by 4% of subjects in both study groups.

The most commonly reported unsolicited treatment emergent AEs were injection site pain (7% vs. 6% in Men+Tdap+HPV vs. Placebo+Tdap+HPV) and pharyngitis (6% vs. 5%).

There was no death reported in this study. A total of 7 subjects (4 subjects in the Men+Tdap+HPV group and 3 subjects in the Placebo+Tdap+HPV group) reported 9 SAEs during the entire study period. Haematuria, abdominal adhesions, small intestinal obstruction, aggression, hypothyroidism, and type 1 diabetes mellitus were SAEs reported in subjects in the Men+Tdap+HPV group. Peritonsillar abscess, accidental overdose and affective disorder were reported in subjects in the Placebo+Tdap+HPV group.

All subjects recovered from the SAEs except for one subject (119/017) with persistent affective disorder. None of the SAEs were considered to be related to study vaccine.

Pyrexia and headache in subject 108/035 and vasovagal syncope in subject 114/047 led to the premature withdrawal in the Men+Tdap+HPV group. Subject 114/047 was not vaccinated during the study. Toothache, influenza and laceration led to delay in study vaccination in 2 subjects from the Men+Tdap+HPV group and 1 subject from the Placebo+Tdap+HPV group.

Assessor's comments:

Safety findings are in line with the known safety profile of Menveo.

V59_49

Description

A phase 3, multicenter, open-label study to evaluate immunogenicity and safety of Novartis Meningococcal ACWY conjugate vaccine (MenACWY-CRM) in healthy subjects from 2 to 18 years in Taiwan.

Methods

Objectives

Primary Immunogenicity Objective:

To assess the immunogenicity of a single injection of MenACWY-CRM as measured by the percentage of subjects with hSBA seroresponse, directed against N meningitidis serogroups A, C, W135 and Y.

Secondary Immunogenicity Objectives

- To assess the immunogenicity of a single injection of MenACWY-CRM vaccine as measured by the percentage of subjects with hSBA seroresponsea, directed against N meningitidis serogroups A, C, W135 and Y by age group (2-10b, 11-18c years).
- To assess the immunogenicity of a single injection of MenACWY-CRM as measured by hSBA geometric mean titers (GMTs and GMRd) and by the percentage of subjects with hSBA titer ≥ 1:8, directed against N meningitidis serogroups A, C, W135 and Y, overall and by age group.

Safety objectives

To assess the safety profile following MenACWY-CRM vaccination in terms of percentages and numbers of subjects with:

- Local and systemic reactionse reported from day 1 (day of vaccination) through day 7 postvaccination.
- All other adverse eventse (AEs) reported from day 1 through day 7 postvaccination
- Serious AEs (SAEs), medically attended AEs and AEs resulting in premature withdrawal from day 1 through day 29.

Study design

This was a phase 3, multicenter, single armed open-label study to evaluate immunogenicity and safety of MenACWY-CRM in healthy subjects ≥ 2 to ≤ 18 years of age in Taiwan.

CHMP's comments:

Note that the study design was a recommendation of the Taiwanese authorities.

Study population /Sample size

Inclusion criteria: Subjects eligible to be enrolled in this study were those who were ≥2 to ≤18 years of age, those whose parent/legal representative provided written informed consent (≥2 to ≤18 years of age) and who provided written assent (≥7 to ≤18 years of age), were available for both study visits, and were in good health based on the clinical judgment of the investigator. Exclusion criteria: Serious, acute, or chronic illnesses were reasons for exclusion.

A total of 340 subjects (170 subjects in each age group) were planned to be enrolled in the study. A total of 341 subjects were actually enrolled; 173 subjects in the age group ≥ 2 to ≤ 10 years and 168 subjects in the age group ≥ 11 to ≤ 18 years. A total of 340 (173 subjects in the age group ≥ 2 to ≤ 10 years and 167 subjects in the age group ≥ 11 to ≤ 18 years) subjects completed the study and were analyzed for safety, 336 (170 subjects in the age group ≥ 2 to ≤ 10 years and 166 subjects in the age group ≥ 11 to ≤ 18 years) subjects were included in the modified-intent-to-treat (MITT) and per protocol (PP) immunogenicity analyses

Treatments

Investigational (Test) vaccine, Novartis MenACWY (vial/vial) [Lot no. M11006 (expiry date August 2012)] was obtained by extemporaneous mixing of the lyophilized MenA component with the liquid MenCWY component just before injection. One 0.5 mL dose of MenACWY-CRM was administered by intramuscular (IM) injection in the deltoid area of nondominant arm.

Outcomes/endpoints

Immunogenicity

Primary Endpoint

- Percentage of subjects with hSBA seroresponse to N meningitidis serogroups A, C, W135 and Y at day 29 in the overall subjects (≥ 2 to ≤ 18 years of age).

Seroresponse is defined as:

- for subjects with a prevaccination hSBA titer < 1:4, a postvaccination hSBA titer ≥ 1:8.
- for subjects with a prevaccination hSBA titer ≥ 1:4, an increase in hSBA titer of at least four times the prevaccination titer.

Secondary Endpoints

- Percentage of subjects with hSBA seroresponse to N meningitidis serogroups A, C, W135 and Y at day 29 by age group (≥ 2 to ≤ 10 years and ≥ 11 to ≤ 18 years).

- hSBA GMTs to N meningitidis serogroups A, C, W135 and Y at day 1 and day 29, overall and by age group.
- hSBA geometric mean ratio (GMR) to N meningitidis serogroups A, C, W135 and Y, overall and by age group.
- Percentage of subjects with hSBA titer ≥ 1:8 to N meningitidis serogroups A, C, W135 and Y at day 1 and day 29, overall and by age group.

Safety Endpoints

Numbers and percentages of subjects with reported solicited local and systemic AEs and unsolicited AEs.

Statistical Methods

For this study there was no hypothesis to be statistically tested. Endpoints were reported descriptively, overall and by age group.

Definition of data sets analyzed:

a. Enrolled set: all subjects who signed an informed consent, underwent screening procedure(s), and were assigned a subject number.

b. Exposed set: all enrolled subjects who actually received the study vaccination.

c. Safety set: all subjects in the exposed set who provided any postbaseline safety data.

d. Modified intent-to-treat (MITT) set: This set was defined by visit (visit 1, visit 2, both visits) and by serogroup. All subjects in the exposed set who provided evaluable serum samples whose assay results were available for at least one serogroup on day 1 and/or day 29. The primary and secondary objectives were based on MITT Population

e. Per protocol (PP) set: all subjects in MITT who had no major protocol violations.

The number and percentage of subjects with hSBA seroresponse and associated two-sided 95% Clopper-Pearson confidence intervals (CIs) were computed for each N meningitidis serogroups A, C, W135 and Y at day 29, for all subjects overall.

Results

Recruitment / Number analysed

Date of first enrollment: 15-08-2011; Date of last visit: 21-01-12

There were 341 subjects enrolled into the study and 340 subjects completed the study. One subject in the age group ≥ 11 to ≤ 18 years was prematurely withdrawn from the study due to withdrawal of consent. The primary analysis set was MITT that included nearly all subjects (336; 99%).

Baseline data

The mean age of age group ≥ 2 to ≤ 10 years and ≥ 11 to ≤ 18 years was 6.3 and 14.0 years, respectively and nearly a similar number of male and female subjects participated in both age groups.

Table 2-3: Demographic and Other Baseline Characteristics – Enrolled Set

	≥ 2 to ≤ 10 years	≥11 to ≤18 years	Total
	N=173	N=168	N=341
Age (Years):	6.3±2.6	14.0±2.2	10.1±4.5
Gender:			
Male	81 (47%)	80 (48%)	161 (47%)
Female	92 (53%)	88 (52%)	180 (53%)
Ethnic origin:			
Asian	173 (100%)	168 (100%)	341 (100%)
Weight (kg):	24.87±10.75	53.98±12.38	39.21±18.60
Height (cm):	119.4±18.3	160.6±9.1	139.7±25.2
Body mass index:	16.70±2.94	20.76±3.66	18.70±3.89
Met entry criteria:			
Yes	173 (100%)	168 (100%)	341 (100%)

Source: Table 14.1.1.3
Categorical parameters: N (%); Non-categorical parameters: Mean±Std.

Efficacy results

Primary objective

The overall seroresponse rates at day 29 after MenACWY-CRM vaccination were 83%, 93%, 50%, and 65% respectively for the serogroups A, C, W135, and Y. Highest seroresponse was observed against the serogroup C (93%) and the lowest against the serogroup W135 (50%). The majority of subjects entered the study with hSBA titer ≥ 1:4 against the serogroup W135 (201 out of 334 subjects; 60%).

In the subjects with the negative prevaccination titer (baseline titer < 1:4), hSBA seroresponse was 83%, 96%, 89%, and 77% respectively for the serogroups A, C, W135, and Y after MenACWY-CRM vaccination.

Table 11.4.1.1-1: Percentages of Subjects (95% CI)[a] with hSBA seroresponse to *N meningitidis* Serogroups A, C, W_{135} and Y at Day 29, Overall Subjects – MITT Set

	Subjects ≥ 2 to ≤ 18 years			
	MenA	MenC	$MenW_{135}$	MenY
Seroresponse - baseline titer < 1:4	268 (83%) (78%-87%) N=323	220 (96%) (92%-98%) N=230	119 (89%) (83%-94%) N=133	184 (77%) (71%-82%) N=239
Seroresponse - baseline titer ≥ 1:4	10 (83%) (52%-98%) N=12	90 (87%) (79%-93%) N=103	48 (24%) (18%-30%) N=201	33 (35%) (26%-46%) N=94
Overall Seroresponse	278 (83%) (79%-87%) N=335	310 (93%) (90%-96%) N=333	167 (50%) (45%-55%) N=334	217 (65%) (60%-70%) N=333

Source: Table 14.2.1.1

[a] Two-sided 95% Clopper-Pearson confidence interval; hSBA – human serum bactericidal assay; MITT – modified intent-to-treat. Seroresponse is defined as: for subjects with a prevaccination hSBA titer < 1:4, a postvaccination hSBA titer ≥ 1:8, for subjects with a prevaccination hSBA titer ≥ 1:4, an increase in hSBA titer of at least four times the prevaccination titer.

Table 11.4.1.2-1: Percentages of Subjects (95% CI)[a] with hSBA seroresponse to *N meningitidis* Serogroups A, C, W_{135} and Y at Day 29, By Age Group – MITT Set

	≥ 2 to ≤ 10 years				≥ 11 to ≤ 18 years			
	MenA	MenC	$MenW_{135}$	MenY	MenA	MenC	Men W_{135}	MenY
Seroresponse - baseline titer < 1:4	127 (77%) (69%-83%) N=166	123 (94%) (88%-97%) N=131	73 (86%) (77%-92%) N=85	92 (72%) (63%-79%) N=128	141 (90%) (84%-94%) N=157	97 (98%) (93%-100%) N=99	46 (96%) (86%-99%) N=48	92 (83%) (75%-89%) N=111
Seroresponse - baseline titer ≥ 1:4	4 (100%) (40%-100%) N=4	30 (83%) (67%-94%) N=36	18 (22%) (13%-32%) N=83	10 (26%) (13%-42%) N=39	6 (75%) (35%-97%) N=8	60 (90%) (80%-96%) N=67	30 (25%) (18%-34%) N=118	23 (42%) (29%-56%) N=55
Overall Seroresponse	131 (77%) (70%-83%) N=170	153 (92%) (86%-95%) N=167	91 (54%) (46%-62%) N=168	102 (61%) (53%-69%) N=167	147 (89%) (83%-93%) N=165	157 (95%) (90%-97%) N=166	76 (46%) (38%-54%) N=166	115 (69%) (62%-76%) N=166

Source: Table 14.2.1.1

[a] Two-sided 95% Clopper-Pearson confidence interval; hSBA – human serum bactericidal assay; MITT – modified intent-to-treat. Seroresponse is defined as: for subjects with a prevaccination hSBA titer < 1:4, a postvaccination hSBA titer ≥ 1:8, for subjects with a prevaccination hSBA titer ≥ 1:4, an increase in hSBA titer of at least four times the prevaccination titer.

The baseline GMTs were low for all the serogroups (2.12, 3.19, 10, and 3.56 respectively for A, C, W135 and Y serogroups). At day 29 after MenACWY-CRM vaccination, GMTs increased up to 53, 179, 71 and 38 respectively for the serogroups A, C, W135, and Y. GMR (GMTday 29/GMTday 1) for the serogroups A, C, W135 and Y at day 29 was 25, 57, 6.78 and 11, respectively. The highest increase in GMTs was observed for the serogroup C and lowest for the serogroup W135

Table 11.4.1.2-2: hSBA GMTs and GMRs (95% CI) [a] at Day 1 and Day 29, By Age Group and Overall, – MITT Set

		≥ 2 to ≤ 10 years	≥ 11 to ≤ 18 years	Overall
MenA	**GMT**	**N=170**	**N=165**	**N=335**
	Day 1	2.05 (1.92-2.2)	2.2 (2.05-2.36)	2.12 (2.02-2.24)
	Day 29	32 (24-43)	88 (66-117)	53 (42-65)
	GMR (Day 29/Day 1)	16 (12-21)	40 (30-53)	25 (20-31)
MenC		**N=167**	**N=166**	**N=333**
	Day 1	2.66 (2.35-3.02)	3.64 (3.21-4.12)	3.19 (2.93-3.46)
	Day 29	117 (93-147)	273 (218-342)	179 (151-211)
	GMR (Day 29/Day 1)	44 (35-56)	75 (59-95)	57 (48-69)
$MenW_{135}$		**N=168**	**N=166**	**N=334**
	Day 1	7.32 (5.65-9.49)	15 (12-19)	10 (8.62-13)
	Day 29	49 (40-60)	104 (85-127)	71 (61-82)
	GMR (Day 29/Day 1)	6.66 (5.19-8.54)	6.91 (5.39-8.85)	6.78 (5.63-8.16)
MenY		**N=167**	**N=166**	**N=333**
	Day 1	3.21 (2.69-3.83)	3.95 (3.31-4.71)	3.56 (3.12-4.06)
	Day 29	26 (20-33)	56 (43-72)	38 (31-46)
	GMR (Day 29/Day 1)	8.02 (6.09-11)	14 (11-19)	11 (8.67-13)

Source: Table 14.2.1.3

[a] Two-sided 95% Clopper-Pearson confidence interval; hSBA - human serum bactericidal assay; GMT – geometric mean titer; GMR – geometric mean ratio; MITT – modified intent-to-treat.

Table 11.4.1.2-3: Percentage (95% CI)[a] of Subjects With hSBA Titer ≥1:8 at Day1 and Day 29, By Age Group and Overall – MITT

		≥ 2 to ≤ 10 years	≥ 11 to ≤ 18 years	Overall
MenA		N=170	N=165	N=335
	Day 1	2 (1%) (0%-4%)	7 (4%) (2%-9%)	9 (3%) (1%-5%)
	Day 29	131 (77%) (70%-83%)	148 (90%) (84%-94%)	279 (83%) (79%-87%)
MenC		N=167	N=166	N=333
	Day 1	19 (11%) (7%-17%)	39 (23%) (17%-31%)	58 (17%) (13%-22%)
	Day 29	158 (95%) (90%-98%)	163 (98%) (95%-100%)	321 (96%) (94%-98%)
$MenW_{135}$		N=168	N=166	N=334
	Day 1	79 (47%) (39%-55%)	116 (70%) (62%-77%)	195 (58%) (53%-64%)
	Day 29	156 (93%) (88%-96%)	164 (99%) (96%-100%)	320 (96%) (93%-98%)
MenY		N=167	N=166	N=333
	Day 1	36 (22%) (16%-29%)	43 (26%) (19%-33%)	79 (24%) (19%-29%)
	Day 29	130 (78%) (71%-84%)	142 (86%) (79%-91%)	272 (82%) (77%-86%)

Source: Table 14.2.1.2

[a] Two-sided 95% Clopper-Pearson confidence interval; hSBA - human serum bactericidal assay; MITT – modified intent-to-treat.

The percentage of subjects with prevaccination hSBA titer ≥ 1:8 were low for the serogroups A, C, Y (3%, 17% and 24%, respectively) and high for the serogroups W135 (58%). At day 29 after MenACWY-CRM vaccination, the percentages of subjects with hSBA titer ≥ 1:8 were 83%, 96%, 96%, and 82% respectively for the serogroups A, C, W135, and Y.

CHMP's comments

Results are in line with other immunogenicity studies in the same age groups. The response is slightly higher in older children compared to children aged 2-10 yrs. Here too the limited seroresponse seen in subjects with pre-existing antibody titers against MenW but also MenY is evident – there is a substantial increase in GMT. A relatively high proportion of subjects had pre-existing antibodies against MenW, this proportion increased with age.

Safety results

Of the 341 subjects enrolled in this study, 340 were administered study vaccine. Subject 03/015 was terminated from the study due to withdrawal of consent at visit 1 and was not vaccinated.

Solicited local and systemic AEs

Age group ⩾ 2 to ⩽ 5 years

In the age group ⩾ 2 to ⩽ 5 years, any local AE was reported by 33 subjects (46%) any systemic AE was reported by 19 subjects (26%), and any other AE was reported by 4 subjects (6%). The most

commonly reported solicited local AE was tenderness (27 subjects; 38%), followed by erythema (7 subjects, 10%) and induration (6 subjects, 8%). The majority of solicited local AEs were of mild or moderate intensity. One subject reported tenderness of severe intensity and one subject reported erythema of severe intensity. The most commonly reported systemic AE was vomiting (7 subjects; 10%), followed by irritability (5 subjects; 7%), rash (4 subjects; 6%) and fever ≥38C (4 subjects; 6%). The majority of systemic AEs were of mild or moderate intensity with the exception of an urticarial rash which was reported in 1 subject (1%). Antipyretic/analgesic medications were administered to 4 subjects (6%).

Age group ⩾ 6 to ⩽ 10 years

In the age group ≥ 6 to ≤ 10 years, any local AE was reported by 42 subjects (42%), any systemic AE was reported by 19 subjects (26%), and any other AE was reported by 4 subjects (6%). The most commonly reported solicited local AE was pain (37 subjects; 37%), followed by erythema (17 subjects, 17%) and induration (14 subjects, 14%). All of the solicited local AEs were of mild or moderate intensity. The most commonly reported systemic AE was myalgia (20 subjects; 20%), followed by malaise (13 subjects; 13%), headache (11 subjects; 11%) and nausea (10 subjects; 10%). The majority of systemic AEs were of mild or moderate intensity with the exception of urticarial rash which was reported in 3 subjects (3%). There were 3 subjects (3%) who reported fever ≥ 38 °C, and 2 subjects (2%) who were administered antipyretic/analgesic medications.

Age group ≥ 11 to ≤ 18 years

In the age group ≥ 11 to ≤ 18 years of age, any local AE was reported by 71 subjects (43%), any systemic AE was reported by 63 subjects (38%) and any other AE was reported by 3 subjects (2%). The most commonly reported solicited local AE was pain (62 subjects; 37%), followed by erythema (17 subjects, 10%) and induration (12 subjects, 7%). The majority of solicited local AEs were of mild or moderate intensity, with only 1 subject reporting pain of severe intensity. The most commonly reported systemic AE was myalgia (49 subjects; 29%), followed by malaise (35 subjects; 21%) and headache (29 subjects; 17%). The majority of systemic AEs were of mild or moderate intensity. However, severe intensity reactions were reported in 4 subjects (2%) for headache, in 3 subjects (2%) for urticarial rash, in 2 subjects (1%) each for malaise and myalgia and in 1 subject (1%) for arthralgia. There were 2 subjects (1%) who reported fever ≥ 38 °C, and 3 subjects (2%) who were administered antipyretic/analgesic medications.

Table 12.2.3.1-1: Numbers (%) of Subjects with Any (And Severe / > 100 mm) Local AEs During 7-Day Period After Vaccination, Age Group ≥ 2 to ≤ 5 Years - Safety Set

		Number (%) of Subjects with Local AEs
		≥ 2 to ≤ 5 years N=72
Any local solicited event		40 (56%)
Tenderness	Any	27 (38%)
	Severe	1 (1%)
Erythema (mm)	Any	7 (10%)
	>100 mm	1 (1%)
Induration (mm)	Any	6 (8%)
	>100 mm	0

Source: Table 14.3.1.1.2.1, Table 14.3.1.1.1.1
Note: The numbers (N) in the header is the total number of subjects with documented reactions.

Table 12.2.3.1-2: Numbers (%) of Subjects with Any (And Severe / > 100 mm) Local AEs During 7-Day Period After Vaccination, Age Group ≥ 6 to ≤ 18 Years - Safety Set

		Number (%) of Subjects with Local AEs		
		≥ 6 to ≤ 10 years N=101	≥ 11 to ≤ 18 years N=167	Total N=268
Any local solicited event		50 (50%)	88 (53%)	138 (51%)
Pain	Any	37 (37%)	62 (37%)	99 (37%)
	Severe	0	1 (1%)	1 (<1%)
Erythema (mm)	Any	17 (17%)	17 (10%)	34 (13%)
	> 100 mm	0	0	0
Induration (mm)	Any	14 (14%)	12 (7%)	26 (10%)
	> 100 mm	0	0	0

Source: Table 14.3.1.1.2, Table 14.3.1.1.1
Note: The numbers (N) in the header is the total number of subjects with documented reactions.

Table 12.2.3.1-3: Numbers (%) of Subjects With Any and, Where Relevant, Severe Systemic AEs and Other AEs During 7-Day Period after Vaccination, Age Group ≥ 2 to ≤ 5 Years - Safety Set

		Number (%) of Subjects with Systemic AEs ≥ 2 to ≤ 5 years N=72
Systemic		
Any solicited systemic AE		19 (26%)
Change in eating habits	Present	2 (3%)
Sleepiness	Present	3 (4%)
Irritability	Present	5 (7%)
Vomiting	Present	7 (10%)
Diarrhea	Present	2 (3%)
Rash	Any	4 (6%)
	Urticarial	1 (1%)
Fever (≥ 38 °C)	Yes	4 (6%)
Other		
Any solicited other event		4 (6%)
Temperature (°C)	< 38 °C	68 (94%)
	≥ 40 °C	0
Analgesic/Antipyretic medicines used	Yes	4 (6%)

Table 12.2.3.1-4: Numbers (%) of Subjects With Any and, Where Relevant, Severe Systemic AEs and Other AEs During 7-Day Period After Vaccination, Age Group ≥ 6 to ≤ 18 Years - Safety Set

		Number (%) of Subjects With Systemic AEs		
		≥ 6 to ≤ 10 years N=101	≥ 11 to ≤ 18 years N=167	Total N=268
Systemic				
Chills	Any	2 (2%)	6 (4%)	8 (3%)
	Severe	0	0	0
Nausea	Any	10 (10%)	10 (6%)	20 (7%)
	Severe	0	0	0
Malaise	Any	13 (13%)	35 (21%)	48 (18%)
	Severe	0	2 (1%)	2 (1%)
Myalgia	Any	20 (20%)	49 (29%)	69 (26%)
	Severe	0	2 (1%)	2 (1%)
Arthralgia	Any	3 (3%)	13 (8%)	16 (6%)
	Severe	0	1 (1%)	1 (<1%)
Headache	Any	11 (11%)	29 (17%)	40 (15%)
	Severe	0	4 (2%)	4 (1%)
Rash	Any	7 (7%)	4 (2%)	11 (4%)
	Urticarial	3 (3%)	3 (2%)	6 (2%)
Fever (≥ 38 °C)	Yes	3 (3%)	2 (1%)	5 (2%)
Other				
Temperature (°C)	< 38 °C	98 (97%)	165 (99%)	263 (98%)
	≥ 40 °C	0	0	0
Analgesic/Antipyretic medicines used		2 (2%)	3 (2%)	5 (2%)

Unsolitited AEs

Unsolicited AEs, which were collected from study day 1 (day of vaccination) through to study day 7 postvaccination, were experienced by 16% of subjects in the age group 2 to 10 years and by 12% of subjects in the age group 11 to 18 years.The most commonly reported AEs by SOC in the age group ≥ 2 to ≤ 10 years were infections and infestations (11 subjects; 6%); general disorders and administrative site conditions (9 subjects; 5%); gastrointestinal disorders (3 subjects; 2%); respiratory, thoracic and mediastinal disorders (3 subjects; 2%); and skin and subcutaneous tissue disorders (3 subjects; 2%). The most commonly reported AEs by SOC in the age group ≥ 11 to ≤ 18 years were general disorders and administrative site conditions (7 subjects; 4%); infections and infestations (6 subjects; 4%); and nervous system disorders (6 subjects; 4%)

Table 12.2.3.2-1: Number (%) of Subjects Reporting all AEs Before 7-Day Period by SOC, ≥ 2 to ≤ 18 Years of Age, Unsolicited Safety Set

	Number (%) of Subjects with AEs					
	All			At Least Possibly Related		
SOC	≥ 2 to ≤ 10 years N=173	≥ 11 to ≤ 18 years N=167	Total N=340	≥ 2 to ≤ 10 years N=173	≥ 11 to ≤ 18 years N=167	Total N=340
Any AE	27 (16%)	20 (12%)	47 (14%)	11 (6%)	10 (6%)	21 (6%)
Gastrointestinal disorders	3 (2%)	2 (1%)	5 (1%)	0	0	0
General disorders and administrative site conditions.	9 (5%)	7 (4%)	16 (5%)	9 (5%)	7 (4%)	16 (5%)
Immune system disorders	1 (1%)	0	1 (<1%)	0	0	0
Infections and infestations	11 (6%)	6 (4%)	17 (5%)	0	0	0
Metabolism and nutrition disorders	0	1 (1%)	1 (<1%)	0	0	0
Musculoskeletal, connective tissue and bone disorders	0	2 (1%)	2 (1%)	0	1 (1%)	1 (<1%)
Nervous system disorders	0	6 (4%)	6 (2%)	0	4 (2%)	4 (1%)
Respiratory, thoracic and mediastinal disorders	3 (2%)	2 (1%)	5 (1%)	0	0	0
Skin and subcutaneous tissue disorders	3 (2%)	0	3 (1%)	2 (1%)	0	2 (1%)

Source: Table: 14.3.1.1.9, Table: 14.3.1.1.12

The most commonly reported AEs by PT in the age group ≥ 2 to ≤ 10 years were:

Nasopharyngitis (6 subjects; 3%), injection site induration (4 subjects; 2%), injection site pruritis (4 subjects; 2%), injection site erythema (3 subjects; 2%), and upper respiratory tract infection (3 subjects; 2%). At least possibly related AEs were experienced by 6% of the subjects and were most commonly associated with injection site events.

The most commonly reported AEs by PT in the age group ≥ 11 to ≤ 18 years were:

injection site induration (5 subjects; 3%), dizziness (4 subjects; 2%), upper respiratory tract infection (3 subjects; 2%), headache (2 subjects; 1%), injection site erythema (2 subjects; 1%), injection site swelling (2 subjects; 1%), nasopharyngitis (2 subjects; 1%), and oropharyngeal pain (2 subjects; 1%). At least possibly related AEs were experienced by 6% of the subjects and were most commonly associated with injection site events or dizziness

Deaths, other serious adverse events and other significant adverse events

There were no deaths during the study. There was one SAE reported during the study; subject 03/039 who experienced pneumonia of moderate intensity starting on study day 17 and lasting for 15 days. This was considered unrelated to the study drug. There were no AEs leading to premature withdrawal.

CHMP's comments

The safety profile and adverse events observed in this study is very much in line with the known safety profile of MenACWY.

V59_50

Description

A phase 3, multicenter, open-label study to evaluate immunogenicity and safety of Novartis meningococcal ACWY conjugate vaccine (MenACWY-CRM) in healthy children, adolescents, and adults in Russia

Methods

Objective(s)

Immunogenicity (all at day 29)

Primary:

- To assess the immunogenicity of a single injection of MenACWY-CRM vaccine as measured by the percentage of subjects with hSBA seroresponse1, directed against N meningitidis serogroups A, C, W, and Y.

Secondary:

- To assess the immunogenicity of a single injection of MenACWY-CRM vaccine as measured by the percentage of subjects with hSBA seroresponse1, directed against N meningitidis serogroups A, C, W, and Y by age group (2-10, 11-17, and 18 years and above).
- To assess the immunogenicity of a single injection of MenACWY-CRM vaccine as measured by hSBA geometric mean titers (GMTs) and by the percentage of subjects with hSBA titer ≥ 1:8, directed against N meningitidis serogroups A, C, W, and Y, overall and by age group.

Safety objectives:

To assess the safety profile following MenACWY-CRM vaccination in terms of percentage and number of subjects with:

- local and systemic reactions reported from study day 1 (day of vaccination) through study day 7 postvaccination;
- all other adverse events (AEs) reported from study day 1 through study day 7 postvaccination;
- serious adverse events (SAEs) and medically attended AEs and AEs resulting in premature withdrawal from study day 1 through study day 29.

Study design

This was a phase 3, multicenter, open-label, single arm study to evaluate immunogenicity and safety of Novartis meningococcal ACWY-CRM conjugate vaccine (MenACWY-CRM) in healthy subjects in Russia from the age of 2 years (≥2 years).

Study population /Sample size

A total of approximately 198 subjects (66 subjects in each age group; ≥2 - ≤10 yrs; ≥11-≤17 yrs; ≥18 yrs) were planned for enrollment into this study. Assuming a 10% dropout rate, this would provide approximately 60 evaluable subjects in each age group. The sample size of approximately 180 evaluable subjects was considered reasonable based on 95% confidence intervals (CIs) of the observed seroresponse.

Diagnosis and Main Criteria for Inclusion and Exclusion:

Inclusion criteria: Male and female subjects, from 2 years of age and above (≥2 years), who were generally in good health, available for all study visits, who and/or whose parent/legally acceptable representative had given written informed consent at the time of enrollment.

Exclusion criteria: Serious, acute, or chronic illnesses, as well as confirmed pregnancies led to subject exclusion. Previous or suspected disease caused by *N meningitidis* or previous immunization with meningococcal vaccine were considered exclusion criteria.

Treatments

All persons received MenACWY-CRM (cross-reacting material) conjugate vaccine Lot #: M11052 (vial-vial presentation).

Outcomes/endpoints

The following immunogenicity endpoints were assessed for serogroups A, C, W, and Y.

- Primary: Percentages of subjects with hSBA seroresponse. Seroresponse is defined as (a) for subjects with a prevaccination hSBA <1:4, a postvaccination hSBA titer ≥1:8 or (b) for subjects with a prevaccination hSBA ≥1:4, an increase in hSBA titer of at least four times the prevaccination titer
- Secondary: hSBA GMTs and percentages of subjects with hSBA ≥1:8.

Solicited local and systemic AEs:

Selected local and systemic AEs reported from days 1 through 7 after vaccine administration

Unsolicited AEs:

- All AEs other than solicited local and systemic AEs from days 1 through 7.
- Serious adverse events (SAEs), medically attended AEs, and AEs resulting in premature withdrawal from days 1 through 29.

Statistical Methods

Definition of populations to be analyzed:

(a) All Enrolled Population: All subjects who had signed an informed consent, undergone screening procedure(s), and had a subject number assigned.

(b) Exposed: All enrolled subjects who actually received study vaccination.

(c) Full Analysis Set (FAS) population6, Immunogenicity: This population was defined by serogroup. All subjects in the exposed population who provided one evaluable serum samples whose assay results were available for at least one serogroup at baseline and at day 29.

(d) Per Protocol (PP) Population, Immunogenicity: This population was to be defined by serogroup. All subjects in the FAS who provided evaluable serum samples whose assay results were available for at least one serogroup on day 1 and on day 29 and had no major protocol violations.

Immunogenicity analysis: There was no statistical hypothesis related to the objectives to be tested. Endpoints for each serogroup were descriptively reported for the overall study population and by age group. For each of the serogroups in the vaccine, the numbers, percentages, and 95% CI of the percentages of subjects who have achieved seroresponse were reported. The numbers, percentages, and 95% CI of the percentages of subjects with pre- and post-vaccination hSBA ≥ 1:8 were also summarized. Pre- and postvaccination GMTs and their associated 95% CIs were presented for each serogroup overall and by age group.

Safety analysis: The number and percentage of subjects with the following reports was calculated:

- Solicited local and systemic adverse events reported during days 1 through 7 across age groups– 2 through 3 years (≥2 to ≤3 years), 4 through 5 years (≥4 to ≤5 years), 2 through 5 years (≥2 to ≤5 years), 6 through 10 years (≥6 to ≤10 years), 11 through 17 years (≥11 to ≤17 years), 18 years and above (≥18 years) and also overall summary for 6 years and above (≥6 years).
- All AEs occurring during days 1 through 7 after vaccination across age groups 2 through 10 years (≥2 to ≤10 years), 11 through 17 years (≥11 to ≤17 years), 18 years and above (≥ 18 years) and overall summary for 2 years and above (≥2 years). ▫ all SAEs and medically attended AEs and premature withdrawals due to AEs, occurring during days 1 through 29.

Results

Recruitment / Number analysed

Date of first enrollment: 14 NOV 12; Date of last visit: 19 MAR 13

The primary analysis population for immunogenicity was the Full Analysis Set (FAS). For assessing the robustness of results, the immunogenicity analyses on the primary and secondary endpoints was also assessed on the Per Protocol Set (PPS). Out of the total 198 subjects, 197 (99%) subjects were vaccinated with the study vaccine. One subject (01006) from 2-10 years age group was withdrawn from the study at visit 1 due to withdrawal of consent and did not receive study vaccination

The FAS included 97% of the enrolled subjects (193 subjects). One subject (01006) was excluded from day 1 and day 29 FAS due to withdrawal of consent at visit 1. Additionally 4 subjects (03011, 04012, 05034, 05062) were excluded from day 29 FAS as there was no blood draw analyzed for these subjects, therefore the postvaccination hSBA results were not available. The PPS included 92% of enrolled subjects. A total of 16 subjects (8%) had major protocol deviations and were excluded from PP immunogenicity analysis. Most common reasons for major protocol deviations were that the blood draw was performed outside the protocol specified window (in 5% of subjects) and samples at visit 2 were not analyzed for 4 subjects (2%) (subjects 03011, 04012, 05034 and 05062) for serogroups A, C, W and Y.

Baseline data

The mean age of the overall study population was 19.6 (+15.9) years and a higher percentage of females were enrolled than males (55% versus 45%).

The mean age of the 2 through 10 years age group was 6 (+2.7) years and a slightly higher percentage of females were enrolled than the males (53% versus 47%). The mean age of 11 through 17 years age group was 13.8 (+2.1) years and a higher percentage of males were enrolled than the females (56% versus 44%). The mean age of the ≥18 years age group was 38.8 (+12.5) years and majority of enrolled subjects were females (67% versus 33% males).

The demographic and baseline characteristics of the FAS and PPS were similar to the enrolled set.

Table 11.2-1: Demography and Other Baseline Characteristics of Subjects Receiving MenACWY-CRM – All Enrolled Set

	Overall	By Age Group		
	≥2 years	≥2-≤10 years	≥11-≤17 years	≥18 years
	N=198	N=66	N=66	N=66
Age (years):	19.6±15.9	6±2.7	13.8±2.1	38.8±12.5
Gender				
Male	90 (45%)	31 (47%)	37 (56%)	22 (33%)
Female	108 (55%)	35 (53%)	29 (44%)	44 (67%)
Race:				
White	198 (100%)	66 (100%)	66 (100%)	66 (100%)
Weight (kg)	51.33±23.41	25.65±10.23	55.07±13.09	73.27±14.58
Height (cm)	152.0±25.9	121.6±19.2	164.3±12.5	170.2±8.6
Met entry criteria	197 (99%)	66 (100%)	66 (100%)	65 (98%)

Source: Table 14.1.1.3
Categorical parameter: N (%), noncategorical parameter: Mean±SD.
Abbreviations: SD=Standard Deviation.

Efficacy results

In the overall study cohort, against **serogroup A**, 91% of subjects had a prevaccination hSBA < 1:4 (176 subjects) and 88% of these subjects achieved a postvaccination hSBA ≥1:8. There were 9% of subjects (17 subjects) with a prevaccination hSBA ≥1:4 and 9 subjects (53%) had at least a 4-fold increase. Against **serogroup C**, 66% of subjects (126 subjects) had a prevaccination hSBA< 1:4 and 77% of these subjects achieved a postvaccination hSBA≥ 1:8. There were 34% of subjects (66 subjects) with a prevaccination hSBA≥ 1:4 and 45 of these subjects (68%) had at least a 4 fold increase. Overall, 74% of subjects showed seroresponse against serogroup C, at 4 weeks after one dose of MenACWY conjugate vaccine. Against **serogroup W**, 42% of subjects had a prevaccination hSBA< 1:4 and 93% of these subjects achieved a postvaccination hSBA≥ 1:8. There were 58% of subjects (112 subjects) with a prevaccination hSBA≥ 1:4 and 37% of these subjects (41 subjects) showed at least a 4 fold increase in hSBA titers. Overall, 60%of subjects showed seroresponse against serogroup W, at 4 weeks after one dose of MenACWY conjugate vaccine. Against **serogroup Y**, 79% of subjects had a prevaccination hSBA< 1:4 and 87% of these subjects achieved a postvaccination hSBA≥ 1:8. There were 21% of subjects (40 subjects) with a prevaccination hSBA≥ 1:4 and 70% of these subjects (28 subjects) showed at least a 4 fold increase in hSBA titers. Overall, 83%of subjects

showed seroresponse against serogroup Y, at 4 weeks after one dose of MenACWY conjugate vaccine (Table 11.4.1-1).

Table 11.4.1-1: Number (Percentages) (95% CI) of Subjects with Seroresponse at Day 29 from Day 1 After MenACWY-CRM Vaccination – FAS

		Overall	By Age Group		
		≥2 years	≥2-≤10 years	≥11-≤17 years	≥18 years
MenA	Baseline hSBA<1:4	155 (88%) (82%-92%) N=176	54 (89%) (78%-95%) N=61	55 (92%) (82%-97%) N=60	46 (84%) (71%-92%) N=55
	Baseline hSBA≥1:4	9 (53%) (28%-77%) N=17	2 (100%) (16%-100%) N=2	3 (60%) (15%-95%) N=5	4 (40%) (12%-74%) N=10
	Overall	164 (85%) (79%-90%) N=193	56 (89%) (78%-95%) N=63	58 (89%) (79%-96%) N=65	50 (77%) (65%-86%) N=65
MenC	Baseline hSBA<1:4	97 (77%) (69%-84%) N=126	36 (71%) (56%-83%) N=51	38 (83%) (69%-92%) N=46	23 (79%) (60%-92%) N=29
	Baseline hSBA≥1:4	45 (68%) (56%-79%) N=66	7 (64%) (31%-89%) N=11	15 (79%) (54%-94%) N=19	23 (64%) (46%-79%) N=36
	Overall	142 (74%) (67%-80%) N=192	43 (69%) (56%-80%) N=62	53 (82%) (70%-90%) N=65	46 (71%) (58%-81%) N=65
MenW	Baseline hSBA<1:4	74 (93%) (84%-97%) N=80	39 (93%) (81%-99%) N=42	18 (95%) (74%-100%) N=19	17 (89%) (67%-99%) N=19
	Baseline hSBA≥1:4	41 (37%) (28%-46%) N=112	6 (30%) (12%-54%) N=20	15 (33%) (20%-48%) N=46	20 (43%) (29%-59%) N=46
	Overall	115 (60%) (53%-67%) N=192	45 (73%) (60%-83%) N=62	33 (51%) (38%-63%) N=65	37 (57%) (44%-69%) N=65
MenY	Baseline hSBA<1:4	131 (87%) (80%-92%) N=151	42 (78%) (64%-88%) N=54	47 (96%) (86%-100%) N=49	42 (88%) (75%-95%) N=48
	Baseline hSBA≥1:4	28 (70%) (53%-83%) N=40	5 (71%) (29%-96%) N=7	10 (63%) (35%-85%) N=16	13 (76%) (50%-93%) N=17
	Overall	159 (83%) (77%-88%) N=191	47 (77%) (65%-87%) N=61	57 (88%) (77%-95%) N=65	55 (85%) (74%-92%) N=65

Source: Table 14.2.1.1.

GMTs and GMRs:

Overall (≥2 years):

In the overall study cohort (≥2 years of age), the baseline hSBA GMT against **serogroup A** was 2.35. At 4 weeks after one dose of MenACWY conjugate vaccine, there was 40-fold increase in hSBA titers against serogroup A. The baseline hSBA GMT against **serogroup C** was 4.07 in the overall age group. At 4 weeks after 1 dose of MenACWY conjugate vaccine there was 14-fold increase in GMTs from baseline. Against **serogroup W** the baseline GMT was 12 in the overall age group. At 4 weeks after 1 dose of MenACWY conjugate vaccine there was 9.33-fold increase in GMTs from baseline. Against

serogroup Y, the baseline GMT was 2.93 in the overall age group. At 4 weeks after 1 dose of MenACWY conjugate vaccine, there was 20-fold increase in GMTs from baseline.

Age group:

Serogroup A: At 4 weeks after vaccination, there was 31-fold and 30-fold increase in GMTs from baseline in the 2 to 10 years and ≥18 years age groups respectively; in the 11 to 17 years age group there was 55-fold increase in GMTs from baseline against serogroup A. **Serogroup C:** At 4 weeks after vaccination, there was 7.16-fold increase in GMTs in 2 to 10 years age group, 12-fold increase in 11 to 17 years age group and 25- fold increase in ≥18 years age group against serogroup C. **Serogroup W**: At 4 weeks after vaccination, there was 11-fold increase in GMTs from baseline in 2 to 10 years and ≥18 years age groups; in the 11 to 17 years age group there was 6.48-fold increase in GMTs against serogroup W. **Serogroup Y**: At 4 weeks after vaccination, there was 11-fold increase in GMTs from baseline in 2 to 10 years age group; in 11 to 17 years age group there was 19-fold increase in GMTs from baseline and in ≥18 years age group there was 29-fold increase in GMTs from baseline against serogroup Y.

Table 11.4.1-2: hSBA Geometric Mean Titers (95% CI) at Baseline and After MenACWY-CRM Vaccination and Geometric Mean Ratios (95% CI) – FAS

		Overall	By Age Group		
		≥2 years	≥2-≤10 years	≥11-≤17 years	≥18 years
		N=193	N=63	N=65	N=65
MenA	Day 1 (GMT)	2.35 (2.17-2.55)	2.17 (1.79-2.62)	2.43 (2.01-2.93)	2.61 (2.11-3.23)
	Day 29 (GMT)	93 (73-119)	67 (38-119)	134 (77-233)	76 (41-143)
	Day 29 to Day 1 (GMR)	40 (31-51)	31 (17-55)	55 (31-98)	30 (16-57)
		N=193	N=63	N=65	N=65
MenC	Day 1 (GMT)	4.07 (3.45-4.8)	3.16 (2.18-4.57)	3.59 (2.5-5.15)	6.68 (4.43-10)
	Day 29 (GMT)	59 (43-81) N=192	28 (14-56) N=62	47 (24-92)	112 (52-243)
	Day 29 to Day 1 (GMR)	14 (11-19) N=192	7.16 (3.57-14) N=62	12 (6.02-23)	25 (12-54)
		N=193	N=63	N=65	N=65
MenW	Day 1 (GMT)	12 (9.42-15)	7.93 (4.69-13)	21 (13-36)	13 (7.16-23)
	Day 29 (GMT)	111 (89-139) N=192	94 (56-155) N=62	117 (72-191)	143 (83-248)
	Day 29 to Day 1 (GMR)	9.33 (7.15-12) N=192	11 (5.79-21) N=62	6.48 (3.48-12)	11 (5.47-22)
		N=192	N=62	N=65	N=65
MenY	Day 1 (GMT)	2.93 (2.61-3.28)	3.02 (2.33-3.92)	3.73 (2.89-4.82)	2.74 (2.05-3.66)
	Day 29 (GMT)	58 (46-74)	32 (18-56)	67 (39-115)	80 (43-147)
	Day 29 to Day 1 (GMR)	20 (16-26) N=191	11 (5.92-19) N=61	19 (11-34)	29 (15-54)

Source: Table 14.2.1.3.
Note: The 'N's for each serogroup represent total number of subjects for which the serology results are available.

Against serogroup A, in the overall study cohort (≥2 years) there were 6% subjects with hSBA≥1:8 at baseline. At 4 weeks after MenACWY vaccination there was a significant increase in the percentage of subjects with hSBA≥1:8 against serogroup A (89% of subjects with hSBA≥1:8). Against serogroup C, at baseline 26% of subjects had hSBA≥1:8 from the overall study cohort. At 4 weeks after vaccination, 84% of subjects from the overall age group had hSBA≥1:8 against this serogroup. Against serogroup W, at baseline 57% of subjects from the overall study cohort had hSBA≥1:8. At 4 weeks after vaccination, a large proportion of subjects (97% of subjects) from the overall age group showed hSBA≥1:8 against serogroup W. Against serogroup Y, at baseline, 16% of subjects from the overall study cohort had hSBA≥1:8. At 4 weeks after vaccination, 88% of subjects showed hSBA≥1:8 against this serogroup.

Table 11.4.1-3: Number (Percentages) of Subjects (95%CI) with hSBA ≥1:8 at Baseline and After MenACWY-CRM Vaccination – FAS

		Overall	By Age Group		
		≥2 years	≥2-≤10 years	≥11-≤17 years	≥18 years
		N=193	N=63	N=65	N=65
MenA	Day 1	11 (6%) (3%-10%)	1 (2%) (0.04%-9%)	3 (5%) (1%-13%)	7 (11%) (4%-21%)
	Day 29	171 (89%) (83%-93%)	56 (89%) (78%-95%)	60 (92%) (83%-97%)	55 (85%) (74%-92%)
MenC	Day 1	51 (26%) (20%-33%)	8 (13%) (6%-23%)	11 (17%) (9%-28%)	32 (49%) (37%-62%)
	Day 29	161 (84%) (78%-89%) N=192	47 (76%) (63%-86%) N=62	56 (86%) (75%-93%)	58 (89%) (79%-96%)
MenW	Day 1	110 (57%) (50%-64%)	19 (30%) (19%-43%)	46 (71%) (58%-81%)	45 (69%) (57%-80%)
	Day 29	186 (97%) (93%-99%) N=192	59 (95%) (87%-99%) N=62	64 (98%) (92%-100%)	63 (97%) (89%-100%)
MenY	Day 1	30 (16%) (11%-22%) N=192	6 (10%) (4%-20%) N=62	10 (15%) (8%-26%)	14 (22%) (12%-33%)
	Day 29	168 (88%) (82%-92%) N=192	49 (79%) (67%-88%) N=62	61 (94%) (85%-98%)	58 (89%) (79%-96%)

Source: Table 14.2.1.2.
Note: The 'N' presented for each age group as header represents total number of subjects in FAS for that age group. For some serogroups if the 'N' is different from the FAS, the 'N' is presented within the cell.

CHMP's comments

Again, results are by and large in line with what is known about Menveo. The high % of subjects with baseline titers against MenW is evident in this study too – in particular in persons aged over 11 yrs. In these subjects too you see a reasonable increase in GMTs, in line with the increase seen for MenC, suggesting a good vaccine induced response. Notably, for MenC, MenY and in particular for MenA the response is stronger in subjects aged 11-18 yrs compared to those aged 2-10 years. For MenW the response seems less strong in the 11-18 yr age group.

In general, the immunogenicity findings from the study are in line with what is known already.

Safety results

A total of 99% of the enrolled subjects were included in the safety population

Solicited AEs:

The solicited AEs (local, systemic or other solicited AEs) were reported by 67% of subjects from 2 to 5 years age group and by 64% of subjects from ≥6 years age group. When assessed by age group, the percentage of subjects reporting solicited local, systemic or other solicited AEs in 2 to 3 years, 6 to 10 years, 11 to 17 years and ≥18 years age group was 58% to 67% across these age groups.

Solicited local AEs were reported by 59% of subjects in 2 to 5 years age group and by 53% of subjects in ≥6 years age group. The percentage of subjects reporting solicited AEs in the age groups 2 to 3 years, 6 to 10 years, 11 to 17 years and .18 years was similar to the overall age groups (2 to 5 years and ≥6 years) (47% to 59% across age groups).

Most commonly reported solicited local AE in 2 to 5 years age group was injection site tenderness (41%); a similar percentage of subjects in the 2 to 3 years age group reported tenderness (39%). There were no severe local AEs reported in 2 to 5 years age group.

Most commonly reported solicited local AE in ≥6 years age group was injection site pain (48%) and across the age sub-groups. 42% of subjects from 6 to 10 years, 50% of subjects from 11 to 17 years and 50% of subjects from ≥18 years age groups, reported injection site pain.

Solicited systemic AEs were reported by a low percentage of subjects from 2 to 5 years age group (7%) and 2 to 3 years age group reported 11% of subjects with such AEs. The ≥6 years age group reported 40% of subjects with solicited systemic AEs and across age sub-groups, 32% from 6 to 10 years, 45% from 11 to 17 years and 39% from ≥18 years age groups reported systemic AEs.

Most commonly reported systemic AEs in the ≥6 years age group and in age sub-groups was headache (25% in ≥6 years), malaise (20% in ≥6 years) and myalgia (19% in ≥6 years). Severe systemic AEs were reported by a low percentage of subjects (≤4%).

Unsolicited AEs (including solicited AEs continuing past day 7):

The unsolicited AEs (including solicited AEs continuing past day 7) with onset within days 1 to 7, were reported by 17% of subjects in the overall study cohort (≥2 years of age); most of the unsolicited AEs were solicited local and systemic AEs continuing past 7-day window and these were assessed to be at least possibly related to the study vaccination (10%). Medically attended AEs were reported by 4% of subjects in the overall study cohort and across age sub-groups 2% to 8% subjects reported medically attended AEs. The most commonly reported unsolicited AEs by subjects in 2 to 10 years age group were rhinitis (8%), oropharyngeal pain (3%) and nasopharyngitis (3%). The 11 to 17 years age group commonly reported injection site swelling (5%), injection site pain (3%) and injection site erythema (3%). The ≥18 years age group commonly reported injection site induration (6%) and other injection site AEs such as erythema (5%), pain (3%), and pruritus (3%).

Deaths, serious adverse events or other significant adverse events

No deaths were reported in the study. None of the subjects reported SAEs and there were no premature withdrawals due to AEs.

CHMP's comments

The incidence of AEs is in line with other studies – there is no new safety signal.

V59P14E1

Description

A Phase 3b, Open-Label, Controlled, Multicenter Study to Evaluate the Persistence Of Antibody Responses Among Children Who Previously Received Novartis MenACWY Conjugate Vaccine, conducted in US.

CHMP's comments

Note that the 40 month CSR has been reviewed in context of variation II-18.

V59P14E1 evaluated persistence in children 40 months of age who received 4 doses at 2, 4, 6 and 12 months or either 1 or 2 doses between 12-18 months. Among subjects who received 4 doses rates for hSBA titer ≥8 at 40 months were 10% for A, 34% for C, 76% for W and 67% for Y. Among those who received 1-2 doses rates were 35% for A, 51% for C, 83% for W and 71% for Y.

Methods

Objective(s)

Immunogenicity Objectives:

Primary

▫ To evaluate the persistence of the antibody response in children of 40 and 60 months of age previously vaccinated with MenACWY in study V59P14, as measured by percentage of subjects with human Serum Bactericidal Assay (hSBA) titers ≥1:8 directed against N meningitidis serogroups A, C, W-135, and Y.

Secondary

▫ To evaluate the persistence of the antibody response in children of 40 and 60 months of age previously vaccinated with MenACWY in study V59P14, as measured by the percentage of subjects with hSBA titers ≥1:4 and hSBA geometric mean titers (GMTs) directed against N meningitidis serogroups A, C, W-135, and Y.

▫ To evaluate the functional antibody levels in children of 40 and 60 months of age who were not previously vaccinated with meningococcal vaccine, as measured by percentage of subjects with hSBA titers ≥ 1:4, percentage of subjects with hSBA titers ≥1:8, and hSBA GMTs directed against N meningitidis serogroups A, C, W-135 and Y.

▫ To evaluate the antibody response of MenACWY given at 60 months of age in children who had previously received at least one dose of Novartis MenACWY vaccine in study V59P14 compared to the antibody response to one dose of MenACWY in meningococcal vaccine-naive subjects, as measured by percentage of subjects with seroresponse, the percentage of subjects with hSBA titers ≥1:8, and the percentage of subjects with hSBA titers ≥1:4 directed against N meningitidis serogroups A, C, W-135, and Y, at 1 month1 postvaccination.

Safety Objectives:

▫ To assess the safety and tolerability of a booster dose of MenACWY in subjects who were previously vaccinated with MenACWY.

▫ To assess the safety and tolerability of a single dose of MenACWY in meningococcal vaccine naive subjects 60 months of age.

Study design

This was a phase 3b, multicenter, open-label, controlled study. All US sites participating in the V59P14 trial that had adequate enrollment were approached to participate in this extension study. Subjects from the parent V59P14 study who received either 4 doses of MenACWY (ACWY-42) or 1 or 2 doses of

MenACWY (ACWY-23), were included in this extension study and administered a booster dose of MenACWY at 60 months of age.

Subjects in the ACWY-4 group received a primary vaccination schedule of 3 doses 2 months apart (2, 4 and 6 months of age) followed by a fourth dose at 12 or 13 months. Subjects in the ACWY-2 group received the first dose at 12 or 13 months and the second dose at 15 months of age or a single dose at 18 months. A group of naive subjects (Naive404 and Naive605), age-matched to the subjects in the ACWY-4 and ACWY-2 groups, were enrolled at visit 9 (40 months of age) and visit 10 (60 months of age), respectively and served as a reference for immunogenicity analyses.

Study population /Sample size

Subjects who participated in the V59P14 trial were recruited for this extension study.

Target enrollment for this extension study was 500 subjects. A total of approximately 400 subjects who participated in study V59P14 were to be enrolled (ACWY-4 and ACWY-2) at 40 and 60 months of age. Additionally, a total of approximately 50 naïve subjects 40 months of age (Naive40) and 60 months of age (Naive60) were to be recruited age-matched with ACWY-4 and ACWY-2 at visit 9 and 10, respectively.

Children eligible to be enrolled in the study were those whose parents provided written informed consent, and who were generally in good health based on the clinical judgment of the investigators. ACWY-4 and ACWY-2 subjects should have participated in the original V59P14 study and have been 40±3 months of age at the time of the 40-month visit (visit 9) and 60±3 months of age at the time of the 60-month visit (visit 10).

Naive 40 and Naive60 subjects were healthy, meningococcal vaccine-naive children aged 40±3 months (visit 9) or 60±3 months (visit 10), respectively, at the time of enrollment.

Serious, acute, or chronic illnesses were reasons for exclusion. Other exclusion criteria included the following:

▫ Subjects who received any vaccine (excluding influenza vaccines) 28 days preceding the enrollment visit. Influenza vaccines (including FluMist®) were excluded for the 14 days prior to the enrollment visit.

▫ Subjects who received any meningococcal vaccine since birth (Naive60) or last study vaccination in the V59P14 trial (ACWY-4 and ACWY-2).

Treatments

Novartis MenACWY [Lot Numbers: (vial/prefilled syringe; PFS) Lot no. 091601A (expiry date April, 2013); (vial/vial) Lot no. M11016 (expiry date August, 2012)] was obtained by extemporaneous mixing just before injection of the lyophilized MenA component with the liquid MenCWY component. One 0.5 mL dose of MenACWY was administered by intramuscular (IM) injection in the left deltoid.

Outcomes/endpoints

Immunogenicity Endpoints:

Primary

▫ Percentages of subjects with hSBA titers ≥1:8 for serogroups A, C, W-135, and Y.

Secondary

▫ Percentages of subjects with hSBA titers ≥1:4 for serogroups A, C, W-135, and Y;

▫ hSBA GMTs.

Safety Endpoints

▫ The percentages of subjects with solicited local and systemic AEs within 7 days after vaccination with MenACWY.

▫ The percentages of subjects with unsolicited AEs within 7 days after vaccination with MenACWY and SAEs, medically attended AEs, and AEs resulting in premature withdrawal for 28 days after vaccination at 60 months (from visit 10 through visit 11).

Statistical Methods

There is no statistical hypothesis associated with the immunogenicity objective. All analyses are descriptive. The primary analysis was performed on the per protocol set (PPS).

Primary measures of immunogenicity:

Percentages of subjects with hSBA .1:8 and associated 2-sided 95% Clopper-Pearson confidence intervals (CIs) were computed for each serogroup and for each vaccination group and visit. There is no formal statistical hypothesis associated with this endpoint.

Secondary measures of immunogenicity:

Persistence at 40 and 60 months of age in subjects previously vaccinated with MenACWY as infants or toddlers in study V59P14. The percentages of subjects with hSBA titer ≥1:4 against N. meningitidis serogroups A, C, W-135 and Y and associated 2 sided 95% Clopper- Pearson CIs were calculated and presented by vaccine group. For subjects in the Naive60 group, the percentages of subjects with hSBA ≥1:8 were also calculated.

Geometric mean titers (GMT) at the three timepoints (visits 9, 10, 11) were calculated for each serogroup and for each vaccine group with available data at the visits. The hSBA titers were logarithmically transformed (base10) and GMTs and associated 2-sided 95% CIs computed by exponentiating (base10) the corresponding log-transformed means and 95% confidence limits for the log-transformed means. These were obtained from an analysis of variance (ANOVA) with vaccine group and center as effects in the model. Titers below the limit of detection were set to half that limit for the purposes of the analysis. Titers reported as being above a cutoff value, were set to that cutoff value in the analyses.

Immune response at 1 month after vaccination with MenACWY

The percentage of subjects in ACWY-4, ACWY-2 and Naive60 groups with hSBA≥1:8, hSBA≥1:4 against *N. meningitidis* serogroups A, C, W and Y and associated two sided 95% Clopper- Pearson confidence interval (CIs) were calculated at baseline (Visit 10) and 1 month after vaccination (Visit 11) for each serogroup and were presented by vaccine group

Geometric Mean Titer (GMT) at the three timepoints (visits 9, 10, 11) was calculated for each serogroup and for each vaccine group with available data at the visit. The hSBA titers were logarithmically transformed (base10).

Results

Recruitment / Number analysed

Date of first enrollment: July 26, 2010

Date of last visit: April 23, 2013

A total of 335 subjects from the parent V59P14 were enrolled in the extension study at the 40 month time point, including 214 subjects in the ACWY-4 group and 121 subjects in the ACWY-2 group. A total of 225 subjects remained enrolled at the 60 month time point, including 136 subjects in the ACWY-4 group, and 89 subjects in ACWY-2 group. In the Naive 60 group, 45 subjects age-matched to subjects in the ACWY-4 and ACWY-2 groups were enrolled at the 60 months age visit.

In total, 4 subjects were early terminated from the study between visit 10 and visit 11.

Table 10.1-2: Summary of Study Terminations- Between 60-Month Timepoint (Visit 10) and Study Termination (Visit 11)

	ACWY-4	ACWY-2	Naive60	Total
Enrolled (N) (Visit 10)	136	89	45	270
Completed study	134 (99%)	87 (98%)	45 (100%)	266 (99%)
Premature withdrawals	2 (1%)	2 (2%)	0	4 (1%)
Withdrew consent	0	2 (2%)	0	2 (<1%)
Lost to follow-up	2 (1%)	0	0	2 (<1%)

Source: Table 14.1.1.2.1

Table 11.1-1: Overview of Datasets Analyzed – As Randomized

	ACWY-4 N=214	ACWY-2 N=121	Naive60 N=45
Enrolled	214 (100%)	121 (100%)	45 (100%)
Enrolled population at 60 months	136 (64%)	89 (74%)	45 (100%)
FAS – persistence population			
60-month persistence	136 (64%)	86 (71%)	45 (100%)
60-month post MenACWY immunogenicity	136 (64%)	88 (73%)	45 (100%)
PPS – persistence population			
60-month persistence	123 (57%)	80 (66%)	45 (100%)
60-month post MenACWY immunogenicity	116 (54%)	76 (63%)	45 (100%)

Source: Table 14.1.1.1.
Abbreviations: FAS, Full Analysis Set; PPS, Per Protocol Set.

Baseline data

The mean age of subjects at enrollment was 59.7 months, 59.6 months and 60 months in the ACWY-4, ACWY-2 and Naive60 groups, respectively (Table 11.2-1). There were more males than females in both the ACWY-4 (53% and 47%, respectively) and ACWY-2 (53% and 47% respectively) vaccine groups.

The Naive60 group had more females (58%) than males (42%). The most commonly reported ethnic origin in all 3 groups was Caucasian (44% to 67% across groups).

Weight and height were not measured at 60 months of age (visit 10) for subjects in ACWY-4 and ACWY-2 groups. Mean weight and height of subjects enrolled in the Naïve 60 group were 20.06 kg and 110.71 cm, respectively (Table 11.2-1).

Table 11.2-1: Demographic and Other Baseline Characteristics – Enrolled Population at 60 Months

	ACWY-4 N=136	ACWY-2 N=89	Naive60 N=45
Age at visit 10 (months):	59.7±2.2	59.6±2.4	60.0±1.7
Sex:			
Male	72 (53%)	47 (53%)	19 (42%)
Female	64 (47%)	42 (47%)	26 (58%)
Ethnic origin:			
Asian	12 (9%)	6 (7%)	7 (16%)
Black	14 (10%)	6 (7%)	5 (11%)
Caucasian	80 (59%)	60 (67%)	20 (44%)
Hispanic	22 (16%)	11 (12%)	7 (16%)
Other	8 (6%)	6 (7%)	6 (13%)
Weight (kg):	-	-	20.06±3.08
Height (cm):	-	-	110.71±4.84
Months since last vaccination	47.1 (±2.3) (N=132)	43.1 (±3.4) (N=88)	-

Source: Table 14.1.1.3.1.1; Table 14.1.1.5.1
Categorical parameters: N (%); non-categorical parameters: Mean±Std.
Subject 35/337 did not meet the age eligibility criterion at the 40-month visit and is excluded from the 40 month PPS. However, this subject did meet the age criterion at the 60-month visit and is included in the 60 month PPS (Appendix 16.2.2.2).

Efficacy results

The percentages of subjects with hSBA ≥ 1:8 against 4 serogroups at 60 months of age are presented in Table 11.4.1-1.

Specifically, for groups ACWY-2, ACWY-4, and Naive60, the percentages of subjects with hSBA ≥ 1:8 against serogroup A were 25%, 6% and 2%, respectively; 43%, 27% and 22% for serogroup C; 74%, 69%, and 40% for serogroup W-135; and 69%, 56%, and 25% for serogroup Y.

Antibody levels against serogroups W and Y were higher for both groups than background rates of bactericidal antibodies in age-matched naive control (Naive60). For serogroups A and C, antibody levels were higher than those of naive control (Naive60) for subjects who had received 1 or 2 doses of MenACWY (ACWY-2) in the parent study. Among subjects who received the 4-dose infant series in the parent study (ACWY-4), antibody levels against serogroups A and C were generally only slightly higher than those of naive control (Naive60).

Table 11.4.1-1: Number (%) (95% CI) of Subjects with hSBA ≥ 1:8 at 60 Months of Age - PPS 60- Month Persistence

Serogroup	ACWY-4	ACWY-2	Naive60
	N=123	N=80	N=45
MenA	7 (6%) (2%-11%)	20 (25%) (16%-36%)	1 (2%) (0.056%-12%)
	N=123	N=80	N=45
MenC	33 (27%) (19%-36%)	34 (43%) (32%-54%)	10 (22%) (11%-37%)
	N=121	N=78	N=45
MenW-135	83 (69%) (60%-77%)	58 (74%) (63%-84%)	18 (40%) (26%-56%)
	N=122	N=80	N=44
MenY	68 (56%) (46%-65%)	55 (69%) (57%-79%)	11 (25%) (13%-40%)

Source: Table 14.2.1.1.1.

Abbreviations: PPS, Per Protocol Set; CI, Confidence Interval; hSBA, human Serum Bactericidal Assay

CHMP's comments

Note that in the ACWY-4 group the antibody levels are not much different to those in the naïve group. Similarly for MenC, where 95% CIs also overlap.

The antibody response was assessed at 2,7,12,13, 40 and 60 months of age in subjects for whom serological data from the V59P14 study were available as measured by the percentages of subjects with hSBA ≥ 1:8 and GMTs. The persistence of bactericidal antibodies in children 40 and 60 months of age previously vaccinated with MenACWY was also evaluated as measured by hSBA GMTs and percentage of subjects with hSBA titers ≥1:4 against N meningitidis serogroups A, C, W-135, and Y.

The antibody response of MenACWY given at 60 months of age in children who had previously received at least one dose of Novartis MenACWY vaccine in study V59P14 was compared to the antibody response to one dose of MenACWY in meningococcal vaccine-naive subjects. This was measured by percentage of subjects with seroresponse, percentage of subjects with hSBA titers „d 1:8, and percentage of subjects with hSBA titers ≥ 1:4 directed against N meningitidis serogroups A, C, W-135, and Y at 28 days postvaccination.

The results are presented in the tables below.

60-Month Persistence:

Table 11.4.1-2: Number (%) (95% CI) of Subjects with hSBA ≥ 1:8 at 2, 7, 12, 13, 40, and 60 Months of Age for Subjects in Groups with Serological Data Available from V59P14 – PPS 60-Month Persistence

		ACWY-4		ACWY-2
		US1A	US1B	US2
		N=30	N=25	N=32
MenA	2 months of age	2 (8%) (1%-25%) N=26	0 (0%) (0%-15%) N=23	1 (5%) (0%-23%) N=22
	7 months of age	18 (64%) (44%-81%) N=28	15 (63%) (41%-81%) N=24	0 (0%) (0%-16%) N=21
	12 months of age	3 (11%) (2%-28%) N=28	4 (16%) (5%-36%)	0 (0%) (0%-12%) N=30
	13 months of age	24 (86%) (67%-96%) N=28	3 (13%) (3%-32%) N=24	17 (57%) (37%-75%) N=30
	40 months of age	2 (7%) (1%-22%)	4 (16%) (5%-36%)	10 (31%) (16%-50%)
	60 months of age	2 (7%) (1%-22%)	2 (8%) (1%-26%)	7 (22%) (9%-40%)
		N=30	N=25	N=32
MenC	2 months of age	0 (0%) (0%-13%) N=26	1 (4%) (0%-22%) N=23	1 (5%) (0%-23%) N=22
	7 months of age	25 (89%) (72%-98%) N=28	23 (96%) (79%-100%) N=24	0 (0%) (0%-16%) N=21
	12 months of age	14 (50%) (31%-69%) N=28	11 (44%) (24%-65%)	1 (3%) (0.084%-17%) N=30
	13 months of age	27 (96%) (82%-100%) N=28	8 (33%) (16%-55%) N=24	24 (80%) (61%-92%) N=30
	40 months of age	8 (27%) (12%-46%)	8 (32%) (15%-54%)	18 (56%) (38%-74%)
	60 months of age	6 (20%) (8%-39%)	6 (24%) (9%-45%)	18 (56%) (38%-74%)
		N=30	N=25	N=32
MenW-135	2 months of age	1 (4%) (0.097%-20%)	2 (9%) (1%-28%)	1 (5%) (0%-23%)

		ACWY-4		ACWY-2
		US1A	US1B	US2
		N=26	N=23	N=22
	7 months of age	26 (93%) (76%-99%) N=28	20 (83%) (63%-95%) N=24	0 (0%) (0%-16%) N=21
	12 months of age	19 (68%) (48%-84%) N=28	18 (72%) (51%-88%)	1 (3%) (0.084%-17%) N=30
	13 months of age	27 (96%) (82%-100%) N=28	13 (54%) (33%-74%) N=24	15 (50%) (31%-69%) N=30
	40 months of age	21 (70%) (51%-85%)	17 (68%) (46%-85%)	28 (88%) (71%-96%)
	60 months of age	18 (60%) (41%-77%)	17 (68%) (46%-85%)	25 (78%) (60%-91%)
		N=30	**N=25**	**N=32**
	2 months of age	2 (8%) (1%-25%) N=26	1 (4%) (0%-22%) N=23	0 (0%) (0%-15%) N=22
	7 months of age	26 (93%) (76%-99%) N=28	19 (79%) (58%-93%) N=24	0 (0%) (0%-16%) N=21
MenY	12 months of age	16 (57%) (37%-76%) N=28	13 (52%) (31%-72%)	1 (3%) (0.084%-17%) N=30
	13 months of age	27 (96%) (82%-100%) N=28	10 (42%) (22%-63%) N=24	15 (50%) (31%-69%) N=30
	40 months of age	16 (53%) (34%-72%)	15 (60%) (39%-79%)	26 (81%) (64%-93%)
	60 months of age	15 (50%) (31%-69%)	12 (48%) (28%-69%)	26 (81%) (64%-93%)

Source: Table 14.2.1.1.3.
Abbreviations: CI, Confidence Interval; hSBA, human Serum Bactericidal Assay; PPS, Per Protocol Set.

Immune response to MenACWY

Table 11.4.1-5: Number (%) (95% CI) of Subjects with Seroresponse, hSBA ≥1:8, hSBA ≥1:4, and Vaccine Group Differences, and hSBA GMTs (95% CI) and Vaccine Group Ratios, at 28 Days After Vaccination at 60 Months of Age– PPS Post MenACWY

					Vaccine Group Differences[a]/Ratios[b]		
		ACWY-4	ACWY-2	Naive60	ACWY-4 vs ACWY-2	ACWY-4 vs Naive60.	ACWY-2 vs Naive60
Men A		N=116	N=76	N=45			
	Seroresponse[c]	112 (97%) (91%,99%)	73 (96%) (89%,99%)	39 (87%) (73%,95%)	0% (-5%,8%)	10% (2%,23%)	9% (0%,23%)
	hSBA ≥1:8	112 (97%) (91%,99%)	74 (97%) (91%,100%)	39 (87%) (73%,95%)	-1% (-6%,6%)	10% (2%,23%)	11% (2%,24%)
	hSBA ≥1:4	112 (97%) (91%,99%)	74 (97%) (91%,100%)	40 (89%) (76%,96%)	-1% (-6%,6%)	8% (0%,20%)	8% (0%,21%)
	GMT	159 (120,210)	330 (237,459)	47 (30,73)	0.48 (0.32,0.73)	3.38 (2.04,5.58)	7.01 (4.1,12)
Men C		N=115	N=75	N=45			
	Seroresponse[c]	100 (87%) (79%,93%)	65 (87%) (77%,93%)	33 (73%) (58%,85%)	0% (-9%,11%)	14% (1%,29%)	13% (-1%,29%)
	hSBA ≥1:8	110 (96%) (90%,99%)	74 (99%) (93%,100%)	38 (84%) (71%,94%)	-3% (-9%,3%)	11% (2%,25%)	14% (5%,28%)
	hSBA ≥1:4	112 (97%) (93%,99%)	75 (100%) (95%,100%)	39 (87%) (73%,95%)	-3% (-7%,2%)	11% (3%,24%)	13% (6%,26%)
	GMT	195 (142,267)	569 (392,826)	44 (27,71)	0.34 (0.21,0.55)	4.48 (2.55,7.85)	13 (7.15,24)
MenW-135		N=104	N=70	N=44			
	Seroresponse[c]	103 (99%) (95%,100%)	70 (100%) (95%,100%)	25 (57%) (41%,72%)	-1% (-5%,4%)	42% (29%,57%)	43% (30%,58%)
	hSBA ≥1:8	104 (100%) (97%,100%)	70 (100%) (95%,100%)	39 (89%) (75%,96%)	0% (-4%,5%)	11% (5%,24%)	11% (5%,24%)

					Vaccine Group Differences[a]/Ratios[b]		
		ACWY-4	ACWY-2	Naive60	ACWY-4 vs ACWY-2	ACWY-4 vs Naive60.	ACWY-2 vs Naive60
	hSBA ≥1:4	104 (100%) (97%,100%)	70 (100%) (95%,100%)	40 (91%) (78%,97%)	0% (-4%,5%)	9% (4%,21%)	9% (4%,21%)
	GMT	1950 (1408,2701)	1645 (1124,2407)	37 (23,61)	1.19 (0.74,1.91)	52 (30,92)	44 (24,81)
Men Y		N=111	N=74	N=44			
	Seroresponse[c]	109 (98%) (94%,100%)	73 (99%) (93%,100%)	23 (52%) (37%,68%)	0% (-5%,6%)	46% (32%,60%)	46% (32%,61%)
	hSBA ≥1:8	111 (100%) (97%,100%)	74 (100%) (95%,100%)	32 (73%) (57%,85%)	0% (-3%,5%)	27% (16%,42%)	27% (16%,42%)
	hSBA ≥1:4	111 (100%) (97%,100%)	74 (100%) (95%,100%)	35 (80%) (65%,90%)	0% (-3%,5%)	20% (11%,35%)	20% (11%,35%)
	GMT	1089 (812,1461)	922 (659,1290)	18 (11,28)	1.18 (0.78,1.79)	61 (37,100)	51 (30,88)

Source: Table 14.2.1.4.1; Table 14.2.1.5; Table 14.2.1.6; Table 14.2.1.7.

Summary of main immunogenicity results

60-Month Persistence:

▫ The observed percentages of subjects with hSBA ≥1:8 at 60-months of age in the ACWY-4, ACWY-2 and Naive60 groups were: 6%, 25% and 2%, respectively, for serogroup A, 27%, 43% and 22%, respectively, for serogroup C, 69%, 74% and 40%, respectively, for serogroup W-135, and 56%, 69% and 25%, respectively, for serogroup Y.

▫ The observed percentages of subjects with hSBA ≥1:4 at 60-months of age in the ACWY-4, ACWY-2 and Naive60 groups were: 9%, 33% and 2%, respectively, for serogroup A, 46%, 60% and 33%,

respectively, for serogroup C, 74%, 83% and 42%, respectively, for serogroup W-135, and 65%, 74% and 25%, respectively, for serogroup Y (Table 11.4.1-4).

▫ Geometric mean titers at 60-months of age in the ACWY-4, ACWY-2 and Naive60 groups were: 2.27, 3.74 and 2.14, respectively, for serogroup A, 5.17, 9.26 and 3.87, respectively, for serogroup C, 17, 20 and 6.63, respectively for serogroup W-135, and 11, 14 and 4.1, respectively, for serogroup Y (Table 11.4.1-4).

Immune response to MenACWY:

▫ The percentages of subjects in the ACWY-4, ACWY-2 and Naive60 groups with seroresponse at 28 days after the MenACWY-CRM vaccination at 60-months of age were: 97%, 96% and 87%, respectively, for serogroup A, 87%, 87% and 73%, respectively, for serogroup C, 99%, 100% and 57%, respectively, for serogroup W, and 98%, 99% and 52%, respectively, for serogroup Y. The vaccine group difference was significantly higher than 0% for all serogroups for the ACWY-4 minus Naive60 comparison and for serogroups W and Y for the ACWY-2 minus Naive60 comparison (lower limit of the 2-sided 95% CI for the vaccine group difference was greater than 0%; Table 11.4.1-5).

▫ The observed percentages of subjects in the ACWY-4, ACWY-2 and Naive60 groups with hSBA ≥1:8 at 28 days after the MenACWY-CRM vaccination at 60-months of age were: 97%, 97% and 87%, respectively, for serogroup A, 96%, 99% and 84%, respectively, for serogroup C, 100%, 100% and 89%, respectively, for serogroup W, and 100%, 100% and 73%, respectively, for serogroup Y. The vaccine group difference was significantly higher than 0% for all serogroups for both the ACWY-4 minus Naive60 comparison as well as for the ACWY-2 minus Naive60 comparison (lower limit of the 2-sided 95% CI for the vaccine group difference was greater than 0%; Table 11.4.1-5).

▫ The observed percentages of subjects in the ACWY-4, ACWY-2 and Naive60 groups with hSBA ≥1:4 at 28 days after the MenACWY-CRM vaccination at 60-months of age were: 97%, 97% and 89%, respectively, for serogroup A, 97%, 100% and 87%, respectively, for serogroup C, 100%, 100% and 91%, respectively, for serogroup W, and 100%, 100% and 80%, respectively, for serogroup Y. The vaccine group difference was significantly higher than 0% for serogroups C, W and Y for both the ACWY-4 minus Naive60 comparison as well as for the ACWY-2 minus Naive60 comparison (lower limit of the 2-sided 95% CI for the vaccine group difference was greater than 0%; Table 11.4.1-5).

▫ Geometric mean titers in the ACWY-4, ACWY-2 and Naive60 groups at 28 days after the MenACWY vaccination at 60-months of age were: 159, 330 and 47, respectively, for serogroup A, 195, 569 and 44, respectively, for serogroup C, 1950, 1645 and 37, respectively, for serogroup W, and 1089, 922 and 18, respectively, for serogroup Y.

The ratio of the least square GMTs was significantly higher than 1 for all serogroups for both the ACWY-4 vs. Naive60 comparison as well as for the ACWY-2 vs. Naive60 comparison (lower limit of the 2-sided 95% CI for the vaccine group ratio was greater than 1). Additionally, the ratio of the ACWY-4 vs. ACWY-2 least square GMTs was significantly lower than 1 for serogroups A and C (upper limit of the 2-sided 95% CI for the vaccine group ratio was less than 1; Table 11.4.1-5).

CHMP's comments

Antibody persistence is greater among subjects in the MenACWY2 group compared to those who had received the 4-dose infant series – this is likely attributable to the age at when the final dose was received or could reflect the maturity of the immune system at the time of priming. The low

persistence for MenA seen here is in line with earlier observations in other studies and resulted in a warning in the SmPC. Moreover, an update of section 4.2 based upon further persistence data is currently being considered in variation II/42. Note that the MAH indicates that an increasing numbers of publications are suggesting that hSBA need not be an optimal assay for persistence assessment, especially for serogroup A. The greatest difference observed between immunogenicity results using hSBA and rSBA assays. A discrepancy could be attributable to known differences between assays due to differences in target strain susceptibilities for the complement sources (Findlow H, 2009, Poolman JT, 2011).

The response to vaccination with MenACWY is clearly better in those subjects vaccinated previously with MenACWY compared tot the Naive60 group.

As the present data are collected in subjects outside the indication and do not add to what is already known about the vaccine they do not need to be included in the SmPC.

Safety results

All subjects received a single dose of MenACWY on day 1, at approximately 60 months of age. Subjects in group ACWY-4 had previously received 4 doses of MenACWY, at 2, 4, 6 and 12 or 13 months of age; those in study group ACWY-2 had previously received either 2 doses of MenACWY, at 12 and 15 months or at 13 and 15 months of age, or a single dose of MenACWY at 18 months of age. Subjects in study group Naïve-60 had not previously received any MenACWY vaccination. Among all treated subjects, 98% in both the ACWY-4 and ACWY-2 study groups were included in the overall safety set, while 100% of the subjects in the Naive60 group constituted the overall safety set.

Table 12.1-2: Overview of Study Population – As Treated

	ACWY-4 N=210	ACWY-2 N=120	Naive60 N=50
Safety			
Overall safety set	205 (98%)	118 (98%)	50 (100%)
Post MenACWY at 60 months safety set[a]	132 (63%)	87 (73%)	50 (100%)
Solicited safety set			
Solicited safety set (30 minutes)	132 (63%)	87 (73%)	49 (98%)
Solicited safety set (6 hours through day 7)	129 (61%)	83 (69%)	49 (98%)

Source: Table 14.1.1.1.1.

[a] The Post MenACWY at 60 months safety set was used for analyses of unsolicited adverse events.

Local and systemic solicited AEs

The frequencies of subjects who reported solicited AEs in any category were similar between the AWCY-4 and ACWY-2 study groups, and were somewhat higher in the Naive60 group. Among subjects in the ACWY-4, ACWY-2, and Naive60 groups, 62%, 64%, and 76%, respectively, reported any solicited AEs; 52%, 53%, and 59%, respectively, reported any local solicited AEs; and 35%, 31%, and 47%, respectively, reported any systemic solicited AEs. Any other indicator of reactogenicity was reported by 13% to 14% of subjects for all 3 study groups. Severe local AEs were reported by 7% and 11% of subjects in the ACWY-4 and ACWY-2 groups, respectively, versus 14% of subjects in the Naive60 group.

The most commonly reported was pain, in 42%, 40%, and 49% of subjects, respectively. Smaller percentages of subjects reported each of the other local solicited AEs: 20%, 24%, and 27%, respectively, reported erythema and 14%, 17%, and 20%, respectively, reported induration. For each of these local AEs, differences between groups were small, and did not approach statistical significance. None of the subjects reported severe pain. Severe erythema (> 100 mm) was reported by

2 subjects (2%) in the ACWY-4 group, none in the ACWY—2 group, and one in the Naive60 group, while severe induration (> 100 mm) was reported by a single subject in the ACWY-4 group and none of the subjects in the ACWY-2 and Naive60 groups.

The most commonly reported were irritability, reported by 19%, 17%, and 16% of subjects, respectively, and sleepiness, reported by 16%, 11%, and 14% of subjects, respectively. The only other systemic solicited AE reported by > 10% of subjects in either group was change in eating habits, reported by 11%, 6%, and 8% of subjects, respectively. There were no appreciable patterns in the frequencies of AEs among the study groups.

Unsolicited AEs

Previously vaccinated subjects:

From day 1 through day 7 postvaccination, a total of 7%, 8%, and 12% of subjects in the ACWY-4, ACWY-2, and Naive60 study groups, respectively, reported 1 or more unsolicited AEs. The only AEs, by preferred term, reported by more than 2 subjects in any group were pyrexia, in 3 (2%), 1 (1%), and 2 (4%) subjects in the ACWY-4, ACWY-2, and Naive60 groups, respectively, and cough, in 2 (2%), 3 (3%), and 0 subjects in the ACWY-4, ACWY-2, and Naive60 groups, respectively. The only SOCs in which more than 2 subjects in any group reported an AE were “general disorders and administration site conditions” (4 (3%), 2 (2%), and 3 (6%) subjects in the ACWY-4, ACWY-2, and Naive60 groups, respectively), and “respiratory, thoracic and mediastinal disorders”(with 3 (2%), 3 (3%), and 1 (2%) subjects in the 3 groups, respectively), and “infections and infestations” (with 2 (2%), 0 and 3 (6%) subjects in the 3 groups, respectively; Table 12.2.3-2).

The only AE, from day 1 through day 7 postvaccination that was considered at least possibly related to vaccination by more than 1 subject was pyrexia: it was considered at least possibly related in 4 subjects across 3 study groups (Table 12.2.3-2).

From day 8 postvaccination through study termination (nominally 28 days postvaccination), a total of 8%, 13%, and 10% of subjects in the ACWY-4, ACWY-2, and Naive60 study groups, respectively, reported 1 or more unsolicited medically-attended AEs. The only AEs, by preferred term, reported in more than 2 subjects in any study group was conjunctivitis, in 0, 1 (1%), and 3 (6%) subjects in the ACWY-4, ACWY-2, and Naive60 groups, respectively. The only SOCs in which AEs were reported, from day 8 postvaccination through study termination, by more than 2 subjects in any group were “infections and infestations,” reported by 8 (6%), 6 (7%), and 1 (2%) subjects in the ACWY-4, ACWY-2, and Naive60 groups, respectively, “respiratory, thoracic and mediastinal disorders,” reported by 1 (1%), 1 (1%), and 3 (6%) subjects in the 3 groups, respectively, and ”eye disorders,” reported by 0, 1 (1%), and 3 (6%) subjects in the 3 groups, respectively.

Table 12.2.3-2: Numbers (%) of Subjects[a] Reporting All and at Least Possibly Related Unsolicited AEs From Day 1 Through Day 7 After Vaccination – Post MenACWY at 60 Months Safety Set

SOC/PT	All			At Least Possibly Related		
	ACWY-4	ACWY-2	Naive60	ACWY-4	ACWY-2	Naive60
	N=132	N=87	N=50	N=132	N=87	N=50
Any adverse event	9 (7%)	7 (8%)	6 (12%)	5 (4%)	5 (6%)	3 (6%)
Eye disorders	**0**	**0**	**2 (4%)**	**0**	**0**	**1 (2%)**
Astigmatism	0	0	1 (2%)	0	0	0
Conjunctivitis	0	0	1 (2%)	0	0	1 (2%)
Gastrointestinal disorders	**0**	**2 (2%)**	**0**	**0**	**2 (2%)**	**0**
Diarrhoea	0	1 (1%)	0	0	1 (1%)	0
Gingival pain	0	1 (1%)	0	0	1 (1%)	0
Lip swelling	0	1 (1%)	0	0	1 (1%)	0
General disorders and administrative site conditions	**4 (3%)**	**2 (2%)**	**3 (6%)**	**3 (2%)**	**2 (2%)**	**2 (4%)**
Injection site erythema	0	1 (1%)	0	0	1 (1%)	0
Injection site swelling	1 (1%)	0	0	1 (1%)	0	0
Irritability	2 (2%)	0	0	1 (1%)	0	0
Pyrexia	3 (2%)	1 (1%)	2 (4%)	1 (1%)	1 (1%)	2 (4%)
Vessel puncture site pain	0	0	1 (2%)	0	0	0
Infections and infestations	**2 (2%)**	**0**	**3 (6%)**	**1 (1%)**	**0**	**1 (2%)**
Gastroenteritis viral	1 (1%)	0	0	0	0	0
Pharyngitis	1 (1%)	0	0	1 (1%)	0	0
Pneumonia	0	0	1 (2%)	0	0	1 (2%)
Upper respiratory tract infection	0	0	1 (2%)	0	0	0
Viral upper respiratory tract infection	0	0	1 (2%)	0	0	0

SOC/PT	All			At Least Possibly Related		
	ACWY-4	ACWY-2	Naive60	ACWY-4	ACWY-2	Naive60
	N=132	N=87	N=50	N=132	N=87	N=50
Musculoskeletal, connective tissue & bone disorders	**1 (1%)**	**1 (1%)**	**0**	**0**	**1 (1%)**	**0**
Arthralgia	0	1 (1%)	0	0	1 (1%)	0
Growing pains	1 (1%)	0	0	0	0	0
Psychiatric disorders	**2 (2%)**	**0**	**0**	**0**	**0**	**0**
Eating disorder	2 (2%)	0	0	0	0	0
Nervous system disorders	**1 (1%)**	**1 (1%)**	**0**	**0**	**1 (1%)**	**0**
Headache	0	1 (1%)	0	0	1 (1%)	0
Somnolence	1 (1%)	0	0	0	0	0
Respiratory, thoracic and mediastinal disorders	**3 (2%)**	**3 (3%)**	**1 (2%)**	**1 (1%)**	**1 (1%)**	**1 (2%)**
Bronchospasm	0	0	1 (2%)	0	0	1 (2%)
Cough	2 (2%)	3 (3%)	0	0	1 (1%)	0
Oropharyngeal pain	1 (1%)	0	0	0	0	0
Rhinorrhoea	2 (2%)	2 (2%)	0	1 (1%)	1 (1%)	0
Skin and subcutaneous tissue disorders	**1 (1%)**	**0**	**0**	**1 (1%)**	**0**	**0**
Rash vesicular	1 (1%)	0	0	1 (1%)	0	0

There were no deaths or SAEs in this study. No subject withdrew prematurely from the study due to an AE.

Chronic conditions with new onset reported from termination of the parent study (V59P14), at approximately 18 through 21 months of age, through Visit 10 of the current study, at approximately 60 months of age, were recorded for subjects in the ACWY-4 and ACWY-2 groups.

The most commonly reported chronic conditions with new onset in the ACWY-4 and ACWY-2 groups were asthma (13% and 10% of subjects, respectively) and allergic rhinitis (8% and 5%, respectively).

In addition, 3% of subjects in each group reported 'contact dermatitis and other eczema' as a new chronic disease. Other than 'certain adverse effects not elsewhere classified' in the injury and poisoning SOC, no other chronic condition, by preferred term, was reported in more than 2% of subjects in either the ACWY-4 or ACWY-2 group. Among subjects in the Naive60 group, the most commonly reported new chronic conditions, by preferred term, were 'specific delays in development' in 6 subjects (13%), 'personal history of allergy to medicinal agents', asthma and 'certain adverse effects not elsewhere classified', each in 4 subjects (9%), and allergic rhinitis and 'contact dermatitis or other eczema', each in 3 subjects (7%).

The profile of new onset chronic conditions reported by subjects since the end of the parent study V59P14 is consistent with diseases typical for the age group enrolled, suggesting acceptable longterm vaccine safety.

CHMP's comments

No safety concerns were identified during the study. The frequencies of solicited AEs were similar to the previously reported in this age group.

V59_33

Description

This phase III open label, randomized, controlled, multicentre study aimed to evaluate the immunogenicity and safety of four doses of MenACWY when administered concomitantly with routine vaccines to healthy infants at 2, 4, 6 and 12 months of age, conducted in US, Canada and Australia.

Methods

Objective(s)

Primary Immunogenicity Objectives

1. To assess the sufficiency of the immune response following 4 doses of MenACWY vaccine given at 2, 4, 6 and 12 months in healthy infants in terms of the proportion of subjects with an hSBA ≥1:8 at 1 month post vaccination, for each of the four meningococcal vaccine serogroups.

Secondary Immunogenicity Objectives

1. To evaluate the hSBA GMTs after 4 doses of MenACWY at 2, 4, 6 and 12 months against each of the four MenACWY serogroups.

2. To evaluate the proportion of subjects with post vaccination hSBA ≥1:8, fourfold rise, and hSBA GMTs after 3 doses of MenACWY at 2, 4, and 6 months against each of the four MenACWY serogroups.

3. To demonstrate that the immune responses to routine concomitant vaccinations (pneumococcal, IPV, HBV, Hib, DTaP) are non-inferior when given with MenACWY compared with when given without MenACWY.

4. To assess the persistence of MenACWY immune responses at 12 months of age prior to the fourth dose.

5. To evaluate the proportion of subjects with four-fold rise in hSBA at 1 month post 4th dose as compared to the pre-4th dose hSBA against each of the four MenACWY serogroups.

Safety Objectives

To assess the safety of MenACWY when given concomitantly with routine infant vaccines at 2, 4, 6 and 12 months of age (i.e., DTaP, IPV, pneumococcal conjugate, HBV and Hib at 2, 4 and 6 months of age and MMR and pneumococcal conjugate at 12 months of age).

Study design

This was an open label, randomized, controlled, multicentre study. Eligible subjects were randomized at visit 1 to receive either MenACWY and concomitant routine vaccines or routine vaccines only in a 1:1 ratio. Group 1 subjects received four injections of MenACWY plus concomitant routine vaccinations. Group 2 subjects received only routine vaccination through the time of the blood draw at 13 month visit, with one dose of MenACWY given at 18 months of age. An overview of the study design is provided below.

Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Age	**2 months**	**4 months**	**6 months**	**7 months**	**12 months**	**13 months**	**18 months**
Study day (window)	1	**56 days after visit 1** (+/- 7 days)	**56 days after visit 2** (+/- 7 days)	**28 days after visit 3** (-4 to +14 days)	**Day of life 365** (+14 days)	**28 days after visit 5** (-4 to +14 days)	**180 days after visit 5** (+/- 70 days)
Group 1 N=260	**ACWY**	**ACWY**	**ACWY**		**ACWY**		Phone call
	Pentacel Prevnar, HBV	Pentacel Prevnar, HBV[a]	Pentacel Prevnar, HBV		MMR, Prevnar		
	Blood draw			Blood draw	Blood draw	Blood draw	
Group 2 N=260	Pentacel Prevnar, HBV	Pentacel Prevnar, HBV[a]	Pentacel Prevnar, HBV		MMR, Prevnar		Office visit
	Blood draw			Blood draw	Blood draw	Blood draw	ACWY[b]

Study population /Sample size

Health infants (aged 55-89 days at enrolment) who were born after an estimated gestational age ≥37 weeks and a birth weight of ≥ 2.5 kg, without any history of confirmed or suspected disease caused by agents to which vaccination was intended nor with a history of vaccination with vaccines given in study (meningococcal, diphtheria, tetanus, pertussis, polio (IPV), *H. influenzae* type b (Hib) or pneumococcus vaccines).

A total of 520 subjects (260 subjects per group) were planned to be enrolled in the study.

Treatments

Group 1: MenACWY conjugate vaccine along with routine vaccinations intramuscularly at 2, 4, 6 and 12 months of age.

Group 2: Routine vaccinations intramuscularly at 2, 4, 6, and 12 months of age. In addition subjects were offered a dose of MenACWY conjugate vaccine at 18 months as a benefit of participating in this study.

Outcomes/endpoints

Immunogenicity

Primary Endpoint

- Percentage of subjects with an (human serum bactericidal assay) hSBA ≥1:8 against each of the four meningococcal vaccine serogroups

Success criteria:

The lower limit of the two-sided 95% CI for the percentage of subjects with hSBA ≥1:8, at 1 month after the fourth dose, to be greater than 85% for serogroups C, W, or Y and greater than 80% for serogroup A.

Secondary Endpoints:

- Percentage of subjects with at least four-fold rise in hSBA.
- hSBA GMT.
- Routine vaccines were assessed according to the endpoints described in Table 2-2.

Table 2-2: Immunogenicity Endpoints for Routine Vaccine Antigens

Vaccine	Test	Antigen	Key Secondary Endpoint One month after vaccination	Other Secondary Endpoints One month after vaccination
Pentacel (Post 6 month dose)	ELISA	Diphtheria (D)	% Subjects ≥0.1 IU/mL	GMC
	ELISA	Tetanus (T)	% Subjects ≥0.1 IU/mL	GMC
	ELISA	PT FHA Pertactin FIM	GMC Seroresponse: In initially seronegative infants, ≥4 times LLQ; in initially seropositive infants, at least 4 times pre-vaccination concentration	
	ELISA	PRP-T Hib	% Subjects ≥0.15 µg/mL	GMC % Subjects ≥1.0 µg/mL
	NT	Polio Type 1 Polio Type 2 Polio Type 3	% Subjects ≥1:8	GMC
Prevnar® (Post 6 and 12 month dose)	ELISA	PnC 4 PnC 6B PnC 9V PnC 14 PnC 18C PnC 19F PnC 23F	GMC (Post 12 month dose) % Subjects ≥0.35 µg /mL (Post 6 month dose)	% Subjects ≥0.35 µg /mL (Post 12 month dose) GMC (post 6 month dose) % Subjects ≥1.0 µg /mL (post 6 and 12 month dose)
HBV (post 6 month dose)	ELISA	HBsAg	% Subjects ≥10 mIU/mL	GMC

Safety Endpoints

Safety was assessed for all subjects in terms of the frequency and percentage of subjects with reported SAEs or medically attended AEs.

Statistical Methods

Primary Immunogenicity Objectives:

a. The primary immunogenicity objective was to show sufficiency of the immune response as measured by the percentage of subjects with serum bactericidal activity (hSBA) ≥1:8 at 1 month following the fourth dose of MenACWY given to infants at 2, 4, 6 and 12 months of age.

H0: PMenA ≤0. 80 or PMenC ≤0.85 or PMenW ≤0.85 or PMenY ≤0.85

H1: PMenA >0.80 and PMenC >0.85 and PMenW >0.85 and PMenY >0.85

Where PMenA, C, W, or Y was the proportion of subjects with hSBA ≥1:8 at 1 month following the fourth dose of MenACWY. The study was considered a success if the lower limit of the 95% CI for each serogroup met the levels as specified above.

Key Secondary Immunogenicity Objectives:

a. The null hypothesis associated with the pertussis non-inferiority objective was that for either PT, FHA, pertactin, or FIM, the lower limit of the two-sided 95% CI for the ratio of the GMCs (GMCMenACWY +Pentacel / GMCPentacel) at 1 month after the 6-month vaccination (third dose) was less than or equal to 0.67.

H0: GMCMenACWY +Pentacel / GMCPentacel ≤0.67

H1: GMCMenACWY +Pentacel / GMCPentacel >0.67

The other key secondary endpoint for the pertussis antigens non-inferiority assessments was the percentage of subjects with seroresponse at 1 month after the 6-month vaccination.

H0: PMenACWY+Pentacel – PPentacel ≤-10%

H1: PMenACWY+Pentacel – PPentacel >-10%

b. The null hypothesis associated with the pneumococcal non-inferiority objective was that for any of the seven serotypes in Prevnar/Prevenar, the lower limit of the two-sided 95% CI for the ratio of the GMCs (GMCMenACWY + Prevnar / GMCPrevnar) at 1 month after the 12-month vaccination (fourth dose) was less than or equal to 0.50.

H0: GMCMenACWY + Prevnar / GMCPrevnar ≤0. 50

H1: GMCMenACWY + Prevnar / GMCPrevnar >0.50

The other key secondary endpoint for the pneumococcal non-inferiority assessments was the percentage of subjects with antibody level ≥0.35 µg/mL at 1 month after dose 3.

H0: PMenACWY+Prevnar – PPrevnar ≤-10%

H1: PMenACWY+Prevnar – PPrevnar >-10%

c. The null hypothesis associated with other key secondary non-inferiority immunogenicity objectives was that, for Hib, diphtheria, tetanus, poliovirus and HBV antigens administered with and without MenACWY, the lower limit of the two-sided 95% CI for the difference between the groups (PRoutine

Vaccine + MenACWY minus PRoutine Vaccine) in the percentage of subjects with antibody response greater than or equal to the antigen-specific cut-off level was ≤-10% (-5% for the polio antigens)

H0 PRoutine Vaccine + MenACWY – PRoutine Vaccine ≤-Δ%

H1 PRoutine Vaccine + MenACWY – PRoutine Vaccine >-Δ%

Where -Δ% is -5% for polio antigens and -10% for all others.

The primary and secondary objectives were based on the PP populations which included subjects who received all vaccinations, provided blood draws within a pre-specified window, and had no major protocol deviations. The primary objective was also assessed using the modified intent to treat (MITT) population. Subjects who were exposed but excluded from the per protocol analyses for immunogenicity were still evaluable for safety.

To address the multiplicity issue the non-inferiority testing was performed sequentially.

Results

Recruitment / Number analysed

A total of 529 subjects were enrolled and were randomized in a 1:1 ratio to receive either MenACWY concomitantly with routine vaccines (N=258) or routine vaccines alone (N=271). A total of 525 (255+270) subjects were analyzed for safety, 411 (202+209) subjects were included in infant per protocol (PP) analysis and 352 (172+180) subjects were included in toddler PP analysis.

Baseline data

The demographic and other baseline characteristics were similar between subjects receiving MenACWY concomitantly with routine vaccines vaccination (Group 1) and those receiving only routine vaccinations (Group 2).

Table 11.2-1: Demographic and Other Baseline Characteristics - Randomized Population

	ACWY+R (Group 1) N=258	Routine (Group 2) N=271	Total N=529
Age (Days):	64.7±6.5	65.4±7.4	65.1±7.0
Sex:			
Male	133 (52%)	141 (52%)	274 (52%)
Female	125 (48%)	130 (48%)	255 (48%)
Race:			
Asian	3 (1%)	1 (<1%)	4 (<1%)
Black	20 (8%)	29 (11%)	49 (9%)
Caucasian	168 (65%)	177 (65%)	345 (65%)
Hispanic	44 (17%)	45 (17%)	89 (17%)
Other	23 (9%)	19 (7%)	42 (8%)
Weight (kg):	5.36±0.70 (N=257)	5.38±0.71	5.37±0.71 (N=528)
Height (cm):	58.14±2.59 (N=257)	58.31±2.68 (N=270)	58.23±2.63 (N=527)

Source: Table 14.1.1.3.1; Categorical parameters: N (%), non-categorical parameters: Mean±Std`

Efficacy results

Primary objective:

Table 11.4.1-1: Percentage of Subjects With hSBA ≥1:8 at 1 Month After Toddler MenACWY Dose (4th Dose) - PP Toddler MenACWY Population

	Number (%) of Subjects (95% CI)							
	Men A		Men C		Men W		Men Y	
	ACWY+R (Group 1) N=168	Routine (Group 2) N=175	ACWY+R (Group 1) N=156	Routine (Group 2) N=171	ACWY+R (Group 1) N=153	Routine (Group 2) N=165	ACWY+R (Group 1) N=153	Routine (Group 2) N=159
Post-Toddler Dose	149 (89%) (83%-93%)	3 (2%) (0-5%)	148 (95%) (90%-98%)	4 (2%) (1%-6%)	149 (97%) (93%-99%)	11 (7%) (3%-12%)	147 (96%) (92%-99%)	2 (1%) (0-4%)

Source: Table 14.2.1.1.1; **Bold**= success criterion met (the lower limit of the two-sided 95% CI is greater than 80%, 85%, 85% and 85% for MenA, MenC, MenW and MenY, respectively)

One month post-toddler dose (13 months), 89%, 95%, 97% and 96% of the subjects in Group 1 achieved an hSBA ≥1:8 against serogroups A, C, W and Y, respectively. The percentages were very low (1%-7%) in the routine vaccination only group (Group 2). The lower limit of the two-sided 95% CI (83%, 90%, 93% and 92%) were greater than 80%, 85%, 85% and 85% for MenA, MenC, MenW and MenY, respectively in subjects who received MenACWY vaccination (Table 11.4.1-1). Thus, the primary objective was met.

Secondary Objectives:

1. Immune response after three doses of infant vaccination series (PP infant MenACWY Population)

hSBA ≥1:8

At baseline (day 1), the percentages of subjects with hSBA ≥1:8 were similar between the two groups (A: 2% vs, 1%, C: 7% each, W: 13% vs. 15%, Y: 8% vs. 4%). One month postinfant series

vaccination (7 months), 76%, 94%, 98% and 94% of the subjects in Group 1 achieved hSBA ≥1:8 against serogroups A, C, W and Y, respectively. The percentages remained very low (1%-3%) after the infant series in routine vaccination only group (Group 2) (Table 11.4.1-2).

At Least Four-Fold Rise in hSBA

One month post-infant series vaccination (7 months), 78%, 94%, 93% and 93% of the subjects in Group 1 had at least four-fold rise in hSBA against serogroups A, C, W and Y, respectively. The percentages were very low (1%-2%) after the infant series routine vaccination only group (Group 2) (Table 11.4.1-2).

hSBA GMTs

The hSBA GMTs in Group 1 increased over the baseline (A: 2.09 to 21, C: 2.49 to 74, W: 2.94 to 79, Y: 2.52 to 51) while those in Group 2 remained at the similar levels of baseline against each of the serogroups (Table 11.4.1-2).

Similar responses in terms of hSBA ≥1:8 and hSBA GMTs were observed in the subset of the infants who continued in the study to receive a toddler dose (PP toddler MenACWY population; Table 11.4.1-3).

Table 11.4.1-2: Immune Response 1 Month after Three Doses of Infant Series MenACWY Vaccination - PP Infant MenACWY Population

	Number (%) of Subjects or GMTs (95% CI)							
	Men A		Men C		Men W		Men Y	
	ACWY+R (Group 1)	Routine (Group 2)	ACWY+R (Group 1)	Routine (Group 2)	ACWY+R (Group 1)	Routine (Group 2)	ACWY+R (Group 1)	Routine (Group 2)
hSBA ≥1:8	**N=202**	**N=208**	**N=199**	**N=206**	**N=194**	**N=202**	**N=188**	**N=196**
Pre-infant series	3 (2%) (0-5) N=170	1 (1%) (0.014-3) N=178	11 (7%) (3-12) N=166	12 (7%) (4-12) N=174	20 (13%) (8-20) N=152	24 (15%) (10-21) N=164	11 (8%) (4-13) N=144	6 (4%) (1-9) N=150
Post-infant series	153 (76%) (69-81)	3 (1%) (0-4)	188 (94%) (90-97)	3 (1%) (0-4)	190 (98%) (95-99)	7 (3%) (1-7)	176 (94%) (89-97)	5 (3%) (1-6)
At Least 4-Fold Rise	**N=170**	**N=177**	**N=164**	**N=171**	**N=147**	**N=158**	**N=135**	**N=142**
Post-infant series	133 (78%) (71-84)	3 (2%) (0-5)	154 (94%) (89-97)	2 (1%) (0-4)	136 (93%) (87-96)	3 (2%) (0-5)	125 (93%) (87-96)	3 (2%) (0-6)
hSBA GMTs	**N=202**	**N=208**	**N=199**	**N=206**	**N=194**	**N=202**	**N=188**	**N=196**
Pre-infant series	2.09 (2-2.18) N=170	2.05 (1.98-2.12) N=178	2.49 (2.25-2.76) N=166	2.39 (2.18-2.61) N=174	2.94 (2.52-3.43) N=152	2.98 (2.58-3.45) N=164	2.52 (2.28-2.77) N=144	2.26 (2.12-2.41) N=150
Post-infant series	21 (17-26)	2.08 (1.99-2.17)	74 (62-87)	1.94 (1.64-2.3)	79 (67-92)	1.94 (1.68-2.24)	51 (43-61)	2.13 (2.02-2.25)

Source: Table 14.2.1.2, Table 14.2.1.3, Table 14.2.1.5

2. Persistence of MenACWY immune responses at 12 months of age

Prior to toddler dose (12 months), 37%, 70% and 53% of the subjects in Group 1 maintained an hSBA ≥1:8 against serogroups C, W and Y, respectively. The percentages were low against serogroup A in Group 1 (7%) and also against all serogroups in Group 2 (2%-5%) (Table 11.4.1-3).

hSBA GMTs and associated 95% CI were assessed at 12 months of age prior to the fourth dose. The hSBA GMTs were higher in Group 1 compared with those in Group 2 for the serogroups C (5.98 vs. 2.15), W (15 vs. 2.23) and Y (8.39 vs. 2.09) while the hSBA GMTs were similar for serogroup A (2.52 vs. 2.12) (Table 11.4.1-3).

CHMP's comments

In line with results from earlier studies the persistence for MenA is very poor between the 3rd dose of MenACWY at 6 months and the subsequent dose at 12 months. A strong decline in antibodies against MenC is also seen, from 96% after the 3rd dose to 37% prior to the fourth.

3. hSBA GMTs after 4 doses of MenACWY (Toddler MenACWY PP Population)

One month after the toddler dose (13 months of age), the hSBA GMTs in Group 1 were significantly higher compared to Group 2 for all vaccine serogroups (A: 54 vs. 1.87, C: 135 vs. 1.94, W: 215 vs. 2.15; Y: 185 vs. 1.89) (Table 11.4.1-3; Figure 11.4.1-1).

Table 11.4.1-3: Immune Response against MenACWY - PP Toddler MenACWY Population

	Number (%) of Subjects or GMTs (95% CI)							
	Men A		Men C		Men W		Men Y	
	ACWY+R (Group 1)	Routine (Group 2)	ACWY+R (Group 1)	Routine (Group 2)	ACWY+R (Group 1)	Routine (Group 2)	ACWY+R (Group 1)	Routine (Group 2)
hSBA ≥1:8	**N=168**	**N=175**	**N=156**	**N=171**	**N=153**	**N=165**	**N=153**	**N=159**
Pre-infant series	2 (1%) (0-5) N=139	0 (0-3) N=145	9 (7%) (3-13) N=126	11 (8%) (4-14) N=136	17 (15%) (9-23) N=113	19 (15%) (9-23) N=126	7 (6%) (3-13) N=108	6 (5%) (2-11) N=113
Post-infant series	121 (76%) (69-82) N=159	3 (2%) (0-5) N=160	139 (96%) (91-98) N=145	3 (2%) (0-6) N=156	135 (97%) (93-99) N=139	7 (5%) (2-9) N=149	123 (91%) (85-95) N=135	6 (4%) (2-9) N=145
Pre-Toddler Dose	12 (7%) (4-12)	3 (2%) (0-5)	58 (37%) (30-45)	4 (2%) (1-6)	107 (70%) (62-77)	8 (5%) (2-9)	81 (53%) (45-61)	4 (3%) (1-6)
Post-Toddler Dose	149 (89%) (83-93)	3 (2%) (0-5)	148 (95%) (90-98)	4 (2%) (1-6)	149 (97%) (93-99)	11 (7%) (3-12)	147 (96%) (92-99)	2 (1%) (0-4)
At Least 4-Fold Rise	**N=168**	**N=175**	**N=156**	**N=171**	**N=153**	**N=165**	**N=153**	**N=159**
Post-Toddler Dose	149 (89%) (83-93)	1 (1%) (0.014-3)	144 (92%) (87-96)	2 (1%) (0-4)	146 (95%) (91-98)	4 (2%) (1-6)	147 (96%) (92-99)	1 (1%) (0.016-3)
hSBA GMTs	**N=168**	**N=175**	**N=156**	**N=171**	**N=153**	**N=165**	**N=153**	**N=159**

	Men A		Men C		Men W		Men Y	
	ACWY+R (Group 1)	Routine (Group 2)	ACWY+R (Group 1)	Routine (Group 2)	ACWY+R (Group 1)	Routine (Group 2)	ACWY+R (Group 1)	Routine (Group 2)
Pre-infant series	2.07 (1.98-2.16) N=139	2.01 (1.99-2.03) N=145	2.49 (2.2-2.83) N=126	2.44 (2.2-2.7) N=136	2.99 (2.49-3.6) N=113	2.97 (2.52-3.51) N=126	2.43 (2.19-2.71) N=108	2.32 (2.13-2.52) N=113
Post-infant series	22 (17-27) N=159	2.1 (1.99-2.23) N=160	83 (66-105) N=145	2.31 (1.83-2.91) N=156	74 (60-91) N=139	2.06 (1.7-2.5) N=149	48 (39-59) N=135	2.24 (2.05-2.44) N=145
Pre-Toddler Dose	2.52 (2.26-2.82)	2.12 (2-2.25)	5.98 (4.81-7.43)	2.15 (2.02-2.3)	15 (12-18)	2.23 (2.06-2.4)	8.39 (6.9-10)	2.09 (2-2.19)
Post-Toddler Dose	54 (44-67)	1.87 (1.55-2.27)	135 (107-171)	1.94 (1.56-2.4)	215 (167-277)	2.15 (1.77-2.6)	185 (148-233)	1.89 (1.56-2.29)

4. At least four-fold rise in hSBA after toddler dose (PP Toddler MenACWY Population)

One month post-toddler dose (13 months of age), 89%, 92%, 95% and 96% of the subjects in Group 1 had at least four-fold rise in hSBA against serogroups A, C, W and Y, respectively. The percentages remained very low (1%-2%) after the 12-month vaccination in the routine vaccination group (Group 2) (Table 11.4.1-3).

5. Immune responses to routine vaccine antigens

The ratio of GMCs (GMCMenACWY + Pentacel GMCPentacel) for the pertussis antigens ranged from 1.02 – 1.09 with the lower limit of two sided 95% CI (0.81 to 0.9) being greater than 0.67 for each antigen. The non-inferiority objectives for pertussis antigens after infant series in terms of GMC were demonstrated.

Table 11.4.1-5: Percentage of Subjects with Seroresponse to Pertussis Antigens (95% CI) at 1 Month after Three Doses of Infant Series Vaccination - PP Infant Pertussis Population

	Number (%) of Subjects (95% CI)		
	ACWY+R (Group 1)	Routine (Group 2)	ACWY+R Routine
	N=185	N=191	
PT	143 (77%) (71-83)	155 (81%) (75-86)	-4% (-12.1-4.3)
FHA	129 (70%) (63-76)	125 (65%) (58-72)	4% (-5.1-13.6)
Pertactin	135 (73%) (66-79)	139 (73%) (66-79)	0% (-8.8-9.1)
FIM	137 (74%) (67-80)	145 (76%) (69-82)	-2% (-10.6-6.8)

Source: Table 14.2.1.10, Table 14.2.1.11, Table 14.2.1.12, Table 14.2.1.13; Seroresponse for pertussis antigens defined as 1. In initially seronegative infants ≥4 times LLQ; 2. In initially seropositive; infants at least 4 times increase of pre-vaccination concentration.

The lower limit of two sided 95% CI for the difference in the seroresponse rates between groups (PPentacel + MenACWY PPentacel) for FHA and pertactin was greater than -10% while for PT it was -12.1% and for FIM it was -10.6%.

Because the group difference for PT and FIM in the percentage of subjects with seroresponse did not meet the required non-inferiority criterion, the multiplicity procedure required that testing be stopped.

Results post-infant series

The lower limit of two sided 95% CI for the difference between the antibody response rates (PRoutine Vaccine + MenACWY minus PRoutine Vaccine) for diphtheria, tetanus, hepatitis B and Hib was greater than -10% (met non-inferiority margin). For all polio antigens (types 1, 2, 3) the difference was greater than -5% (met non-inferiority margin).

The difference between Group 1 and Group 2 in percentage of subjects with antibody concentration ≥0.35 µg/mL varied from 0 to -5%, the lower limit of 95% CI on the difference was greater than -10% (met non-inferiority margin) for all of the antigens except for PnC 6B (-10.3%) and PnC 23F (-11.4%).

The ratio of GMCs (GMC Routine Vaccine + MenACWY GMCRoutine Vaccine) or GMTs for diphtheria, tetanus, poliovirus, HBV and Hib antigens ranged from 0.83 – 1.36 with the lower limit of two sided

95% CI being greater than 0.50.The results demonstrated that the pre-defined equivalency criteria for these antigens were achieved. The ratio of GMCs (GMCMenACWY + routine / GMCRoutine) for the pneumococcal antigens ranged from 0.79 – 0.96 with the lower limit of two sided 95% CI (0.62 to 0.81) being greater than pre-defined margin of 0.5 for each antigen.

Table 11.4.1-6: Key Secondary Endpoints Seroresponse Rates (95% CI) of Concomitant Antigens at 1 Month after Three Doses of Infant Series Vaccination - PP Infant Populations

	Number (%) of Subjects (95% CI)		
	ACWY+R (Group 1)	Routine (Group 2)	ACWY+R Routine Difference
	N=207	N=218	
Diphtheria (≥0.1 IU/mL)	204 (99%) (96-100)	215 (99%) (96-100)	0% (-2.9-2.6)
Tetanus (≥0.1 IU/mL)	201 (97%) (94-99)	211 (97%) (93-99)	0% (-3.3-3.9)
Polio antigens			
Polio Type 1 (≥1:8)	114 (99%) (95-100) N=115	111 (98%) (94-100) N=113	1% (-3.1-5.4)
Polio Type 2 (≥1:8)	185 (100%) (98-100) N=185	178 (99%) (97-100) N=179	1% (-1.4-3)
Polio Type 3 (≥1:8)	163 (99%) (97-100) N=164	162 (100%) (98-100) N=162	-1% (-3.3-1.7)
Hepatitis B	N=138	N=148	
HBV (≥10 mIU/mL)	133 (96%) (92%-99%)	143 (97%) (92%-99%)	0% (-5.2%-4.5%)
PRP-Hib	N=187	N=194	
Hib (≥0.15 µg/mL)	177 (95%) (90-97)	173 (89%) (84-93)	5% (0.0-11.2)
PnC (≥0.35 µg/mL)	N=183	N=178	
PnC 4	181 (99%) (96-100)	174 (98%) (94-99)	1% (-1.9-4.6)
PnC 6B	158 (86%) (80-91)	160 (90%) (84-94)	-4% (-10.3-3.2)
PnC 9V	167 (91%) (86-95)	168 (94%) (90-97)	-3% (-8.7-2.3)
PnC 14	181 (99%) (96-100)	176 (99%) (96-100)	0% (-2.8-3.0)
PnC 18C	173 (95%) (90-97)	173 (97%) (94-99)	-3% (-7.3-1.6)
PnC 19F	183 (100%) (98-100)	172 (97%) (93-99)	3% (1.3-7.1)
PnC 23F	162 (89%) (83-93)	167 (94%) (89-97)	-5% (-11.4-0.5)

Results post-toddler dose

One month post-toddler dose (13 months), the ratio of GMCs (GMC MenACWY + Prevnar GMCPrevnar) for the pneumococcal antigens ranged from 0.76 to 1.04 with the lower limit of two sided 95% CI

being greater than 0.50 for all antigens. The lower limit of 95% CI for the difference (P MenACWY + Prevnar PPrevnar) in percentages of subjects achieving a concentration of ≥0.35 µg/mL was greater than -10% (Group 1 non-inferior to Group 2) for all of the pneumococcal antigens. For percentage of subjects with the stricter cut-off antibody concentration ≥1.0 µg/mL, the lower limit of 95% CI on the difference between groups after the toddler dose was greater than -10% (met non-inferiority criteria) for PnC antigens PnC 6B, PnC 14, PnC 18C, PnC 19F and PnC 23F.

Safety results

Out of a total of 529 subjects enrolled in the study, 525 (99%) subjects were exposed to at least one study vaccination and provided safety data; these subjects were included in the safety analysis.

Safety was assessed for all subjects in terms of the frequency and percentage of subjects with reported SAEs or medically attended AEs.

CHMP's comments

Note that reactogenicity, local and systemic, was not solicited during the study.

During the infant series vaccination (2-7 months), the percentages of subjects with AEs were similar between the vaccination groups (72% in Group 1 and 70% in Group 2) with low rates (2% and <1% subjects in the respective groups) having AEs that were at least possibly related to the study vaccination. Between the third and fourth vaccination (7-12 months), the percentages of subjects with AEs were similar between the vaccination groups (75% in Group 1 and 74% in Group 2) with none of the subjects in either group having AEs that were judged to be related to the study vaccination. Twenty eight days after toddler dose at 12 months, the percentages of subjects with AEs were similar between the vaccination groups (36% in Group 1 and 35% in Group 2) with none of the subjects in either group having AEs that were judged to be related to the study vaccination.

Adverse events

The most commonly reported AEs by preferred term were upper respiratory tract infections (56% 57%, similar between Group 1 and Group 2) followed by otitis media (39% in each group), conjunctivitis (23% and 19%), viral infections (15% and 19%), pyrexia (17% in each group), bronchiolitis (16% and 15%), gastroenteritis (15% and 12%), and dermatitis due to diaper (13% and 15%). None of these AEs was judged to be related to the study vaccination.

Table 12.2.3-1: Number (%) of Subjects with AEs by Preferred Term (≥5%) - Safety Population

Preferred Term	Number (%) of Subjects with Adverse Events	
	ACWY+R (Group 1)	Routine (Group 2)
	N=255	N=270
Upper Respiratory Tract Infection	144 (56%)	154 (57%)
Otitis Media	100 (39%)	106 (39%)
Conjunctivitis	58 (23%)	52 (19%)
Viral Infection	37 (15%)	51 (19%)
Pyrexia	43 (17%)	45 (17%)
Bronchiolitis	40 (16%)	41 (15%)
Gastroenteritis	38 (15%)	32 (12%)
Dermatitis Diaper	33 (13%)	40 (15%)
Cough	34 (13%)	27 (10%)
Otitis Media Acute	31 (12%)	31 (11%)
Pharyngitis	24 (9%)	32 (12%)
Vomiting	19 (7%)	31 (11%)
Eczema	29 (11%)	28 (10%)
Diarrhea	25 (10%)	27 (10%)
Candidiasis	16 (6%)	24 (9%)
Constipation	18 (7%)	24 (9%)
Croup Infectious	16 (6%)	22 (8%)
Rhinitis Allergic	17 (7%)	21 (8%)
Rhinitis	19 (7%)	20 (7%)
Dermatitis Atopic	17 (7%)	17 (6%)
Candida Nappy Rash	6 (2%)	17 (6%)
Teething	16 (6%)	7 (3%)
Wheezing	16 (6%)	8 (3%)
Bronchial Hyperreactivity	15 (6%)	8 (3%)
Bronchitis	15 (6%)	15 (6%)
Rash	13 (5%)	15 (6%)
Sinusitis	11 (4%)	15 (6%)
Ear Pain	13 (5%)	7 (3%)

Source: Table 14.3.1.1.10

The most commonly affected SOC was “Infections and Infestations” (82% in Group 1 and 83% in Group 2, similar in both groups), followed by “Skin and Subcutaneous Tissue Disorders” (42% and 39%), “Respiratory, Thoracic & Mediastinal Disorders” (30% in each group), “Gastrointestinal Disorders” (29% and 32%), “Eye Disorders” (24% and 20%) and “General Disorders and Administration Site Conditions” (22% and 20%).

Very few subjects (0-<1% for any SOC) had AEs judged to be at least possibly related to the study vaccination (see table below).

Table: summary of Possibly or Probably Related Treatment Emergent Adverse Event

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects[1] ACWY+R (N=255)	 Routine (N=270)
ANY ADVERSE EVENT	6 (2%)	2 (1%)
GASTROINTESTINAL DISORDERS	1 (<1%)	1 (<1%)
VOMITING	1 (<1%)	1 (<1%)
GEN. DISORDERS & ADMIN. SITE COND.	1 (<1%)	1 (<1%)
IRRITABILITY	1 (<1%)	0
PYREXIA	0	1 (<1%)
INFECTIONS & INFESTATIONS	3 (1%)	1 (<1%)
BRONCHIOLITIS	1 (<1%)	0
GASTROENTERITIS	1 (<1%)	0
RESPIRATORY TRACT INFECTION	0	1 (<1%)
SKIN INFECTION	1 (<1%)	0
VIRAL INFECTION	1 (<1%)	0
RESP., THORACIC & MEDIASTINAL DIS.	1 (<1%)	0
COUGH	1 (<1%)	0
SKIN & SUBCUTANEOUS TIS. DISORDERS	1 (<1%)	0
HEAT RASH	1 (<1%)	0

Deaths, Serious adverse events and other significant adverse events

No deaths were reported in this study. 21 (8%) subjects in Group 1 and 20 (7%) subjects in Group 2 experienced SAEs with none of the SAEs being judged to be related to the study vaccination. Two subjects (Subject no. 28/0025 in Group 1 and Subject no. 28/0053 in Group 2) had seizures as SAEs. In the opinion of the investigator these SAEs were unrelated to the study vaccine.

Subject No. 28/0025: Febrile Seizure and Enteroviral Meningitis

This subject was vaccinated concomitantly with MenACWY, Pentacel Prevnar, and RotaTeq on 23 FEB 2010, 26 APR 2010 and 30 JUN 2010. On 08 SEP 2010 (70 days after the third vaccination), the subject suffered a new onset of seizure (assessed as non-serious AE by the investigator). On 13 SEP 2010 (75 days after the third vaccination), he was hospitalized after he experienced a fever of 103.4° F and a tonic-clonic seizure lasting 30 seconds. There were no further high fevers nor seizures noted during the hospitalization. Neurological exam was non-focal. Cerebrospinal fluid was positive for enterovirus by polymerase chain reaction (PCR) testing. The subject was diagnosed with enteroviral meningitis and possible febrile seizure, treated with acetaminophen and ibuprofen, and was discharged on 14 SEP 2010. The subject had fully recovered from the febrile seizure and enteroviral meningitis by 13 SEP 2010 and 16 SEP 2010, respectively. The study dropped out of the study as a result of the event.

Subject No. 28/0053: Seizure (non-febrile).

This subject was vaccinated with routine vaccinations Pentacel, Prevnar, RotaTeq on 30 MAR 2010, 01 JUN 2010, 03 AUG 2010, Engerix-B on 30 MAR 2010, 03 AUG 2010 and Prevnar and MMR II on 07 FEB 2011; Fluzone on 05 NOV 2010 and 07 MAR 2011, hepatitis B vaccine on 05 NOV 2010, hepatitis A vaccine on 07 MAR 2011, and varicella vaccine on 07 MAR 2011. Prior to study period, the subject was vaccinated with hepatitis B vaccine on 03 FEB 2010.

The subject was in the control group and did not receive study vaccine. On 17 MAR 2011(39 days after the fourth vaccinations with Prevnar and MMR II), the subject experienced a viral syndrome and vomiting. The subject was treated with azithromycin and albuterol. On the same day, one hour after symptom onset, the subject experienced a seizure episode and was admitted to the hospital. Chest x-ray was normal. The subject was treated with levetiracetam. The subject recovered from the events on 19 MAR 2011. On 23 MAR 2011, upon discharge from hospital, the subject was noted to sustain an episode of “eyes rolled back” for one minute duration. No further seizures were noted. The subject dropped out of the study as a result of the event.

CHMP’s comments

It is agreed with the MAH that these serious AEs are unlikely related to the study medication.

III. Discussion on clinical aspects

The MAH submitted the clinical study reports of 6 recently completed studies involving the use of MenACWY in the paediatric population, as per Article 46 of the European Paediatric Regulation (EC N0 1901/2006). Of these 6 paediatric studies, 4 were in children 2 years of age and above (studies V59_39, V59_40, V59_49, and V59_50) and 2 in children < 2 years of age (studies V59_33 and V59P14E1).

Thee studies evaluated the safety and immunogenicity of MenACWY in different age group for registrational purposes in Korea, Taiwan and Russia (V59P39, V59P49 and V59P50). The findings of these studies are largely in line with those of studies previously submitted by the MAH to support immunogenicity and safety of MenACWY in children aged 2 to 18 years of age. No safety concerns were identified during the studies. The frequencies of solicited AEs were similar to those previously reported in this age group.

Two studies considered the immunogenicity and safety of MenACWY and routine vaccines following concomitant vaccination (V59P33, V59P40). The main findings of these studies are in line with findings from previous interaction studies with the same vaccines in similar age groups; namely that MenACWY can safely be given with routine vaccinations (pneumococcal, IPV, HBV, Hib, DTaP, Tdap). In Study V59P40 too the response to FHA and PRN is significantly lower (albeit non-inferiority was demonstrated) when Tdap is given concomitantly with MenACWY, confirming earlier findings from study V59P18. This information is already reflected in section 4.5 of the SmPC, i.e. that there is evidence to suggest negative effect of concomitant vaccination with MenACWY and HPV on the response to pertussis antigens FHA and PRN yet the clinical relevance is unknown.

For study V59P40 the immunogenicity analysis for the second primary objective (assessment of immune response against HPV antigens) are yet to be presented in an addendum to the clinical study report as soon as results are available. **The MAH should provide these results when available.**

Finally, the MAH also submitted the 60 months data from study V59P14Ee1 of which the 40 month data have been previously submitted. These data showed that antibody persistence is greater among subjects who received the 2 dose series compared to those who had received the 4-dose infant series This is likely attributable to the age at when the final dose was received or could reflect the maturity of the immune system at the time of priming. The low persistence for MenA seen in V59P14Ee1 is in line with earlier observations in other studies which resulted in a warning in the SmPC. Moreover, an update of section 4.2 based upon further persistence data is currently being considered in variation II/42. Note that the MAH indicates that an increasing number of publications is suggesting that hSBA need not be an optimal assay for persistence assessment, especially for serogroup A. A discrepancy observed between the results with the rSBA (which shows good persistence for MenA) and hSBA assay (which shows poor persistence for MenA) could be attributable to known differences between assays due to differences in target strain susceptibilities for the complement sources (Findlow H, 2009, Poolman JT, 2011). This would merit further discussion in future in order to see whether the poor persistence of antibodies as measured with the hSBA assay reflects a true decline in Abs. Importantly, the response to vaccination with MenACWY is clearly better in those subjects vaccinated previously with MenACWY compared tot the Naive60 group pointing towards good priming for all serogroups.

With regards to the safety data from these 6 studies, these are largely in line with the known safety profile of MenACWY. The incidence of solicited AEs in different age groups is similar to that previously reported. No new safety concerns were identified. **The MAH could include the safety data from studies in children aged ≥2 years in section 4.8 to add to the body of evidence in support of the good safety profile of this vaccine. This could be done with a future type II variation.**

IV. Rapporteur's overall conclusion and recommendation

It is agreed with the MAH that the data submitted does not change the benefit-risk balance of MenACWY, which remains positive.

The MAH has not proposed any changes to the Product Information which is largely agreed however, the MAH could include the safety data from studies in children aged ≥2 years in section 4.8 to add to the body of evidence in support of the good safety profile of this vaccine. This could be done with a future type II variation.

Secondly, it is advised that the MAH should provide the assessment of immune response against HPV antigens from study V59P40 when available.

V. Overall conclusion

Recommendation

☐ **Fulfilled:**

☒ **Not fulfilled:**

VI. Additional clarifications requested

Type II variation to be requested from the MAH by 31 December 2014 to amend the product information as follows:

- To include the safety data from studies in children aged ≥2 years in section 4.8 to add to the body of evidence in support of the good safety profile of this vaccine

The MAH should provide the assessment of immune response against HPV antigens from study V59P40 when available.

(*Post script: A type II variation EMEA/H/C/1095/II/051-G was submitted on 30 December 2014 to add to the Product Literature, the safety data from studies in children aged ≥2 years).*