Clinical trial results:
A Phase IIIb, Open-Label, Controlled, Multi-Center Study to Evaluate the Persistence Of Antibody Responses Among Children Who Previously Received Novartis MenACWY Conjugate Vaccine or Meningococcal C Conjugate Vaccine

Summary

EudraCT number	2010-023858-37
Trial protocol	DE
Global end of trial date	08 September 2011

Results information

Result version number	v1
This version publication date	11 May 2016
First version publication date	28 December 2014

Trial information

Trial identification

Sponsor protocol code	V59P22E1

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01345721
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Vaccine and Diagnostics
Sponsor organisation address	Via Fiorentina, 1, Siena, Italy, 53100
Public contact	Novartis Vaccines, Novartis Vaccines, anh.phung@novartis.com
Scientific contact	Novartis Vaccines, Novartis Vaccines, anh.phung@novartis.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	03 May 2012
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	08 September 2011
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Co-primary objectives:
1.To evaluate the persistence of the antibody response in children previously vaccinated with one or two doses of MenACWY or MenC in study V59P22, as measured by percentage of subjects with human Serum Bactericidal Assay (hSBA) titers ≥ 1:8 directed against N. meningitidis serogroups A, C, W and Y.
2.To evaluate the antibody response to a booster dose of MenACWY in children previously vaccinated with one or two doses of MenACWY as measured by of percentage of subjects with hSBA titers ≥ 1:8, and hSBA GMTs directed against N.meningitidis serogroups A, C, W, Y.
3.To evaluate the antibody response to one dose of MenACWY in children previously vaccinated with MenC as measured by of percentage of subjects with hSBA titers ≥ 1:8, and hSBA GMTs directed against N. meningitidis serogroups A, C, W, Y.
Safety Objective: To assess the safety and tolerability of a dose of MenACWY in subjects who were previously vaccinated with one or two doses of MenACWY or MenC.

Protection of trial subjects:

Study vaccines were not administered to individuals with known hypersensitivity to any component of the vaccines. An oral temperature ≥38.0°C (≥100.4°F) or serious active infection was a reason for delaying vaccination. Standard immunization practices were observed and care was taken to administer the injection intramuscularly. As with all injectable vaccines, appropriate medical treatment and supervision was readily available in case of rare anaphylactic reactions following administration of the study vaccine. Epinephrine 1:1000 and diphenhydramine was available in case of any anaphylactic reactions. Care was taken to ensure that the vaccine is not injected into a blood vessel.

Background therapy:

MenACWY

Evidence for comparator:

MenC

Actual start date of recruitment	25 May 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 205
Worldwide total number of subjects	205
EEA total number of subjects	205

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	205
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects for this extension study were enrolled between 25 May 2011 and 08 September 2011 from only sites in Germany that participated in the parent study.

Pre-assignment

Screening details:

Subjects were 22 to 45 months of age at the time of enrolment into V59P22E1 and had participated in the original V59P22 study.

Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	MenACWY_2 doses + MenACWY booster

Arm description:

Subjects, who had received two doses of MenACWY (at 6 to 8 months and 12 months of age) in the parent study, were administered a booster dose of MenACWY at 22 to 45 months of age in this extension study.

Arm type	Experimental
Investigational medicinal product name	MenACWY-CRM
Investigational medicinal product code	
Other name	Meningococcal (groups A, C, Y, and W-135 vaccine) Oligosaccharide Diptheria-CRM197 Conjugate Vaccine
Pharmaceutical forms	Powder and suspension for suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

MenACWY 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 IM injection in the left deltoid.

Arm title	MenACWY_1 dose + MenACWY booster

Arm description:

Subjects, who had received one dose of MenACWY (at 12 months of age) in the parent study, were administered a booster dose of MenACWY at 22 to 45 months of age in this extension study.

Arm type	Experimental
Investigational medicinal product name	MenACWY-CRM
Investigational medicinal product code	
Other name	Meningococcal (groups A, C, Y, and W-135 vaccine) Oligosaccharide Diptheria-CRM197 Conjugate Vaccine
Pharmaceutical forms	Powder and suspension for suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

MenACWY 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 IM injection in the left deltoid.

Arm title	Men C + MenACWY booster

Arm description:

Subjects, who had received one dose of the comparator MenC vaccine (at 12 months of age) in the parent study, were administered a booster dose of MenACWY at 22 to 45 months of age in this extension study.

Arm type	Experimental
Investigational medicinal product name	MenACWY-CRM
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and suspension for suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

MenACWY 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 IM injection in the left deltoid.

Number of subjects in period 1	MenACWY_2 doses + MenACWY booster	MenACWY_1 dose + MenACWY booster	Men C + MenACWY booster
Started	74	66	65
Completed	74	66	65

Baseline characteristics

Reporting groups	
Reporting group title	MenACWY_2 doses + MenACWY booster
Reporting group description:	
Subjects, who had received two doses of MenACWY (at 6 to 8 months and 12 months of age) in the parent study, were administered a booster dose of MenACWY at 22 to 45 months of age in this extension study.	
Reporting group title	MenACWY_1 dose + MenACWY booster
Reporting group description:	
Subjects, who had received one dose of MenACWY (at 12 months of age) in the parent study, were administered a booster dose of MenACWY at 22 to 45 months of age in this extension study.	
Reporting group title	Men C + MenACWY booster
Reporting group description:	
Subjects, who had received one dose of the comparator MenC vaccine (at 12 months of age) in the parent study, were administered a booster dose of MenACWY at 22 to 45 months of age in this extension study.	

Reporting group values	MenACWY_2 doses + MenACWY booster	MenACWY_1 dose + MenACWY booster	Men C + MenACWY booster
Number of subjects	74	66	65
Age categorical Units: Subjects			
Children (2-11 years)	74	66	65
Age continuous Units: months			
arithmetic mean	36.7	37.4	37.9
standard deviation	± 5.3	± 5.6	± 5.3
Gender categorical Units: Subjects			
Female	34	30	37
Male	40	36	28

Reporting group values	Total		
Number of subjects	205		
Age categorical Units: Subjects			
Children (2-11 years)	205		
Age continuous Units: months			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	101		
Male	104		

Subject analysis sets

Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis

Subject analysis set description:

All subjects in the Exposed population who received at least one dose of study vaccine, and provided some post-vaccination safety data

Subject analysis set title	Per Protocol Persistence Population
Subject analysis set type	Per protocol

Subject analysis set description:

All subjects who provided evaluable serum samples at visit 7 and had no major protocol violation as defined prior to the end of the study

Reporting group values	Safety Population	Per Protocol Persistence Population	
Number of subjects	140	136	
Age categorical Units: Subjects			
Children (2-11 years)	140	136	
Age continuous Units: months arithmetic mean standard deviation	±	±	
Gender categorical Units: Subjects			
Female Male			

End points

End points reporting groups

Reporting group title	MenACWY_2 doses + MenACWY booster

Reporting group description:

Subjects, who had received two doses of MenACWY (at 6 to 8 months and 12 months of age) in the parent study, were administered a booster dose of MenACWY at 22 to 45 months of age in this extension study.

Reporting group title	MenACWY_1 dose + MenACWY booster

Reporting group description:

Subjects, who had received one dose of MenACWY (at 12 months of age) in the parent study, were administered a booster dose of MenACWY at 22 to 45 months of age in this extension study.

Reporting group title	Men C + MenACWY booster

Reporting group description:

Subjects, who had received one dose of the comparator MenC vaccine (at 12 months of age) in the parent study, were administered a booster dose of MenACWY at 22 to 45 months of age in this extension study.

Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis

Subject analysis set description:

All subjects in the Exposed population who received at least one dose of study vaccine, and provided some post-vaccination safety data

Subject analysis set title	Per Protocol Persistence Population
Subject analysis set type	Per protocol

Subject analysis set description:

All subjects who provided evaluable serum samples at visit 7 and had no major protocol violation as defined prior to the end of the study

Primary: Percentage of Subjects with Human Serum Bactericidal Antibody Titer ≥1:8 by Time Since the Last Dose of Primary Vaccination

End point title	Percentage of Subjects with Human Serum Bactericidal Antibody Titer ≥1:8 by Time Since the Last Dose of Primary Vaccination[1]

End point description:

Booster response is presented as the percentage of subjects with human Serum Bactericidal Assay (hSBA) ≥1:8 directed against N. meningitidis serogroups A, C, W-135, and Y at visit 7 prior to the MenACWY dose on day 1 in study V59P22E1. Persistence was summarized by time period since the last vaccination in the parent study, V59P22 (time intervals of ≤23 months, 24 to 31 months, and ≥32 months since last vaccination).

End point type	Primary

End point timeframe:

13-33 months post-primary vaccination

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There were no statistical hypotheses associated with the co-primary or secondary immunogenicity objectives. All analyses were run descriptively.

End point values	MenACWY_2 doses + MenACWY booster	MenACWY_1 dose + MenACWY booster	Men C + MenACWY booster	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	52	41	43	
Units: Percentage of Subjects				
number (confidence interval 95%)				

≤23 Months – MenA (25,17,19)	16 (5 to 36)	6 (0 to 29)	0 (0 to 18)	
≤23 Months – MenC (25,16,18)	36 (18 to 57)	38 (15 to 65)	44 (22 to 69)	
≤23 Months – MenW (25,17,19)	48 (28 to 69)	76 (50 to 93)	21 (6 to 46)	
≤23 Months – MenY (25,17,19)	40 (21 to 61)	53 (28 to 77)	5 (0 to 26)	
24-31 Months – MenA (26,22,14)	12 (2 to 30)	9 (1 to 29)	0 (0 to 14)	
24-31 Months – MenC (26,22,14)	19 (7 to 39)	14 (3 to 35)	29 (13 to 51)	
24-31 Months – MenW (26,22,24)	54 (33 to 73)	55 (32 to 76)	4 (0 to 21)	
24-31 Months- MenY (26,22,24)	38 (20 to 59)	27 (11 to 50)	29 (13 to 51)	
≥32 Months – MenA (1,2,0)	0 (0 to 98)	0 (0 to 84)	0 (0 to 0)	
≥32 Months – MenC (1,2,0)	0 (0 to 98)	50 (1 to 99)	0 (0 to 0)	
≥32 Months – MenW (1,2,0)	0 (0 to 98)	50 (1 to 99)	0 (0 to 0)	
≥32 Months – MenY (1,2,0)	100 (3 to 100)	50 (1 to 99)	0 (0 to 0)	

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects with human Serum Bactericidal Antibody Titer ≥1:8 at 1 Month after Booster

End point title	Percentage of Subjects with human Serum Bactericidal Antibody Titer ≥1:8 at 1 Month after Booster[2]

End point description:

Booster response is presented as the percentage of subjects with human Serum Bactericidal Assay (hSBA) ≥1:8 directed against N. meningitidis serogroups A, C, W-135, and Y at visit 7 prior to the MenACWY dose on day 1 in study V59P22E1 and at visit 8 one month after.

End point type	Primary

End point timeframe:

1 month post-booster vaccination

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There were no statistical hypotheses associated with the co-primary or secondary immunogenicity objectives. All analyses were run descriptively.

End point values	MenACWY_2 doses + MenACWY booster	MenACWY_1 dose + MenACWY booster	Men C + MenACWY booster	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	52	41	43	
Units: Percentage of Subjects				
number (confidence interval 95%)				
MenA – pre-booster (52,41,41)	13 (6 to 26)	7 (2 to 20)	0 (0 to 9)	
MenA – 1 month post-booster (52,41,41)	96 (87 to 100)	98 (87 to 100)	61 (45 to 76)	
MenC – pre-booster (52,40,39)	27 (16 to 41)	25 (13 to 41)	36 (21 to 53)	
MenC – 1 month post-booster (52,40,39)	100 (93 to 100)	100 (91 to 100)	100 (91 to 100)	
MenW– pre-booster (52,41,41)	50 (36 to 64)	63 (47 to 78)	12 (4 to 26)	
MenW– 1 month post-booster (52,41,41)	100 (93 to 100)	100 (91 to 100)	95 (83 to 99)	
MenY– pre-booster (52,41,41)	40 (27 to 55)	39 (24 to 55)	20 (9 to 35)	

MenY– 1 month post-booster (52,41,41)	100 (93 to 100)	100 (91 to 100)	95 (83 to 99)	

Statistical analyses

No statistical analyses for this end point

Primary: Geometric Mean Titers of Human Serum Bactericidal Antibodies at 1 Month after Booster

End point title	Geometric Mean Titers of Human Serum Bactericidal Antibodies at 1 Month after Booster[3]

End point description:

hSBA geometric mean titers (GMTs) for N. meningitidis serogroups A, C, W-135, and Y, measured before and after the booster dose.

End point type	Primary

End point timeframe:

1 month post-booster vaccination

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There were no statistical hypotheses associated with the co-primary or secondary immunogenicity objectives. All analyses were run descriptively.

End point values	MenACWY_2 doses + MenACWY booster	MenACWY_1 dose + MenACWY booster	Men C + MenACWY booster	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	52	41	43	
Units: Titers				
geometric mean (confidence interval 95%)				
MenA – pre-booster (52,41,41)	2.82 (2.35 to 3.38)	2.52 (2.05 to 3.09)	2 (1.63 to 2.45)	
MenA – 1 month post-booster (52,41,41)	182 (118 to 281)	214 (131 to 350)	20 (12 to 32)	
MenC –pre-booster (52,40,39)	3.92 (2.92 to 5.26)	3.91 (2.79 to 5.48)	4.83 (3.44 to 6.77)	
MenC – 1 month post-booster (52,40,39)	541 (399 to 733)	968 (682 to 1372)	1530 (1077 to 2173)	
MenW–pre-booster (52,41,41)	9.37 (6.3 to 14)	12 (7.51 to 18)	2.82 (1.81 to 4.39)	
MenW– 1 month post-booster (52,41,41)	799 (564 to 1133)	1267 (854 to 1879)	54 (37 to 80)	
MenY–pre-booster (52,41,41)	6.79 (4.86 to 9.5)	6.04 (4.13 to 8.82)	3.05 (2.09 to 4.44)	
MenY– 1 month post-booster (52,41,41)	650 (448 to 941)	676 (444 to 1027)	54 (35 to 81)	

Statistical analyses

No statistical analyses for this end point

Secondary: Subjects Reporting Local and Systemic Reactions during 7-Day Period after Booster Vaccination

End point title	Subjects Reporting Local and Systemic Reactions during 7-Day Period after Booster Vaccination

End point description:

The number of subjects with solicited local and systemic reactions within 7 days after booster vaccination with MenACWY.

End point type	Secondary

End point timeframe:

Day 1 to 7 after vaccination

End point values	MenACWY_2 doses + MenACWY booster	MenACWY_1 dose + MenACWY booster	Men C + MenACWY booster	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	53	44	43	
Units: Number of Subjects				
number (not applicable)				
Local reactions	17	21	19	
Pain	10	15	13	
Erythema	14	17	15	
Induration	6	8	7	
Systemic reactions	28	18	25	
Arthralgia	1	5	4	
Headache	5	6	1	
Vomiting	0	2	1	
Change in Eating Habits	6	8	6	
Rash	0	2	1	
Sleepiness	10	13	10	
Fever	8	7	7	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Local and systemic reactions and all adverse events (AEs) were collected from day 1 to day 7.. From day 8 after booster vaccination to visit 8, medically-attended AEs were recorded.Serious Adverse Events (SAEs) were collected throughout the study.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	10

Reporting groups

Reporting group title	Men ACWY_1 dose

Reporting group description:

Subjects who received one dose of MenACWY at 12 months of age, and who were administered a booster dose of MenACWY at 22 to 45 months of age

Reporting group title	Men ACWY_2 doses

Reporting group description:

Subjects who received two doses of MenACWY, one at 6 to 8 months and another at 12 months of age, and who were administered a booster dose of MenACWY at 22 to 45 months of age.

Reporting group title	Men C

Reporting group description:

Subjects who received one dose of Menjugate (MenC) at 12 months of age, and who were administered a booster dose of MenACWY at 22 to 45 months of age

Serious adverse events	Men ACWY_1 dose	Men ACWY_2 doses	Men C
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 44 (0.00%)	0 / 53 (0.00%)	0 / 43 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Men ACWY_1 dose	Men ACWY_2 doses	Men C
Total subjects affected by non-serious adverse events			
subjects affected / exposed	31 / 44 (70.45%)	33 / 53 (62.26%)	30 / 43 (69.77%)
Nervous system disorders			
Somnolence			
alternative assessment type: Systematic			
subjects affected / exposed	13 / 44 (29.55%)	10 / 53 (18.87%)	10 / 43 (23.26%)
occurrences (all)	15	11	10
Headache			

alternative assessment type: Systematic			
subjects affected / exposed	6 / 44 (13.64%)	5 / 53 (9.43%)	1 / 43 (2.33%)
occurrences (all)	6	5	1
General disorders and administration site conditions			
Irritability			
subjects affected / exposed	8 / 44 (18.18%)	12 / 53 (22.64%)	14 / 43 (32.56%)
occurrences (all)	9	13	16
Pyrexia			
alternative assessment type: Systematic			
subjects affected / exposed	8 / 44 (18.18%)	8 / 53 (15.09%)	7 / 43 (16.28%)
occurrences (all)	9	11	10
Injection site erythema			
alternative assessment type: Systematic			
subjects affected / exposed	17 / 44 (38.64%)	14 / 53 (26.42%)	15 / 43 (34.88%)
occurrences (all)	17	14	15
Injection site induration			
alternative assessment type: Systematic			
subjects affected / exposed	8 / 44 (18.18%)	6 / 53 (11.32%)	7 / 43 (16.28%)
occurrences (all)	8	6	7
Injection site pain			
alternative assessment type: Systematic			
subjects affected / exposed	15 / 44 (34.09%)	10 / 53 (18.87%)	13 / 43 (30.23%)
occurrences (all)	16	10	14
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 44 (4.55%)	4 / 53 (7.55%)	8 / 43 (18.60%)
occurrences (all)	3	6	9
Psychiatric disorders			
Eating disorder			
alternative assessment type: Systematic			
subjects affected / exposed	8 / 44 (18.18%)	6 / 53 (11.32%)	6 / 43 (13.95%)
occurrences (all)	10	6	7
Musculoskeletal and connective tissue disorders			

Arthralgia			
alternative assessment type: Systematic			
subjects affected / exposed	5 / 44 (11.36%)	1 / 53 (1.89%)	4 / 43 (9.30%)
occurrences (all)	5	1	6

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

1 site was excluded as not compliant with the protocol requirements for safety reporting,(65 subjects [21 subjects in MenACWY 2-dose group, 22 subjects in MEnACWY 1-dose group and 22 subjects in MenC 1-dose group])

Notes: