Clinical trial results:
A phase 3, multi-center, observer-blind, placebo-controlled, randomized study to evaluate the immunogenicity and safety of Novartis Meningococcal ACWY conjugate vaccine in healthy subjects from 11 to 55 years of age in Korea.

Due to a system error, the data reported in v1 is not correct and has been removed from public view.

Summary

EudraCT number	2014-005055-11
Trial protocol	Outside EU/EEA
Global end of trial date	16 March 2011

Results information

Result version number	v2 (current)
This version publication date	10 June 2016
First version publication date	02 April 2015
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	V59_39

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01274897
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Vaccines and Diagnostics S.r.l
Sponsor organisation address	Via Fiorentina, 1, Siena, Italy, 53100
Public contact	Posting director, Novartis Vaccines and Diagnostics S.r.l, RegistryContactVaccinesUS@novartis.com
Scientific contact	Posting director, Novartis Vaccines and Diagnostics S.r.l, RegistryContactVaccinesUS@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	04 October 2011
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 March 2011
Global end of trial reached?	Yes
Global end of trial date	16 March 2011
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary Immunogenicity objectives :
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.

Protection of trial subjects:

This trial was performed with the ethical principles that have their origin in the Declaration of Helsinki, that are consistent with Good Clinical Practice (GCP) according to International Conference on Harmonisation (ICH) guidelines, the applicable regulatory requirements(s) for the country in which the study was conducted, and applicable standard operating procedures (SOPs).

Background therapy: -

Evidence for comparator:

Placebo - One 0.5mL of saline placebo was administered by intramuscular (IM) injection in the deltoid area of the nondominant arm.

Actual start date of recruitment	20 December 2010
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	Korea, Democratic People's Republic of: 450
Worldwide total number of subjects	450
EEA total number of subjects	0

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)	37
Adolescents (12-17 years)	230
Adults (18-64 years)	183
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were enrolled from 8 centres in Korea.

Pre-assignment

Screening details:

All enrolled subjects were included in the trial.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	MenACWY-CRM

Arm description:

Subjects received one dose of MenACWY-CRM conjugate vaccine.

Arm type	Experimental
Investigational medicinal product name	Meningococcal (groups A, C, W, and Y) oligosaccharide diphtheria CRM-197 conjugate vaccine.
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

One 0.5mL dose of MenACWY was administered by intramuscular (IM) injection in the deltoid area of nondominant arm.

Arm title	Placebo

Arm description:

Subjects received the saline placebo.

Arm type	Placebo
Investigational medicinal product name	Saline Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

One 0.5mL of saline placebo was administered by intramuscular (IM) injection in the deltoid area of the nondominant arm.

Number of subjects in period 1	MenACWY-CRM	Placebo
Started	297	153
Completed	297	153

Baseline characteristics

Reporting groups	
Reporting group title	MenACWY-CRM
Reporting group description:	
Subjects received one dose of MenACWY-CRM conjugate vaccine.	
Reporting group title	Placebo
Reporting group description:	
Subjects received the saline placebo.	

Reporting group values	MenACWY-CRM	Placebo	Total
Number of subjects	297	153	450
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	19.6	19.3	
standard deviation	± 9.2	± 8.9	-
Gender categorical Units: Subjects			
Female	139	77	216
Male	158	76	234

End points

End points reporting groups

Reporting group title	MenACWY-CRM
Reporting group description:	
Subjects received one dose of MenACWY-CRM conjugate vaccine.	
Reporting group title	Placebo
Reporting group description:	
Subjects received the saline placebo.	
Subject analysis set title	Modified Intention-to-treat (MITT) population
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
All randomized subjects who received the vaccine, and provided at least one evaluable serum sample before and one after vaccination.	
Subject analysis set title	Per protocol population - Immunogenicity
Subject analysis set type	Per protocol
Subject analysis set description:	
All subjects in the MITT Set who received all the relevant doses of vaccine correctly, and provided evaluable serum samples at the relevant timepoints, and had no major protocol violation as defined prior to unblinding. A "major" deviation is defined as a protocol deviation that is considered to have a significant impact on the immunogenicity results of the subject compared to the result that would have possibly otherwise been obtained.	
Subject analysis set title	Safety population
Subject analysis set type	Safety analysis
Subject analysis set description:	
All subjects who were injected and who had post-injection safety data.	

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.

End point title	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.

End point description:

Seroresponse is 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.

End point type	Primary

End point timeframe:

At day 29 post-vaccination.

End point values	MenACWY-CRM	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	295	152		
Units: Percentage of subjects				
number (confidence interval 95%)				
Men A Seroresponse -baseline < 4 (N=246,120)	76 (70 to 81)	2 (0 to 6)		

Men A Seroresponse -baseline >= 4 (N=49,32)	76 (61 to 87)	0 (0 to 11)		
Men A Overall Seroresponse (N=295,152)	76 (71 to 81)	1 (0 to 5)		
Men C Seroresponse -baseline < 4 (N=111,67)	96 (91 to 99)	3 (0 to 10)		
Men C Seroresponse -baseline >= 4 (N=182,83)	80 (74 to 86)	0 (0 to 4)		
Men C Overall Seroresponse (N=293,150)	86 (82 to 90)	1 (0 to 5)		
Men W Seroresponse -baseline < 4 (N=32,20)	84 (67 to 95)	30 (12 to 54)		
Men W Seroresponse -baseline >= 4 (N=261,131)	21 (16 to 26)	0 (0 to 3)		
Men W Overall Seroresponse (N=293,151)	28 (23 to 33)	4 (1 to 8)		
Men Y Seroresponse -baseline < 4 (N=119,62)	89 (82 to 94)	5 (1 to 13)		
Men Y Seroresponse -baseline >= 4 (N=175,90)	55 (47 to 62)	0 (0 to 4)		
Men Y Overall Seroresponse (N=294,152)	69 (63 to 74)	2 (0 to 6)		

Statistical analyses

Statistical analysis title	Immune response in serogroup Men A
Statistical analysis description:	
Statistical Analysis 1 for Percentages of Subjects With Seroresponse, Directed Against Neisseria Meningitidis Serogroups A, C, W and Y After MenACWY-CRM Vaccination	
Comparison groups	MenACWY-CRM v Placebo
Number of subjects included in analysis	447
Analysis specification	Pre-specified
Analysis type	other
Method	Clopper Pearson
Parameter estimate	Vaccine group differences
Point estimate	75
Confidence interval	
level	95 %
sides	2-sided
lower limit	69
upper limit	79
Variability estimate	Standard deviation

Statistical analysis title	Immune response in serogroup Men C.
Statistical analysis description:	
Statistical Analysis 2 for Percentages of Subjects With Seroresponse, Directed Against Neisseria Meningitidis Serogroups A, C, W and Y After MenACWY-CRM Vaccination.	
Comparison groups	MenACWY-CRM v Placebo

Number of subjects included in analysis	447
Analysis specification	Pre-specified
Analysis type	other
Method	Clopper Pearson
Parameter estimate	Vaccine group differences
Point estimate	85
Confidence interval	
level	95 %
sides	2-sided
lower limit	80
upper limit	89

Statistical analysis title	Immune response in serogroup Men W.
Statistical analysis description:	
Statistical Analysis 3 for Percentages of Subjects With Seroresponse, Directed Against Neisseria Meningitidis Serogroups A, C, W and Y After MenACWY-CRM Vaccination.	
Comparison groups	MenACWY-CRM v Placebo
Number of subjects included in analysis	447
Analysis specification	Pre-specified
Analysis type	other
Method	Clopper Pearson
Parameter estimate	Vaccine group differences
Point estimate	24
Confidence interval	
level	95 %
sides	2-sided
lower limit	18
upper limit	30

Statistical analysis title	Immune response in serogroup Men Y.
Statistical analysis description:	
Statistical Analysis 2 for Percentages of Subjects With Seroresponse, Directed Against Neisseria Meningitidis Serogroups A, C, W and Y After MenACWY-CRM Vaccination.	
Comparison groups	MenACWY-CRM v Placebo
Number of subjects included in analysis	447
Analysis specification	Pre-specified
Analysis type	other
Method	Clopper Pearson
Parameter estimate	Vaccine group differences
Point estimate	67
Confidence interval	
level	95 %
sides	2-sided
lower limit	61
upper limit	72

Primary: Number of Subjects Who Reported Local and Systemic Reactogenicity During 7 Days After MenACWY-CRM Vaccination

End point title	Number of Subjects Who Reported Local and Systemic Reactogenicity During 7 Days After MenACWY-CRM Vaccination[1]

End point description:

Numbers of subjects with reported local and systemic reactions and other AEs.

End point type	Primary

End point timeframe:

During 7 days after 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 was no statistical null hypothesis associated with this safety objective.

End point values	MenACWY-CRM	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	297	153		
Units: Number of Subjects				
Any Local	83	14		
Pain	69	12		
Erythema	30	3		
Induration	30	0		
Systemic	83	43		
Chills	17	7		
Nausea	22	10		
Myalgia	45	13		
Arthralgia	6	4		
Headache	39	25		
Rash	1	0		
Fever (≥38°C)	3	1		
Stayed home due to reaction	9	2		
Analgesic/antipyretic medication use	7	3		

Statistical analyses

No statistical analyses for this end point

Secondary: To assess the immunogenicity of MenACWY as measured by the percentage of subjects with hSBA ≥1:8 directed against N. meningitidis serogroups A, C, W and Y

End point title	To assess the immunogenicity of MenACWY as measured by the percentage of subjects with hSBA ≥1:8 directed against N. meningitidis serogroups A, C, W and Y

End point description:

Percentage of subjects with hSBA ≥ 1:8 to N. meningitidis serogroups A, C, W135 and Y.

End point type	Secondary

End point timeframe:

At day 1 and day 29 post-vaccination.

End point values	MenACWY-CRM	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	295	152		
Units: Percentages of subjects				
number (confidence interval 95%)				
Men A Day 1 (N=295,152)	13 (9 to 17)	15 (10 to 22)		
Men A Day 29 (N=295,152)	79 (74 to 84)	16 (10 to 23)		
Men C Day 1 (N=293,150)	49 (44 to 55)	39 (31 to 47)		
Men C Day 29 (N=293,150)	99 (97 to 100)	37 (30 to 46)		
Men W Day 1 (N=293,151)	89 (85 to 92)	87 (80 to 92)		
Men W Day 29 (N=293,151)	98 (96 to 99)	88 (82 to 93)		
Men Y Day 1 (N=294,152)	54 (48 to 60)	53 (44 to 61)		
Men Y Day 29 (N=294,152)	94 (91 to 97)	51 (42 to 59)		

Statistical analyses

No statistical analyses for this end point

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

End point title	To assess the immunogenicity of MenACWY as measured by the hSBA geometric mean titers (GMTs) directed against N. meningitidis serogroups A, C, W and Y.

End point description:

Immunogenicity was assessed as hSBA GMTs and associated 95% CI, measured against N. meningitidis serogroups A, C, W and Y, before the vaccination (baseline, day 1) and at day 29 (28 days after MenACWY-CRM vaccination).

End point type	Secondary

End point timeframe:

At day 1 and day 29 post-vaccination.

End point values	MenACWY-CRM	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	295	152		
Units: GMT				
geometric mean (confidence interval 95%)				
Men A Day 1 (N=295,152)	2.7 (2.47 to 2.95)	2.86 (2.53 to 3.24)		
Men A Day 29 (N=295,152)	48 (39 to 57)	3 (2.31 to 3.88)		

Men C Day 1 (N=293,150)	7.82 (6.76 to 9.05)	5.94 (4.85 to 7.27)		
Men C Day 29 (N=293,150)	231 (198 to 269)	6.04 (4.89 to 7.47)		
Men W Day 1 (N=293,151)	51 (44 to 61)	48 (38 to 60)		
Men W Day 29 (N=293,151)	147 (125 to 171)	47 (38 to 58)		
Men Y Day 1 (N=294,152)	9.01 (7.64 to 11)	8.82 (7.02 to 11)		
Men Y Day 29 (N=294,152)	107 (89 to 128)	8.4 (6.54 to 11)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Solicited local and systemic AEs, oral temperature, all other AEs, and all concomitant medications were collected for 7 days following each vaccination. SAEs and AEs leading to withdrawal from the study were collected throughout the entire study period.

Adverse event reporting additional description:

Analysis was done on safety population ie, the subjects in the exposed population who provided post-baseline safety data.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

Subjects received the saline placebo

Reporting group title	MenACWY-CRM

Reporting group description:

Subjects received one dose of MenACWY-CRM conjugate vaccine

Serious adverse events	Placebo	MenACWY-CRM	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 153 (0.00%)	0 / 297 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Placebo	MenACWY-CRM	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	50 / 153 (32.68%)	117 / 297 (39.39%)	
Nervous system disorders			
Headache	Additional description: For Occurences MedDRA 17.1 version was used		
subjects affected / exposed	25 / 153 (16.34%)	39 / 297 (13.13%)	
occurrences (all)	27	48	
General disorders and administration site conditions			
Chills	Additional description: For occurences MedDRA 17.1 version was used.		

subjects affected / exposed	7 / 153 (4.58%)	17 / 297 (5.72%)	
occurrences (all)	8	22	
Injection site erythema	Additional description: For occurences MedDRA 17.1 version was used		
subjects affected / exposed	3 / 153 (1.96%)	30 / 297 (10.10%)	
occurrences (all)	3	30	
Injection site induration	Additional description: For Occurences MedDRA 17.1 version was used		
subjects affected / exposed	0 / 153 (0.00%)	30 / 297 (10.10%)	
occurrences (all)	0	30	
Injection site pain	Additional description: For Occurences MedDRA 17.1 version was used		
subjects affected / exposed	12 / 153 (7.84%)	69 / 297 (23.23%)	
occurrences (all)	12	72	
Malaise	Additional description: For Occurences MedDRA 17.1 version was used		
subjects affected / exposed	9 / 153 (5.88%)	21 / 297 (7.07%)	
occurrences (all)	9	23	
Gastrointestinal disorders			
Nausea	Additional description: For Occurences MedDRA 17.1 version was used		
subjects affected / exposed	10 / 153 (6.54%)	22 / 297 (7.41%)	
occurrences (all)	11	27	
Musculoskeletal and connective tissue disorders			
Myalgia	Additional description: For Occurences MedDRA 17.1 version was used		
subjects affected / exposed	13 / 153 (8.50%)	46 / 297 (15.49%)	
occurrences (all)	15	50	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 November 2010	This single amendment to the original protocol was implemented to clarify AE relatedness definitions and to correct the way indications of rash are captured. None of the revisions significantly altered the study conduct or would influence the interpretation of the study results

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported