



Clinical trial results:

A Phase 3, Open Label, Randomized, Controlled, Multi-Center Study to Evaluate the Safety and Immunogenicity of Novartis Meningococcal B Recombinant Vaccine When Administered Concomitantly With Routine Vaccines to Healthy Infants in Taiwan.

Summary

EudraCT number	2014-005568-14
Trial protocol	Outside EU/EEA
Global end of trial date	17 June 2016

Results information

Result version number	v1
This version publication date	08 March 2017
First version publication date	08 March 2017

Trial information

Trial identification

Sponsor protocol code	205249
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02173704
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	GlaxoSmithKline Biologicals
Sponsor organisation address	Rue de l'Institut 89, Rixensart, Belgium, B-1330
Public contact	Clinical Trials Call Center, GlaxoSmithKline Biologicals, 044 2089904466, GSKClinicalSupportHD@gsk.com
Scientific contact	Clinical Trials Call Center, GlaxoSmithKline Biologicals, 044 2089904466, GSKClinicalSupportHD@gsk.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	09 December 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 December 2015
Global end of trial reached?	Yes
Global end of trial date	17 June 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

1. To demonstrate the sufficiency of the immune response to Bexsero® vaccine, when administered concomitantly with routine vaccines (i.e. Infanrix-IPV+Hib®, Engerix-B® and Prevenar-13®) to healthy infants at 2, 4, 6 months of age as measured by percentage of subjects with human serum bactericidal activity (h-SBA) titer $\geq 1:5$ against the indicator strains H44/76, 5/99 and NZ98/254 at 1 month after the third vaccination (at 7 months of age);
2. To assess the safety of a 3-dose schedule (at 2, 4, 6 months) of Novartis Meningococcal B recombinant vaccine followed by a booster dose at 12 months when concomitantly administered with routine vaccines in healthy infants;
3. To assess serious adverse events (SAEs), medically attended adverse events (AEs), AEs leading to withdrawal throughout the entire study.

Protection of trial subjects:

This clinical study was designed and shall be implemented and reported in accordance with the International Conference of harmonization (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations, Novartis codes on protection of human rights, and with the ethical principles laid down in the Declaration of Helsinki (European Council 2001, US Code of Federal Regulations, ICH 1997).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 September 2014
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	Taiwan: 225
Worldwide total number of subjects	225
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	225

months)	
Children (2-11 years)	0
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 were recruited from 2 sites in Taiwan.

Pre-assignment

Screening details:

All subjects were enrolled.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

The study was an open-label study. Therefore, no blinding procedures were utilized.

Arms

Are arms mutually exclusive?	Yes
Arm title	Bexsero + Routine Group

Arm description:

Subjects received three doses of Bexsero® vaccine at 2, 4, 6 months followed by a booster dose at 12 months, concomitantly administered with routine vaccines (i.e. combined Infanrix-IPV+Hib® and Prevenar-13® at 2, 4, 6 months of age; Engerix-B® at 6 months of age; Priorix® and Varilrix® at 12 months of age.

Arm type	Experimental
Investigational medicinal product name	Bexsero®
Investigational medicinal product code	rMenB+OMV NZ
Other name	Novartis Meningococcal Recombinant B with Outer Membrane Vesicles (OMV) Vaccine
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL dose, administered in the anterolateral area of the right or left thigh.

Investigational medicinal product name	Prevenar-13®
Investigational medicinal product code	
Other name	Pfizer 13-valent pneumococcal conjugate vaccine
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL dose, administered in the anterolateral area of the right or left thigh.

Investigational medicinal product name	Infanrix-IPV+Hib®
Investigational medicinal product code	
Other name	GSK 5-in-1 DTPa-IPV-Hib vaccine
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL dose, administered in the anterolateral area of the right or left thigh.

Investigational medicinal product name	Engerix-B®
Investigational medicinal product code	
Other name	GSK Hepatitis B vaccine
Pharmaceutical forms	Solution for injection

Routes of administration	Intramuscular use
Dosage and administration details:	
0.5 mL dose, administered in the anterolateral area of the right or left thigh.	
Investigational medicinal product name	Priorix®
Investigational medicinal product code	
Other name	GSK Measles, Mumps and Rubella vaccine
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use
Dosage and administration details:	
0.5 mL dose, administered in the anterolateral area of the right or left thigh.	
Investigational medicinal product name	Varilrix®
Investigational medicinal product code	
Other name	GSK Varicella vaccine
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use
Dosage and administration details:	
0.5 mL dose, administered in the anterolateral area of the right or left thigh.	
Arm title	Routine Group
Arm description:	
Subjects received routine vaccines Infanrix-IPV+Hib® and Prevenar-13® at 2, 4, 6 months of age; Engerix-B® vaccine at 6 months; Priorix® and Varilrix® vaccines at 12 months of age.	
Arm type	Active comparator
Investigational medicinal product name	Prevenar-13®
Investigational medicinal product code	
Other name	Pfizer 13-valent pneumococcal conjugate vaccine
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use
Dosage and administration details:	
0.5 mL dose, administered in the anterolateral area of the right or left thigh.	
Investigational medicinal product name	Infanrix-IPV+Hib®
Investigational medicinal product code	
Other name	GSK 5-in-1 DTPa-IPV-Hib vaccine
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use
Dosage and administration details:	
0.5 mL dose, administered in the anterolateral area of the right or left thigh.	
Investigational medicinal product name	Engerix-B®
Investigational medicinal product code	
Other name	GSK Hepatitis B vaccine
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use
Dosage and administration details:	
0.5 mL dose, administered in the anterolateral area of the right or left thigh.	
Investigational medicinal product name	Priorix®
Investigational medicinal product code	
Other name	GSK Measles, Mumps and Rubella vaccine
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use
Dosage and administration details:	
0.5 mL dose, administered in the anterolateral area of the right or left thigh.	

Investigational medicinal product name	Varilrix®
Investigational medicinal product code	
Other name	GSK Varicella vaccine
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

0.5 mL dose, administered in the anterolateral area of the right or left thigh.

Number of subjects in period 1	Bexsero + Routine Group	Routine Group
Started	150	75
Completed	137	71
Not completed	13	4
Consent withdrawn by subject	9	4
Adverse event, non-fatal	1	-
Unspecified	1	-
Lost to follow-up	1	-
Protocol deviation	1	-

Baseline characteristics

Reporting groups

Reporting group title	Bexsero + Routine Group
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Reporting group description:

Subjects received three doses of Bexsero® vaccine at 2, 4, 6 months followed by a booster dose at 12 months, concomitantly administered with routine vaccines (i.e. combined Infanrix-IPV+Hib® and Prevenar-13® at 2, 4, 6 months of age; Engerix-B® at 6 months of age; Priorix® and Varilrix® at 12 months of age.

Reporting group title	Routine Group
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Reporting group description:

Subjects received routine vaccines Infanrix-IPV+Hib® and Prevenar-13® at 2, 4, 6 months of age; Engerix-B® vaccine at 6 months; Priorix® and Varilrix® vaccines at 12 months of age.

Reporting group values	Bexsero + Routine Group	Routine Group	Total
Number of subjects	150	75	225
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	150	75	225
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: days			
arithmetic mean	67.9	68.9	
standard deviation	± 6.46	± 6.86	-
Gender categorical Units: Subjects			
Female	82	27	109
Male	68	48	116

End points

End points reporting groups

Reporting group title	Bexsero + Routine Group
Reporting group description:	
Subjects received three doses of Bexsero® vaccine at 2, 4, 6 months followed by a booster dose at 12 months, concomitantly administered with routine vaccines (i.e. combined Infanrix-IPV+Hib® and Prevenar-13® at 2, 4, 6 months of age; Engerix-B® at 6 months of age; Priorix® and Varilrix® at 12 months of age.	
Reporting group title	Routine Group
Reporting group description:	
Subjects received routine vaccines Infanrix-IPV+Hib® and Prevenar-13® at 2, 4, 6 months of age; Engerix-B® vaccine at 6 months; Priorix® and Varilrix® vaccines at 12 months of age.	

Primary: Percentage of subjects with Serum Bactericidal Activity (SBA) titer $\geq 1:5$ against *Neisseria meningitidis* serogroup B strains

End point title	Percentage of subjects with Serum Bactericidal Activity (SBA) titer $\geq 1:5$ against <i>Neisseria meningitidis</i> serogroup B strains
End point description:	
Percentage of subjects with Serum Bactericidal Activity (SBA) titer $\geq 1:5$ at one month following the third vaccination (at 7 months of age) against the indicator strains H44/76, 5/99, NZ98/254 and strain M10713 when Bexsero® was administered concomitantly with routine vaccines (Infanrix-IPV+Hib®, Prevenar-13® and Engerix®). The analysis was performed on the Full Analysis Set (FAS) population Day 152, which included all subjects in the Exposed set who received at least one dose of a study vaccination and provided immunogenicity data at relevant time points.	
End point type	Primary
End point timeframe:	
At Day 1 and one month after the third vaccination (Day 152)	

End point values	Bexsero + Routine Group	Routine Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	135	71		
Units: Percentage				
number (confidence interval 95%)				
H44/76 (Day 1) (N=116;59)	0 (0 to 3.1)	0 (0 to 6.1)		
H44/76 (Day 152) (N=130;66)	100 (97.2 to 100)	0 (0 to 5.4)		
5/99 (Day 1) (N=124;69)	1 (0.02 to 4.4)	1 (0.04 to 7.8)		
5/99 (Day 152) (N=129;70)	100 (97.2 to 100)	0 (0 to 5.1)		
M10713 (Day 1) (N=100;57)	10 (4.9 to 17.6)	19 (10 to 31.9)		
M10713 (Day 152) (N=123;65)	59 (50.1 to 68.1)	8 (2.5 to 17)		
NZ98/254 (Day 1) (N=134;71)	0 (0 to 2.7)	0 (0 to 5.1)		
NZ98/254 (Day 152) (N=135;71)	79 (71.4 to 85.8)	0 (0 to 5.1)		

Statistical analyses

Statistical analysis title	Statistical analysis H44/76 strain
Statistical analysis description:	
The null hypothesis associated with the primary objective is that the proportion of subjects with SBA titers $\geq 1:5$ one month after the third dose of the Bexsero® vaccine was ≤ 0.70 . Assuming the results for the three strains are independent, the power to reject the null hypothesis associated with the primary objectives to demonstrate sufficiency of response (for all three strains was 92 %).	
Comparison groups	Bexsero + Routine Group v Routine Group
Number of subjects included in analysis	206
Analysis specification	Pre-specified
Analysis type	other ^[1]
Method	Exact test of binomial proportion
Parameter estimate	Single binomial proportion
Point estimate	100
Confidence interval	
level	95 %
sides	2-sided
lower limit	97.2
upper limit	100

Notes:

[1] - The criterion for a sufficient immune response was that the lower limit of the two-sided 95% CI for the percentage of subjects with SBA titer $\geq 1:5$ should be $\geq 70\%$.

Statistical analysis title	Statistical analysis 5/99 strain
Statistical analysis description:	
The power to reject the null hypothesis associated with the primary objective for the 5/99 strain was 99 %.	
Comparison groups	Bexsero + Routine Group v Routine Group
Number of subjects included in analysis	206
Analysis specification	Pre-specified
Analysis type	other ^[2]
Method	Exact test of binomial proportion
Parameter estimate	Single binomial proportion
Point estimate	100
Confidence interval	
level	95 %
sides	2-sided
lower limit	97.2
upper limit	100

Notes:

[2] - The criterion for a sufficient immune response was that the lower limit of the two-sided 95 % CI for the percentage of subjects with SBA titer $\geq 1:5$ should be $\geq 70\%$.

Statistical analysis title	Statistical analysis NZ98/254 strain
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Statistical analysis description:

The power to reject the null hypothesis associated with the primary objective for the NZ98/254 strain was 94 %.

Comparison groups	Bexsero + Routine Group v Routine Group
Number of subjects included in analysis	206
Analysis specification	Pre-specified
Analysis type	other ^[3]
Method	Exact test of binomial proportion
Parameter estimate	Single binomial proportion
Point estimate	79
Confidence interval	
level	95 %
sides	2-sided
lower limit	71.4
upper limit	85.8

Notes:

[3] - The criterion for a sufficient immune response was that the lower limit of the two-sided 95% CI for the percentage of subjects with SBA titer $\geq 1:5$ should be ≥ 70 %.

Secondary: Percentage of subjects with SBA titer $\geq 1:5$ against *Neisseria meningitidis* serogroup B strains, when Bexsero® booster dose was administered with routine vaccines (Priorix® + Varilrix® vaccines)

End point title	Percentage of subjects with SBA titer $\geq 1:5$ against <i>Neisseria meningitidis</i> serogroup B strains, when Bexsero® booster dose was administered with routine vaccines (Priorix® + Varilrix® vaccines)
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End point description:

Percentage of subjects with SBA titer $\geq 1:5$ before booster vaccination and after booster vaccination when Bexsero® booster dose was administered with routine vaccines (Priorix® + Varilrix® vaccines) as compared to when only routine vaccines were administered.

The analysis was performed on the FAS population Day 335, which included all subjects in the Exposed set who received at least one dose of a study vaccination and provided immunogenicity data at relevant time points.

End point type	Secondary
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End point timeframe:

Day 305 and Day 335

End point values	Bexsero + Routine Group	Routine Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	136	71		
Units: Percentage				
geometric mean (confidence interval 95%)				
H44/76 (Day 305) (N=123;64)	81 (73.3 to 87.8)	2 (0.04 to 8.4)		
H44/76 (Day 335) (N=127;64)	99 (95.7 to 99.98)	2 (0.04 to 8.4)		
5/99 (Day 305) (N=135;70)	99 (94.8 to 99.82)	1 (0.04 to 7.7)		
5/99 (Day 335) (N=134;71)	99 (94.7 to 99.82)	0 (0 to 5.1)		
M10713 (Day 305) (N=130;65)	22 (14.8 to 29.6)	11 (4.4 to 20.9)		

M10713 (Day 335) (N=130;69)	92 (86.3 to 96.2)	13 (6.1 to 23.3)		
NZ98/254 (Day 305) (N=136;70)	17 (11 to 24.3)	1 (0.04 to 7.7)		
NZ98/254 (Day 335) (N=136;71)	94 (88.7 to 97.4)	0 (0 to 5.1)		

Statistical analyses

Statistical analysis title

Statistical analysis H44/76 strain

Statistical analysis description:

The null hypothesis associated with the primary objective is that the proportion of subjects with SBA titers $\geq 1:5$ one month after the third dose of the Bexsero® vaccine was ≤ 0.70 . Assuming the results for the three strains are independent, the power to reject the null hypothesis associated with the primary objectives to demonstrate sufficiency of response (for all three strains was 92%).

Comparison groups	Bexsero + Routine Group v Routine Group
Number of subjects included in analysis	207
Analysis specification	Pre-specified
Analysis type	other ^[4]
Method	Exact test of binomial proportion
Parameter estimate	Single binomial proportion
Point estimate	99
Confidence interval	
level	95 %
sides	2-sided
lower limit	95.7
upper limit	99.98

Notes:

[4] - The criterion for a sufficient immune response was that the lower limit of the two-sided 95% CI for the percentage of subjects with SBA titer $\geq 1:5$ should be $\geq 70\%$.

Statistical analysis title

Statistical analysis 5/99 strain

Statistical analysis description:

The power to reject the null hypothesis associated with the secondary objective for the 5/99 strain was 99%.

Comparison groups	Bexsero + Routine Group v Routine Group
Number of subjects included in analysis	207
Analysis specification	Pre-specified
Analysis type	other ^[5]
Method	Exact test for binomial proportion
Parameter estimate	Single binomial proportion
Point estimate	99
Confidence interval	
level	95 %
sides	2-sided
lower limit	94.7
upper limit	99.82

Notes:

[5] - The criterion for a sufficient immune response was that the lower limit of the two-sided 95% CI for the percentage of subjects with SBA titer $\geq 1:5$ should be $\geq 75\%$.

Statistical analysis title

Statistical analysis NZ98/254 strain

Statistical analysis description:

The power to reject the null hypothesis associated with the secondary objective for the NZ98/254 strain was 99%.

Comparison groups	Bexsero + Routine Group v Routine Group
Number of subjects included in analysis	207
Analysis specification	Pre-specified
Analysis type	other ^[6]
Method	Exact test for binomial proportions
Parameter estimate	Single binomial proportion
Point estimate	94
Confidence interval	
level	95 %
sides	2-sided
lower limit	88.7
upper limit	97.4

Notes:

[6] - The criterion for a sufficient immune response was that the lower limit of the two-sided 95% CI for the percentage of subjects with SBA titer $\geq 1:5$ should be $\geq 75\%$.

Secondary: SBA Geometric Mean Titers (GMTs) against *Neisseria meningitidis* serogroup B indicator strains, when Bexsero® vaccine was administered with routine vaccines

End point title	SBA Geometric Mean Titers (GMTs) against <i>Neisseria meningitidis</i> serogroup B indicator strains, when Bexsero® vaccine was administered with routine vaccines
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End point description:

SBA GMTs against the indicator strains H44/76, 5/99, NZ98/254 and strain M10713 were evaluated at baseline (2 months of age, Day 1), 1 month after the third vaccination with Bexsero® with concomitant routine vaccines (Infanrix-IPV+Hib®, Prevenar-13®, Engerix®) (7 months of age, Day 152) or prior to the booster dose of Bexsero® with routine vaccines (Priorix®, Varilrix®) (12 months of age, Day 305) and 1 month after the booster dose (13 months of age, Day 335), as compared to when only routine vaccines were administered.

The analysis was performed on the FAS population, which included all subjects in the Exposed set who received at least one dose of a study vaccination and provided immunogenicity data at relevant time points.

End point type	Secondary
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End point timeframe:

Day 1, Day 152, Day 305 and Day 335

End point values	Bexsero + Routine Group	Routine Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	145	73		
Units: Titers				
geometric mean (confidence interval 95%)				
H44/76 (Day 1) (N=132;65)	1.01 (0.99 to 1.02)	1.02 (0.98 to 1.05)		
H44/76 (Day 152) (N=130;66)	72 (64 to 81)	1.01 (0.99 to 1.03)		
H44/76 (Day 305) (N=123;64)	11 (9.27 to 13)	1.26 (1.06 to 1.5)		
H44/76 (Day 335) (N=127;64)	157 (131 to 188)	1.1 (1.01 to 1.19)		

5/99 (Day 1) (N=141;72)	1.08 (0.98 to 1.18)	1.03 (0.98 to 1.08)		
5/99 (Day 152) (N=129;70)	963 (864 to 1073)	1 (1 to 1)		
5/99 (Day 305) (N=135;70)	205 (174 to 242)	1.1 (0.91 to 1.33)		
5/99 (Day 335) (N=134;71)	2315 (1893 to 2832)	1 (1 to 1)		
M10713 (Day 1) (N=121;64)	1.36 (1.2 to 1.54)	1.75 (1.37 to 2.24)		
M10713 (Day 152) (N=123;65)	8.41 (6.63 to 11)	1.25 (1.08 to 1.46)		
M10713 (Day 305) (N=130;65)	2.18 (1.81 to 2.63)	1.6 (1.34 to 1.91)		
M10713 (Day 335) (N=130;69)	17 (14 to 20)	1.58 (1.33 to 1.89)		
NZ98/254 (Day 1) (N=145;73)	1.01 (0.99 to 1.02)	1 (1 to 1)		
NZ98/254 (Day 152) (N=135;71)	9.2 (7.82 to 11)	1.02 (0.98 to 1.05)		
NZ98/254 (Day 305) (N=136;70)	1.91 (1.63 to 2.25)	1.04 (0.98 to 1.1)		
NZ98/254 (Day 335) (N=136;71)	26 (21 to 31)	1 (1 to 1)		

Statistical analyses

No statistical analyses for this end point

Secondary: SBA Geometric Mean Ratios (GMRs) against Neisseria meningitidis serogroup B strains

End point title	SBA Geometric Mean Ratios (GMRs) against Neisseria meningitidis serogroup B strains
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End point description:

GMRs of post-vaccination versus pre-vaccination of SBA titer against the indicator strains H44/76, 5/99, NZ98/254 and strain M10713 were evaluated at one month after the third vaccination with Bexsero® vaccine and concomitant routine vaccines (Infanrix-IPV+Hib®, Prevenar-13® and Engerix®) (Day 152), as compared to baseline (Day 1) or at one month after the administration of the booster dose of Bexsero® vaccine and routine vaccines (Priorix® and Varilrix®) (Day 335), as compared to prior to the booster dose (Day 305).

The analysis was performed on the FAS population, which included all subjects in the Exposed set who received at least one dose of a study vaccination and provided immunogenicity data at relevant time points.

End point type	Secondary
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End point timeframe:

Day 152 and Day 335

End point values	Bexsero + Routine Group	Routine Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	135	71		
Units: Ratio				
number (confidence interval 95%)				

H44/76 (Day 152/Day 1) (N=116;59)	71 (63 to 80)	0.99 (0.95 to 1.04)		
H44/76 (Day 335/Day 305) (N=113;56)	155 (127 to 188)	1.07 (0.97 to 1.19)		
5/99 (Day 152/Day 1) (N=124;69)	875 (752 to 1019)	0.97 (0.93 to 1.03)		
5/99 (Day 335/Day 305) (N=129;70)	2110 (1674 to 2659)	0.97 (0.93 to 1.03)		
M10713 (Day 152/Day 1) (N=100;57)	5.69 (4.25 to 7.61)	0.68 (0.54 to 0.85)		
M10713 (Day 335/Day 305) (N=105;60)	12 (8.99 to 15)	0.91 (0.68 to 1.21)		
NZ98/254 (Day 152/Day 1) (N=134;71)	9.18 (7.79 to 11)	1.02 (0.98 to 1.05)		
NZ98/254 (Day 335/Day 305) (N=135;71)	25 (21 to 31)	1 (1 to 1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentages of subjects with SBA titers $\geq 1:8$ against *Neisseria meningitidis* serogroup B, when Bexsero® vaccine was administered with routine vaccines

End point title	Percentages of subjects with SBA titers $\geq 1:8$ against <i>Neisseria meningitidis</i> serogroup B, when Bexsero® vaccine was administered with routine vaccines
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End point description:

Percentages of subjects with SBA titers $\geq 1:8$ against *N.meningitidis* serogroup B strains, at one month after concomitant administration of third primary dose of Bexsero® with routine vaccines (Infanrix-IPV+Hib® + Prevenar-13® + Engerix®) and at one month after concomitant administration of Bexsero® booster dose with routine vaccines (Priorix® + Varilrix®), as compared to when only routine vaccines were administered.

The analysis was performed on the FAS-3 population, which included all subjects in the Exposed set who received at least one dose of a study vaccination and who provided immunogenicity data at relevant time points.

End point type	Secondary
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End point timeframe:

At Day 1, Day 152, Day 305 and Day 335

End point values	Bexsero + Routine Group	Routine Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	145	73		
Units: Percentage				
number (confidence interval 95%)				
H44/76 (Day 1) (N=132;65)	0 (0 to 2.8)	0 (0 to 5.5)		
H44/76 (Day 152) (N=130;66)	100 (97.2 to 100)	0 (0 to 5.4)		
H44/76 (Day 305) (N=123;64)	66 (56.8 to 74.2)	2 (0.04 to 8.4)		
H44/76 (Day 335) (N=127;64)	99 (95.7 to 99.98)	0 (0 to 5.6)		

5/99 (Day 1) (N=141;72)	1 (0.02 to 3.9)	0 (0 to 5)		
5/99 (Day 152) (N=129;70)	100 (97.2 to 100)	0 (0 to 5.1)		
5/99 (Day 305) (N=135;70)	99 (94.8 to 99.82)	1 (0.04 to 7.7)		
5/99 (Day 335) (N=134;71)	99 (94.7 to 99.82)	0 (0 to 5.1)		
M10713 (Day 1) (N=121;64)	3 (0.9 to 8.2)	8 (2.6 to 17.3)		
M10713 (Day 152) (N=123;65)	49 (39.7 to 58)	5 (1 to 12.9)		
M10713 (Day 305) (N=130;65)	15 (9.7 to 22.8)	3 (0.37 to 10.7)		
M10713 (Day 335) (N=130;69)	77 (68.7 to 83.9)	6 (1.6 to 14.2)		
NZ98/254 (Day 1) (N=145;73)	0 (0 to 2.5)	0 (0 to 4.9)		
NZ98/254 (Day 152) (N=135;71)	59 (49.7 to 66.9)	0 (0 to 5.1)		
NZ98/254 (Day 305) (N=136;70)	9 (4.6 to 14.9)	0 (0 to 5.1)		
NZ98/254 (Day 335) (N=136;71)	86 (79 to 91.4)	0 (0 to 5.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting any solicited local adverse events (AEs) after receiving Bexsero® vaccine with routine vaccines, at 2, 4 and 6 months of age

End point title	Number of subjects reporting any solicited local adverse events (AEs) after receiving Bexsero® vaccine with routine vaccines, at 2, 4 and 6 months of age
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End point description:

The number of subjects who reported any solicited local symptoms following concomitant administration of Bexsero® vaccine with routine vaccines (Infanrix-IPV+Hib®, Prevenar-13® and Engerix-B®), as compared to when only routine vaccines were administered alone at 2, 4 and 6 months of age. Assessed solicited local symptoms were: Erythema, Induration, Swelling and Tenderness. Any = occurrence of the symptom regardless of intensity grade.

The analysis was performed on the Solicited Safety Set, which included all subjects in the Exposed population who provided post-vaccination reactogenicity data.

End point type	Secondary
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End point timeframe:

From Day 1 (6 hours) to Day 7 after each vaccination

End point values	Bexsero + Routine Group	Routine Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148	73		
Units: Subjects				
Erythema (1st Bexsero® vacc.) (N=148;0)	54	0		
Induration (1st Bexsero® vacc.) (N=147;0)	63	0		
Swelling (1st Bexsero® vacc.) (N=146;0)	34	0		

Tenderness (1st Bexsero® vacc.) (N=147;0)	75	0		
Erythema (1st Infanrix-IPV+Hib® vacc.) (N=148;73)	26	3		
Induration (1st Infanrix-IPV+Hib® vacc.)(N=148;73)	23	11		
Swelling (1st Infanrix-IPV+Hib® vacc.) (N=148;73)	15	3		
Tenderness (1st Infanrix-IPV+Hib® vacc.)(N=146;73)	45	12		
Erythema (1st Prevenar-13® vacc.) (N=148;73)	26	9		
Induration (1st Prevenar-13® vacc.) (N=148;73)	29	15		
Swelling (1st Prevenar-13® vacc.) (N=148;73)	11	4		
Tenderness (1st Prevenar-13® vacc.) (N=147;73)	50	12		
Erythema (2nd Bexsero® vacc.) (N=140;0)	59	0		
Induration (2nd Bexsero® vacc.) (N=140;0)	51	0		
Swelling (2nd Bexsero® vacc.) (N=140;0)	35	0		
Tenderness (2nd Bexsero® vacc.) (N=140;0)	67	0		
Erythema (2nd Infanrix-IPV+Hib® vacc.) (N=140;72)	39	12		
Induration (2nd Infanrix-IPV+Hib® vacc.)(N=140;72)	23	16		
Swelling (2nd Infanrix-IPV+Hib® vacc.) (N=140;72)	18	6		
Tenderness (2nd Infanrix-IPV+Hib® vacc.)(N=140;72)	45	10		
Erythema (2nd Prevenar-13® vacc.) (N=140;72)	35	12		
Induration (2nd Prevenar-13® vacc.) (N=140;72)	18	8		
Swelling (2nd Prevenar-13® vacc.) (N=140;72)	12	6		
Tenderness (2nd Prevenar-13® vacc.) (N=140;72)	44	9		
Erythema (3rd Bexsero® vacc.) (N=138;0)	55	0		
Induration (3rd Bexsero® vacc.) (N=138;0)	57	0		
Swelling (3rd Bexsero® vacc.) (N=138;0)	49	0		
Tenderness (3rd Bexsero® vacc.) (N=138;0)	68	0		
Erythema (3rd Infanrix-IPV+Hib® vacc.) (N=137;72)	28	15		
Induration (3rd Infanrix-IPV+Hib® vacc.)(N=138;72)	25	16		
Swelling (3rd Infanrix-IPV+Hib® vacc.) (N=138;72)	20	10		
Tenderness (3rd Infanrix-IPV+Hib® vacc.)(N=138;72)	42	8		
Erythema (3rd Prevenar-13® vacc.) (N=138;72)	27	12		
Induration (3rd Prevenar-13® vacc.) (N=138;72)	21	11		

Swelling (3rd Prevenar-13® vacc.) (N=138;72)	17	4		
Tenderness (3rd Prevenar-13® vacc.) (N=138;72)	45	9		
Erythema (Engerix-B® vacc.) (N=138;72)	33	12		
Induration (Engerix-B® vacc.) (N=137;72)	33	17		
Swelling (Engerix-B® vacc.) (N=138;71)	25	6		
Tenderness (Engerix-B® vacc.) (N=138;72)	45	7		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting any solicited systemic AEs and other solicited data after receiving Bexsero® vaccine with routine vaccines or routine vaccines alone, at 2, 4 and 6 months of age

End point title	Number of subjects reporting any solicited systemic AEs and other solicited data after receiving Bexsero® vaccine with routine vaccines or routine vaccines alone, at 2, 4 and 6 months of age
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End point description:

The number of subjects who reported any solicited systemic AEs and other solicited data following concomitant administration of Bexsero® vaccine with routine vaccines (Infanrix-IPV+Hib®, Prevenar-13® and Engerix-B®), as compared to when only routine vaccines were administered alone at 2, 4 and 6 months of age. Assessed solicited systemic symptoms were: Change in Eating Habits, Diarrhea, Irritability, Persistent Crying, Rash, Sleepiness, Vomiting and Fever (defined as body temperature ≥ 38.0 °C). Other solicited data included: Prevention of Pain and/or Fever and Treatment of Pain and/or Fever. Any = occurrence of the symptom regardless of intensity grade.

The analysis was performed on the Solicited Safety Set, which included all subjects in the Exposed population who provided post-vaccination reactogenicity data.

End point type	Secondary
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End point timeframe:

From Day 1 (6 hours) to Day 7 after each vaccination

End point values	Bexsero + Routine Group	Routine Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148	73		
Units: Subjects				
Change in Eating Habits (1st vacc.) (N=148;73)	92	26		
Diarrhea (1st vacc.) (N=148;73)	28	8		
Irritability (1st vacc.) (N=148;73)	111	32		
Persistent Crying (1st vacc.) (N=148;73)	96	30		
Rash (1st vacc.) (N=148;73)	18	4		
Sleepiness (1st vacc.) (N=148;73)	79	33		
Vomiting (1st vacc.) (N=148;73)	21	6		
Fever (1st vacc.) (N=148;73)	71	11		

Change in Eating Habits (2nd vacc.) (N=140;72)	72	21		
Diarrhea (2nd vacc.) (N=140;72)	30	9		
Irritability (2nd vacc.) (N=140;72)	90	31		
Persistent Crying (2nd vacc.) (N=140;72)	82	23		
Rash (2nd vacc.) (N=140;72)	18	8		
Sleepiness (2nd vacc.) (N=140;72)	66	21		
Vomiting (2nd vacc.) (N=140;72)	16	9		
Fever (2nd vacc.) (N=140;71)	72	11		
Change in Eating Habits (3rd vacc.) (N=138;72)	72	17		
Diarrhea (3rd vacc.) (N=138;72)	19	4		
Irritability (3rd vacc.) (N=138;72)	94	28		
Persistent Crying (3rd vacc.) (N=138;72)	72	28		
Rash (3rd vacc.) (N=138;72)	16	4		
Sleepiness (3rd vacc.) (N=138;72)	49	13		
Vomiting (3rd vacc.) (N=138;72)	15	7		
Fever (3rd vacc.) (N=138;72)	68	12		
Prevention of Pain/Fever (1st vacc.) (N=147;73)	4	0		
Treatment of Pain/Fever (1st vacc.) (N=147;73)	35	1		
Prevention of Pain/Fever (2nd vacc.) (N=140;71)	4	0		
Treatment of Pain/Fever (2nd vacc.) (N=140;71)	38	2		
Prevention of Pain/Fever (3rd vacc.) (N=138;72)	6	1		
Treatment of Pain/Fever (3rd vacc.) (N=138;72)	30	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting any solicited local AEs after receiving Bexsero® booster dose with routine vaccines, at 12 months of age

End point title	Number of subjects reporting any solicited local AEs after receiving Bexsero® booster dose with routine vaccines, at 12 months of age
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End point description:

The number of subjects who reported any solicited local AEs following concomitant administration of Bexsero® dose with routine vaccines (Priorix® and Varilrix®), as compared to when only routine vaccines were administered alone, at 12 months of age. Assessed solicited local symptoms were: Erythema, Induration, Swelling and Tenderness. Any = occurrence of the symptom regardless of intensity grade.

The analysis was performed on the Solicited Safety Set, which included all subjects in the Exposed population who provided post-vaccination reactogenicity data.

End point type	Secondary
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End point timeframe:

From Day 1 to Day 7 after booster vaccination

End point values	Bexsero + Routine Group	Routine Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	137	72		
Units: Subjects				
Erythema (Bexsero® booster vacc.) (N=136;0)	53	0		
Induration (Bexsero® booster vacc.) (N=136;0)	56	0		
Swelling (Bexsero® booster vacc.) (N=135;0)	44	0		
Tenderness (Bexsero® booster vacc.) (N=136;0)	66	0		
Erythema (Priorix® vacc.) (N=137;72)	24	13		
Induration (Priorix® vacc.) (N=137;72)	15	6		
Swelling (Priorix® vacc.) (N=137;72)	19	4		
Tenderness (Priorix® vacc.) (N=137;72)	37	6		
Erythema (Varilrix® vacc.) (N=137;72)	32	14		
Induration (Varilrix® vacc.) (N=137;72)	14	7		
Swelling (Varilrix® vacc.) (N=137;72)	21	6		
Tenderness (Varilrix® vacc.) (N=137;72)	41	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting any solicited systemic AEs and other solicited data after receiving Bexsero® booster dose with routine vaccines, at 12 months of age

End point title	Number of subjects reporting any solicited systemic AEs and other solicited data after receiving Bexsero® booster dose with routine vaccines, at 12 months of age
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End point description:

The number of subjects who reported any solicited systemic AEs and other solicited data following concomitant administration of Bexsero® booster dose with routine vaccines (Priorix® and Varilrix®), as compared to when only routine vaccines were administered alone at 12 months of age. Assessed solicited systemic AEs were: Change in Eating Habits, Diarrhea, Irritability, Persistent Crying, Rash, Sleepiness, Vomiting, Fever (defined as body temperature ≥ 38.0 °C) and Lymphadenopathy. Other solicited data included: Prevention of Pain and/or Fever and Treatment of Pain and/or Fever. Any = occurrence of the symptom regardless of intensity grade.

The analysis was performed on the Solicited Safety Set, which included all subjects in the Exposed population who provided post-vaccination reactogenicity data.

End point type	Secondary
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End point timeframe:

From Day 1 (6 hours) to Day 7 after vaccination

End point values	Bexsero + Routine Group	Routine Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	137	72		
Units: Subjects				
Change in Eating Habits (N=137;72)	58	19		
Diarrhea (N=137;72)	27	10		
Irritability (N=137;72)	71	16		
Persistent Crying (N=137;72)	58	15		
Rash (N=137;72)	25	9		
Sleepiness (N=137;72)	36	9		
Vomiting (N=137;72)	10	6		
Fever (N=137;72)	60	6		
Lymphadenopathy (N=136;72)	1	1		
Prevention of Pain/Fever (N=137;72)	1	0		
Treatment of Pain/Fever (N=137;72)	20	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting any and Grade 3 solicited systemic AEs after receiving Priorix® and Varilrix® routine vaccines at 12 months of age

End point title	Number of subjects reporting any and Grade 3 solicited systemic AEs after receiving Priorix® and Varilrix® routine vaccines at 12 months of age
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End point description:

The number of subjects who reported any and Grade 3 solicited systemic AEs after the administration of Varilrix® and Priorix® vaccines (with and without Bexsero® vaccine) at 12 months of age. Solicited systemic AEs assessed were Rash and Lymphadenopathy. The symptoms were collected for an extended period of 28 days following Varilrix® and Priorix® vaccinations. Any = occurrence of the symptom regardless of intensity grade. Grade 3 symptom = symptom that prevented normal activity. The analysis was performed on the Safety Set (solicited AEs), which included all subjects in the Exposed population who provided post-vaccination reactogenicity data.

End point type	Secondary
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End point timeframe:

From Day 1 through Day 28 after Priorix® and Varilrix® vaccinations

End point values	Bexsero + Routine Group	Routine Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	137	72		
Units: Subjects				
Any Rash	50	24		
Grade 3 Rash	5	5		
Lymphadenopathy	34	21		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting unsolicited AEs after receiving Bexsero® vaccination with routine vaccines

End point title	Number of subjects reporting unsolicited AEs after receiving Bexsero® vaccination with routine vaccines
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End point description:

The number of subjects who reported any unsolicited AEs following concomitant administration of Bexsero® vaccine with routine vaccines (Infanrix-IPV + Hib®, Prevenar-13®, Engerix-B®, Priorix® and Varilrix®), as compared to when only routine vaccines were administered alone.

An unsolicited AE covers any untoward medical occurrence in a clinical investigation subject temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product and reported in addition to those solicited during the clinical study and any solicited symptom with onset outside the specified period of follow-up for solicited symptoms. Any was defined as the occurrence of any unsolicited AE regardless of intensity grade or relation to vaccination. Possibly or probably related AE = AE assessed by the investigator as related to the vaccination.

The analysis was performed on the Safety Set (Unsolicited AEs).

End point type	Secondary
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End point timeframe:

From Day 1 to Day 7 after each vaccination

End point values	Bexsero + Routine Group	Routine Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	145	72		
Units: Subjects				
Any AEs (1st vacc.) (N=145;72)	46	8		
Possibly/Probably Related AEs(1st vacc.)(N=145;72)	35	6		
Any AEs (2nd vacc.) (N=141;72)	30	7		
Possibly/Probably Related AEs(2nd vacc.)(N=141;72)	22	5		
Any AEs (3rd vacc.) (N=138;72)	51	18		
Possibly/Probably Related AEs(3rd vacc.)(N=138;72)	45	7		
Any AEs (booster) (N=137;72)	43	9		
Possibly/Probably Related AEs (booster) (N=137;72)	37	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting serious adverse events (SAEs), medically attended AEs (MAEs), AEs leading to withdrawal, hospitalization and death

End point title	Number of subjects reporting serious adverse events (SAEs), medically attended AEs (MAEs), AEs leading to withdrawal, hospitalization and death
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End point description:

Number of subjects who reported SAEs, medically attended AEs, AEs leading to withdrawal from the

study, AEs leading to hospitalization and AEs leading to death, following concomitant administration of Bexsero® vaccine with routine vaccines (Infanrix-IPV + Hib®, Prevenar-13®, Engerix-B®, Priorix® and Varilrix®), as compared to when only routine vaccines were administered alone.

SAEs assessed include medical occurrences that result in death, are life-threatening, require hospitalization or prolongation of hospitalization or result in disability/incapacity. Possibly or probably related SAE = SAE assessed by the investigator as related to the vaccination. Medically attended AEs were defined as events for which the subject received medical attention defined as hospitalization, an emergency room visit, or a visit to or from medical personnel (medical doctor) for any reason.

The analysis was performed on the Safety Set (Unsolicited AEs).

End point type	Secondary
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End point timeframe:

Throughout the whole study period (from Day 1 to Day 335)

End point values	Bexsero + Routine Group	Routine Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	145	72		
Units: Subjects				
Any SAEs	13	8		
Possibly or Probably Related SAEs	0	0		
Medically attended AEs	131	66		
AEs leading to withdrawal	4	0		
AEs leading to hospitalization	13	8		
AEs leading to death	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting Grade 3 solicited local AEs after receiving Bexsero® vaccine with routine vaccines, at 2, 4 and 6 months of age

End point title	Number of subjects reporting Grade 3 solicited local AEs after receiving Bexsero® vaccine with routine vaccines, at 2, 4 and 6 months of age
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End point description:

The number of subjects who reported Grade 3 solicited local symptoms following concomitant administration of Bexsero® vaccine with routine vaccines (Infanrix-IPV+Hib®, Prevenar-13® and Engerix-B®), as compared to when only routine vaccines were administered alone at 2, 4 and 6 months of age. Assessed solicited local symptoms were: Erythema, Induration, Swelling and Tenderness. Grade 3 symptom = symptom that prevented normal activity.

The analysis was performed on the Solicited Safety Set, which included all subjects in the Exposed population who provided post-vaccination reactogenicity data.

End point type	Secondary
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End point timeframe:

From Day 1 (6 hours) to Day 7 after each vaccination

End point values	Bexsero + Routine Group	Routine Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148	73		
Units: Subjects				
Grade 3 Erythema (1st Bexsero®) (N=148;0)	0	0		
Grade 3 Induration (1st Bexsero®) (N=147;0)	0	0		
Grade 3 Swelling (1st Bexsero®) (N=146;0)	0	0		
Grade 3 Tenderness (1st Bexsero®) (N=147;0)	8	0		
Grade 3 Erythema (1st Infanrix- IPV+Hib®)(N=148;73)	0	0		
Grade3 Induration(1st Infanrix- IPV+Hib®)(N=148;73)	0	0		
Grade 3 Swelling (1st Infanrix- IPV+Hib®)(N=148;73)	0	0		
Grade3 Tenderness(1st Infanrix- IPV+Hib®)(N=146;73)	2	0		
Grade 3 Erythema (1st Prevenar-13®) (N=148;73)	0	0		
Grade 3 Induration (1st Prevenar-13®) (N=148;73)	0	0		
Grade 3 Swelling (1st Prevenar-13®) (N=148;73)	0	0		
Grade 3 Tenderness (1st Prevenar-13®) (N=147;73)	3	0		
Grade 3 Erythema (2nd Bexsero®) (N=140;0)	0	0		
Grade 3 Induration (2nd Bexsero®) (N=140;0)	0	0		
Grade 3 Swelling (2nd Bexsero®) (N=140;0)	0	0		
Grade 3 Tenderness (2nd Bexsero®) (N=140;0)	5	0		
Grade 3 Erythema (2nd Infanrix- IPV+Hib®)(N=140;72)	0	0		
Grade3 Induration(2nd Infanrix- IPV+Hib®)(N=140;72)	0	0		
Grade 3 Swelling (2nd Infanrix- IPV+Hib®)(N=140;72)	0	0		
Grade3 Tenderness(2nd Infanrix- IPV+Hib®)(N=140;72)	3	0		
Grade 3 Erythema (2nd Prevenar-13®) (N=140;72)	0	0		
Grade 3 Induration (2nd Prevenar-13®) (N=140;72)	0	0		
Grade 3 Swelling (2nd Prevenar-13®) (N=140;72)	0	0		
Grade 3 Tenderness (2nd Prevenar- 13®) (N=140;72)	3	0		
Grade 3 Erythema (3rd Bexsero®) (N=138;0)	0	0		
Grade 3 Induration (3rd Bexsero®) (N=138;0)	0	0		
Grade 3 Swelling (3rd Bexsero®) (N=138;0)	0	0		
Grade 3 Tenderness (3rd Bexsero®) (N=138;0)	6	0		

Grade 3 Erythema (3rd Infanrix-IPV+Hib®)(N=137;72)	0	0		
Grade3 Induration(3rd Infanrix-IPV+Hib®)(N=138;72)	0	0		
Grade 3 Swelling (3rd Infanrix-IPV+Hib®)(N=138;72)	0	0		
Grade3 Tenderness(3rd Infanrix-IPV+Hib®)(N=138;72)	2	0		
Grade 3 Erythema (3rd Prevenar-13®) (N=138;72)	0	0		
Grade 3 Induration (3rd Prevenar-13®) (N=138;72)	0	0		
Grade 3 Swelling (3rd Prevenar-13®) (N=138;72)	0	0		
Grade 3 Tenderness (3rd Prevenar-13®) (N=138;72)	3	0		
Grade 3 Erythema (Engerix-B®) (N=138;72)	0	0		
Grade 3 Induration (Engerix-B®) (N=137;72)	0	0		
Grade 3 Swelling (Engerix-B®) (N=138;71)	0	0		
Grade 3 Tenderness (Engerix-B®) (N=138;72)	3	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting Grade 3 solicited systemic AEs after receiving Bexsero® vaccine with routine vaccines or routine vaccines alone, at 2, 4 and 6 months of age

End point title	Number of subjects reporting Grade 3 solicited systemic AEs after receiving Bexsero® vaccine with routine vaccines or routine vaccines alone, at 2, 4 and 6 months of age
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End point description:

The number of subjects who reported Grade 3 solicited systemic AEs following concomitant administration of Bexsero® vaccine with routine vaccines (Infanrix-IPV+Hib®, Prevenar-13® and Engerix-B®), as compared to when only routine vaccines were administered alone at 2, 4 and 6 months of age. Assessed solicited systemic symptoms were: Change in Eating Habits, Diarrhea, Irritability, Persistent Crying, Rash, Sleepiness and Vomiting. Grade 3 symptom = symptom that prevented normal activity.

The analysis was performed on the Solicited Safety Set, which included all subjects in the Exposed population who provided post-vaccination reactogenicity data.

End point type	Secondary
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End point timeframe:

From Day 1 (6 hours) to Day 7 after each vaccination

End point values	Bexsero + Routine Group	Routine Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148	73		
Units: Subjects				
Grade3 Change in Eating Habits(1st vacc)(N=148;73)	0	0		
Grade 3 Diarrhea (1st vacc.) (N=148;73)	2	1		
Grade 3 Irritability (1st vacc.) (N=148;73)	3	0		
Grade 3 Persistent Crying (1st vacc.) (N=148;73)	5	0		
Grade 3 Rash (1st vacc.) (N=148;73)	0	0		
Grade 3 Sleepiness (1st vacc.) (N=148;73)	0	1		
Grade 3 Vomiting (1st vacc.) (N=148;73)	0	0		
Grade3 Change in Eating Habits(2nd vacc)(N=140;72)	2	0		
Grade 3 Diarrhea (2nd vacc.) (N=140;72)	1	0		
Grade 3 Irritability (2nd vacc.) (N=140;72)	3	1		
Grade 3 Persistent Crying (2nd vacc.) (N=140;72)	5	0		
Grade 3 Rash (2nd vacc.) (N=140;72)	0	1		
Grade 3 Sleepiness (2nd vacc.) (N=140;72)	0	0		
Grade 3 Vomiting (2nd vacc.) (N=140;72)	0	0		
Grade3 Change in Eating Habits(3rd vacc)(N=138;72)	1	0		
Grade 3 Diarrhea (3rd vacc.) (N=138;72)	0	0		
Grade 3 Irritability (3rd vacc.) (N=138;72)	3	1		
Grade 3 Persistent Crying (3rd vacc.) (N=138;72)	3	0		
Grade 3 Rash (3rd vacc.) (N=138;72)	1	0		
Grade 3 Sleepiness (3rd vacc.) (N=138;72)	0	0		
Grade 3 Vomiting (3rd vacc.) (N=138;72)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting Grade 3 solicited local AEs after receiving Bexsero® booster dose with routine vaccines, at 12 months of age

End point title	Number of subjects reporting Grade 3 solicited local AEs after receiving Bexsero® booster dose with routine vaccines, at 12 months of age
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End point description:

The number of subjects who reported solicited local AEs following concomitant administration of Bexsero® dose with routine vaccines (Priorix® and Varilrix®), as compared to when only routine

vaccines were administered alone, at 12 months of age. Assessed solicited local symptoms were: Erythema, Induration, Swelling and Tenderness. Grade 3 symptom = symptom that prevented normal activity.

The analysis was performed on the Solicited Safety Set, which included all subjects in the Exposed population who provided post-vaccination reactogenicity data.

End point type	Secondary
End point timeframe:	
From Day 1 to Day 7 after booster vaccination	

End point values	Bexsero + Routine Group	Routine Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	137	72		
Units: Subjects				
Grade 3 Erythema (Bexsero® booster vacc.)(N=136;0)	0	0		
Grade3 Induration(Bexsero® booster vacc.)(N=136;0)	0	0		
Grade 3 Swelling (Bexsero® booster vacc.)(N=135;0)	0	0		
Grade3 Tenderness(Bexsero® booster vacc.)(N=136;0)	6	0		
Grade 3 Erythema (Priorix® vacc.) (N=137;72)	0	0		
Grade 3 Induration (Priorix® vacc.) (N=137;72)	0	0		
Grade 3 Swelling (Priorix® vacc.) (N=137;72)	0	0		
Grade 3 Tenderness (Priorix® vacc.) (N=137;72)	3	0		
Grade 3 Erythema (Varilrix® vacc.) (N=137;72)	0	0		
Grade 3 Induration (Varilrix® vacc.) (N=137;72)	0	0		
Grade 3 Swelling (Varilrix® vacc.) (N=137;72)	0	0		
Grade 3 Tenderness (Varilrix® vacc.) (N=137;72)	3	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting Grade 3 solicited systemic AEs after receiving Bexsero® booster dose with routine vaccines, at 12 months of age

End point title	Number of subjects reporting Grade 3 solicited systemic AEs after receiving Bexsero® booster dose with routine vaccines, at 12 months of age
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End point description:

The number of subjects who reported Grade 3 solicited systemic AEs following concomitant administration of Bexsero® booster dose with routine vaccines (Priorix® and Varilrix®), as compared to when only routine vaccines were administered alone at 12 months of age. Assessed solicited systemic AEs were: Change in Eating Habits, Diarrhea, Irritability, Persistent Crying, Rash, Sleepiness and Vomiting. Grade 3 symptom = symptom that prevented normal activity.

The analysis was performed on the Solicited Safety Set, which included all subjects in the Exposed population who provided post-vaccination reactogenicity data.

End point type	Secondary
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End point timeframe:

From Day 1 (6 hours) to Day 7 after booster vaccination

End point values	Bexsero + Routine Group	Routine Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	137	72		
Units: Subjects				
Grade 3 Change in Eating Habits (N=137;72)	2	1		
Grade 3 Diarrhea (N=137;72)	1	0		
Grade 3 Irritability (N=137;72)	2	0		
Grade 3 Persistent Crying (N=137;72)	0	1		
Grade 3 Rash (N=137;72)	1	0		
Grade 3 Sleepiness (N=137;72)	0	0		
Grade 3 Vomiting (N=137;72)	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Solicited local and systemic symptoms: from Day 1 to Day 7 after each vaccination; Unsolicited AEs and SAEs: throughout the study period (from Day 1 to Day 335).

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.0
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Reporting groups

Reporting group title	Bexsero + Routine Group
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Reporting group description:

Subjects received three doses of Bexsero® vaccine at 2, 4, 6 months followed by a booster dose at 12 months, concomitantly administered with routine vaccines (i.e. combined Infanrix-IPV+Hib® and Prevenar-13® at 2, 4, 6 months of age; Engerix-B® at 6 months of age; Priorix® and Varilrix® at 12 months of age.

Reporting group title	Routine Group
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Reporting group description:

Subjects received routine vaccines Infanrix-IPV+Hib® and Prevenar-13® at 2, 4, 6 months of age; Engerix-B® vaccine at 6 months; Priorix® and Varilrix® vaccines at 12 months of age.

Serious adverse events	Bexsero + Routine Group	Routine Group	
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 148 (8.78%)	8 / 73 (10.96%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Head injury			
subjects affected / exposed ^[1]	1 / 145 (0.69%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Kawasaki's disease			
subjects affected / exposed ^[2]	0 / 145 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Seizure			

subjects affected / exposed ^[3]	0 / 145 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed ^[4]	1 / 145 (0.69%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Colitis			
subjects affected / exposed ^[5]	0 / 145 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed ^[6]	0 / 145 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchiolitis			
subjects affected / exposed ^[7]	3 / 145 (2.07%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed ^[8]	4 / 145 (2.76%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed ^[9]	1 / 145 (0.69%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hand-foot-and-mouth disease			

subjects affected / exposed ^[10]	2 / 145 (1.38%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media acute			
subjects affected / exposed ^[11]	1 / 145 (0.69%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed ^[12]	1 / 145 (0.69%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus infection			
subjects affected / exposed ^[13]	1 / 145 (0.69%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed ^[14]	1 / 145 (0.69%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Croup infectious			
subjects affected / exposed ^[15]	0 / 145 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Exanthema subitum			
subjects affected / exposed ^[16]	1 / 145 (0.69%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis salmonella			
subjects affected / exposed ^[17]	1 / 145 (0.69%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral herpes			

subjects affected / exposed ^[18]	1 / 145 (0.69%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed ^[19]	0 / 145 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia pneumococcal			
subjects affected / exposed ^[20]	1 / 145 (0.69%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed ^[21]	1 / 145 (0.69%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyuria			
subjects affected / exposed ^[22]	1 / 145 (0.69%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus bronchiolitis			
subjects affected / exposed ^[23]	0 / 145 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salmonella bacteraemia			
subjects affected / exposed ^[24]	1 / 145 (0.69%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed ^[25]	1 / 145 (0.69%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			

subjects affected / exposed ^[26]	2 / 145 (1.38%)	0 / 72 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: The analysis was performed on the Exposed population, only on subjects with their symptom sheets completed.

[2] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

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

Non-serious adverse events	Bexsero + Routine Group	Routine Group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	148 / 148 (100.00%)	72 / 73 (98.63%)	
Nervous system disorders			
Somnolence			
subjects affected / exposed	111 / 148 (75.00%)	45 / 73 (61.64%)	
occurrences (all)	246	84	
General disorders and administration site conditions			

Pyrexia			
subjects affected / exposed	134 / 148 (90.54%)	52 / 73 (71.23%)	
occurrences (all)	357	85	
Crying			
subjects affected / exposed	124 / 148 (83.78%)	50 / 73 (68.49%)	
occurrences (all)	337	109	
Injection site erythema			
subjects affected / exposed	113 / 148 (76.35%)	35 / 73 (47.95%)	
occurrences (all)	285	66	
Injection site pain			
subjects affected / exposed	121 / 148 (81.76%)	27 / 73 (36.99%)	
occurrences (all)	300	47	
Injection site induration			
subjects affected / exposed	105 / 148 (70.95%)	39 / 73 (53.42%)	
occurrences (all)	370	86	
Injection site swelling			
subjects affected / exposed	89 / 148 (60.14%)	24 / 73 (32.88%)	
occurrences (all)	238	41	
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	34 / 148 (22.97%)	21 / 73 (28.77%)	
occurrences (all)	34	21	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	72 / 148 (48.65%)	28 / 73 (38.36%)	
occurrences (all)	134	42	
Vomiting			
subjects affected / exposed	45 / 148 (30.41%)	16 / 73 (21.92%)	
occurrences (all)	67	32	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	10 / 148 (6.76%)	3 / 73 (4.11%)	
occurrences (all)	10	3	
Rhinorrhoea			
subjects affected / exposed	5 / 148 (3.38%)	8 / 73 (10.96%)	
occurrences (all)	5	12	

Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	72 / 148 (48.65%)	30 / 73 (41.10%)	
occurrences (all)	136	50	
Eczema			
subjects affected / exposed	17 / 148 (11.49%)	5 / 73 (6.85%)	
occurrences (all)	21	5	
Dermatitis			
subjects affected / exposed	15 / 148 (10.14%)	4 / 73 (5.48%)	
occurrences (all)	16	5	
Dermatitis atopic			
subjects affected / exposed	8 / 148 (5.41%)	5 / 73 (6.85%)	
occurrences (all)	9	6	
Dermatitis diaper			
subjects affected / exposed	7 / 148 (4.73%)	6 / 73 (8.22%)	
occurrences (all)	8	6	
Psychiatric disorders			
Irritability			
subjects affected / exposed	127 / 148 (85.81%)	50 / 73 (68.49%)	
occurrences (all)	399	121	
Eating disorder			
subjects affected / exposed	125 / 148 (84.46%)	43 / 73 (58.90%)	
occurrences (all)	335	98	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	86 / 148 (58.11%)	45 / 73 (61.64%)	
occurrences (all)	181	105	
Upper respiratory tract infection			
subjects affected / exposed	42 / 148 (28.38%)	16 / 73 (21.92%)	
occurrences (all)	71	30	
Gastroenteritis			
subjects affected / exposed	14 / 148 (9.46%)	13 / 73 (17.81%)	
occurrences (all)	19	13	
Bronchiolitis			
subjects affected / exposed	11 / 148 (7.43%)	5 / 73 (6.85%)	
occurrences (all)	11	5	
Exanthema subitum			

subjects affected / exposed	10 / 148 (6.76%)	6 / 73 (8.22%)	
occurrences (all)	10	6	
Conjunctivitis			
subjects affected / exposed	5 / 148 (3.38%)	4 / 73 (5.48%)	
occurrences (all)	5	4	
Pharyngitis			
subjects affected / exposed	5 / 148 (3.38%)	4 / 73 (5.48%)	
occurrences (all)	5	4	
Tonsillitis			
subjects affected / exposed	4 / 148 (2.70%)	4 / 73 (5.48%)	
occurrences (all)	4	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 July 2013	<ul style="list-style-type: none">- Correction of omission;- Presentation of each commercially available routine vaccines has been changed into "as commercially available";- A fourth dose of Prevenar-13 was included in the schedule treatment to complete the recommended dose schedule;- Other Secondary endpoints were added: The percentage of subjects with SBA titers $\geq 1:8$ at baseline, one month after the third vaccination, at 12 months of age (prior to the booster dose) and at 13 months of age (one month after the booster dose) for each of the three indicator strains (H44/76, 5/99, NZ98/254) and strain M10713.
05 November 2013	<ul style="list-style-type: none">- Exclusion criteria were modified;- Randomization method and stratification factors were clarified;- MMR and Varicella vaccines way of administration was better defined;- Timeframe for solicited data collection was corrected;- Description of statistical analysis for primary endpoint was modified.
08 July 2014	<ul style="list-style-type: none">- Change of the legal entity responsible for the trial to Novartis Pharma Services AG;- The name of the serology manual was changed and protocol was updated with the new manual's title;- Section 3.9 "End of Study" was added to the protocol;- Exclusion criteria were modified to avoid extra clinic visit to the subjects;- Criteria for delay of vaccination and/or blood sampling was changed to avoid extra clinic visit to the subjects;- The extension of the period of observation for adverse events was better specified;- Blood pressure measurement was removed from the list of physical examination to be performed at clinical visit because it is not a routine practice in Taiwan to measure blood pressure of young children.
14 October 2014	<ul style="list-style-type: none">- Inclusion criteria added;- The enrolment process was better specified in that the screening number assigned has to be assigned by the Investigator;- Correction of typo.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported