Clinical trial results:
Clinical Otitis Media and Pneumonia Study (COMPAS): a phase III , double-blind, randomized, controlled, multicentre study to demonstrate the efficacy of GlaxoSmithKline (GSK) Biologicals' 10-valent pneumococcal conjugate vaccine (GSK1024850A) against Community Acquired Pneumonia (CAP) and Acute Otitis Media (AOM)

Summary

EudraCT number	2011-002076-16
Trial protocol	Outside EU/EEA
Global end of trial date	28 July 2011

Results information

Result version number	v1
This version publication date	22 March 2016
First version publication date	15 May 2015

Trial information

Trial identification

Sponsor protocol code	109563

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00466947
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	GlaxoSmithKline Biologicals
Sponsor organisation address	Rue de l'Institut 89, Rixensart, Belgium,
Public contact	Clinical Trials Call Center, GlaxoSmithKline Biologicals, +44 2089904466, GSKClinicalSupportHD@gsk.com
Scientific contact	Clinical Trials Call Center, GlaxoSmithKline Biologicals, +44 2089904466, GSKClinicalSupportHD@gsk.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000673-PIP01-09
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	21 February 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 July 2011
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the efficacy of a 3-dose primary course followed by a booster dose in the second year of life with the 10Pn-PD-DiT vaccine against likely bacterial CAP cases (B-CAP) in the entire study cohort. Likely bacterial CAP is defined as radiologically confirmed CAP cases with either alveolar consolidation/pleural effusion on the chest X-ray (CXR), or with non-alveolar infiltrates but with C-reactive protein (CRP) ≥ 40 mg/L.

Protection of trial subjects:

Subjects' safety was monitored in the study via the following measures and practice: Prior to the study: check of inclusion and exclusion criteria prior to enrolment, completed with check on gestational age, medical and pre-vaccination history of subjects; Throughout the study: regular check for exclusion criteria for further study participation, for risk factors, and for warnings, precautions and contraindications to the vaccine administered.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 June 2007
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 13981
Country: Number of subjects enrolled	Colombia: 2483
Country: Number of subjects enrolled	Panama: 7359
Worldwide total number of subjects	23823
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)	23823
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:

Primary outcome analysis was on 31 August 2010, when at least 535 first bacterial CAP episodes reported from 2 weeks after Dose 3 – total population: 11875 & 11863 subjects in Synflorix and Control groups; according to protocol efficacy cohort: 10295 & 10201 subjects in Synflorix and Control groups. Study end analysis was done on 23597 subjects.

Pre-assignment

Screening details:

During the screening, the following steps occurred: check for inclusion/exclusion criteria, contraindications/precautions, medical history of the subjects and signing of informed consent forms by parent(s)/guardian(s).

Pre-assignment period milestones

Number of subjects started	23823
Number of subjects completed	23597

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Protocol deviation: 226

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Synflorix Group

Arm description:

Subjects received 3 primary doses of Synflorix at 2, 4 and 6 months of age co-administered with Infanrix-hexa and booster dose of Synflorix at 15-18 months of age co-administered with Infanrix-IPV/Hib. All vaccines were administered intramuscularly in the right (Synflorix) or the left (Infanrix-hexa, Infanrix-IPV + Hib) thigh (primary dose) or deltoid (booster dose).

Arm type	Experimental
Investigational medicinal product name	Synflorix
Investigational medicinal product code	
Other name	10Pn, 10Pn-PD-DiT, GlaxoSmithKline (GSK) Biologicals' 10-valent pneumococcal conjugate vaccine, Synflorix™, GSK1024850A
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Subjects received 3 primary doses at 2, 4 and 6 months, administered in the right thigh,and a booster dose at 15-18 months administered in the right thigh or deltoid.

Investigational medicinal product name	Infanrix-IPV + Hib
Investigational medicinal product code	
Other name	Infanrix-IPV/Hib
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details: Subjects received one dose administered at 15-18 months of age in the left thigh or deltoid.	
Investigational medicinal product name	Infanrix Hexa
Investigational medicinal product code	
Other name	DTPa-IPV-HBV / Hib, GSK Biologicals' diphtheria-tetanus-acellular pertussis, hepatitis B virus-inactivated poliovirus and Haemophilus influenzae type b vaccine
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use
Dosage and administration details: Subjects received 3 primary doses at 2, 4 and 6 months administered in the left thigh.	
Arm title	Control Group
Arm description: Subjects received 3 doses of Engerix B at 2,4 and 6 months of age co-administered with Infanrix-IPV + Hib and 1 dose of Havrix 720 Junior co-administered with Infanrix-IPV + Hib at 15-18 months of age. All vaccine were administered in the right (Engerix B Junior, Havrix) or the left (Infanrix-IPV + Hib) thigh.	
Arm type	Active comparator
Investigational medicinal product name	Engerix B Junior
Investigational medicinal product code	
Other name	HBV, Engerix B
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use
Dosage and administration details: Subjects received 3 doses at 2,4 and 6 months of age, administered in the right thigh.	
Investigational medicinal product name	Infanrix-IPV + Hib
Investigational medicinal product code	
Other name	Infanrix-IPV/Hib
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use
Dosage and administration details: Subjects received 3 primary doses at 2,4 and 6 months of age, administered in in the left thigh and one booster dose at 15-18 months of age administered in the left thigh or deltoid.	
Investigational medicinal product name	Havrix 720 Junior
Investigational medicinal product code	
Other name	HAV, Hepatitis A vaccine (inactivated), Havrix
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use
Dosage and administration details: Subjects received 1 dose at 15-18 months of age administered in the right thigh.	

Number of subjects in period 1[1]	Synflorix Group	Control Group
Started	11798	11799
Completed	9302	9265
Not completed	2496	2534
Physician decision	29	29
Consent withdrawn by subject	1264	1267
'Unconformity in team's treatment '	-	1

'Subject without a legal guardian '	1	-
Adverse event, non-fatal	35	43
Forbidden vaccination	21	10
Lost to follow-up	1137	1167
Protocol deviation	9	17

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Among the initial 23823 subjects enrolled in the study, 3 were not allocated to any groups and 2 had non-valid informed consent. In addition, analysis on the primary outcome was performed when at least 535 first bacterial CAP episodes were reported from 2 weeks after vaccine Dose 3 (31 August 2010) with 23738 subjects (11875 and 11863 in Synflorix and Control groups) and analysis at study end was performed on 23597 subjects.

Baseline characteristics

Reporting groups	
Reporting group title	Synflorix Group
Reporting group description:	
Subjects received 3 primary doses of Synflorix at 2, 4 and 6 months of age co-administered with Infanrix-hexa and booster dose of Synflorix at 15-18 months of age co-administered with Infanrix-IPV/Hib. All vaccines were administered intramuscularly in the right (Synflorix) or the left (Infanrix-hexa, Infanrix-IPV + Hib) thigh (primary dose) or deltoid (booster dose).	
Reporting group title	Control Group
Reporting group description:	
Subjects received 3 doses of Engerix B at 2,4 and 6 months of age co-administered with Infanrix-IPV + Hib and 1 dose of Havrix 720 Junior co-administered with Infanrix-IPV + Hib at 15-18 months of age. All vaccine were administered in the right (Engerix B Junior, Havrix) or the left (Infanrix-IPV + Hib) thigh.	

Reporting group values	Synflorix Group	Control Group	Total
Number of subjects	11798	11799	23597
Age categorical			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Units: weeks			
arithmetic mean	9.2	9.2	
standard deviation	± 1.93	± 1.92	-
Gender categorical			
Units: Subjects			
Female	5796	5767	11563
Male	6002	6032	12034

End points

End points reporting groups

Reporting group title	Synflorix Group

Reporting group description:

Subjects received 3 primary doses of Synflorix at 2, 4 and 6 months of age co-administered with Infanrix-hexa and booster dose of Synflorix at 15-18 months of age co-administered with Infanrix-IPV/Hib. All vaccines were administered intramuscularly in the right (Synflorix) or the left (Infanrix-hexa, Infanrix-IPV + Hib) thigh (primary dose) or deltoid (booster dose).

Reporting group title	Control Group

Reporting group description:

Subjects received 3 doses of Engerix B at 2,4 and 6 months of age co-administered with Infanrix-IPV + Hib and 1 dose of Havrix 720 Junior co-administered with Infanrix-IPV + Hib at 15-18 months of age. All vaccine were administered in the right (Engerix B Junior, Havrix) or the left (Infanrix-IPV + Hib) thigh.

Primary: Number of subjects with a first episode reported of bacterial community acquired pneumoniae (B-CAP)

End point title	Number of subjects with a first episode reported of bacterial community acquired pneumoniae (B-CAP)[1]

End point description:

A B-CAP episode was defined as a radiologically confirmed community acquired pneumoniae (CAP) episode with either alveolar consolidation/pleural effusion on the chest X-ray (CXR) or with non-alveolar infiltrates but with C reactive protein (CRP) higher than or equal to (>=) 40 milligrams per liter (mg/L). The results are presented for data lock point for the primary outcome analysis (31 August 2010), which was performed, as per protocol, when at least 535 first B-CAP episodes were reported from 2 weeks after the third vaccination dose. After analysis on primary outcome was performed, re-monitoring activities revealed ICF issues for some subjects. Therefore, a sensitivity analysis excluding 144 subjects was performed. This analysis confirmed the validity of the results for primary outcome.

End point type	Primary

End point timeframe:

Any time from 2 weeks after Dose 3 up to 31 August 2010

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: The analysis of the primary endpoint was descriptive i.e. no statistical hypothesis test was performed.

End point values	Synflorix Group	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10295	10201		
Units: Subjects				
Subjects with B-CAP	240	304		

Statistical analyses

No statistical analyses for this end point

Primary: Time to First or Only Episode of B-CAP

End point title	Time to First or Only Episode of B-CAP

End point description:

The total time to a first episode reported of bacterial community acquired pneumoniae (B-CAP) was tabulated. A B-CAP episode was defined as a radiologically confirmed community acquired pneumoniae (CAP) episode with either alveolar consolidation/pleural effusion on the chest X-ray (CXR) or with non-alveolar infiltrates but with C reactive protein (CRP) higher than or equal to (>=) 40 milligrams per liter (mg/L). The results are presented for data lock point for the primary outcome analysis (31 August 2010), which was performed when at least 535 first B-CAP episodes were reported from 2 weeks after Dose 3 of vaccine. After analysis was performed, re-monitoring activities revealed ICF issues for some subjects. Therefore, a sensitivity analysis excluding 144 subjects was performed, which confirmed the validity of the results for primary outcome.

End point type	Primary

End point timeframe:

Any time from 2 weeks after Dose 3 up to 31 August 2010

End point values	Synflorix Group	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10295	10201		
Units: Years				
number (not applicable)				
Total time to first B-CAP episode	19512.99	19260.15		

Statistical analyses

Statistical analysis title	Vaccine Efficacy for time to first B-CAP episode

Statistical analysis description:

The vaccine efficacy (VE) to prevent the first episode of B-CAP was estimated with 95% confidence interval (CI), as (1 minus the hazard ratio) times 100 obtained from a Cox regression model including the treatment group (Synflorix Group) as only regressor. Censoring occurred either at the time of the last contact, of unblinding or at 18 months of age if the booster dose was not administered or was administered at a later age.

Comparison groups	Synflorix Group v Control Group
Number of subjects included in analysis	20496
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.002 [3]
Method	Regression, Cox
Parameter estimate	VE (see above)
Point estimate	22.033
Confidence interval	
level	95 %
sides	2-sided
lower limit	7.656
upper limit	34.172

Notes:

[2] - Vaccine efficacy analysis, based on a Cox regression proportional hazard model

[3] - Statistical significance was reached if the one-sided p-value for the Wald-Test obtained from the Cox proportional hazard model calculated for the null hypothesisH0= [B-CAP VE =< 0%] (Y = Time to Event) was lower than 0.0175.

Secondary: Number of subjects with serious adverse events (SAEs)

End point title	Number of subjects with serious adverse events (SAEs)

End point description:

SAEs assessed include medical occurrences that result in death, are life threatening, require hospitalization or prolongation of hospitalization, result in disability/incapacity or are a congenital anomaly/birth defect in the offspring of a study subject.

End point type	Secondary

End point timeframe:

Throughout the study (Month 0 to Month 22-25)

End point values	Synflorix Group	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11798	11799		
Units: Subjects				
Number of subjects with SAE(s)	2534	2668		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with any unsolicited adverse event (AE), in the Panama Subset

End point title	Number of subjects with any unsolicited adverse event (AE), in the Panama Subset

End point description:

An unsolicited AE is any AE (i.e. any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with use of a medicinal product, whether or not considered related to the medicinal product) 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. The Panama Subset included all subjects from Panama.

End point type	Secondary

End point timeframe:

Throughout the study (Month 0 to Month 22-25)

End point values	Synflorix Group	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3602	3612		
Units: Subjects				
Number of subjects with AE(s)	3530	3518		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with solicited local symptoms post primary vaccination in the Immunogenicity and Tolerability Subset

End point title	Number of subjects with solicited local symptoms post primary vaccination in the Immunogenicity and Tolerability Subset

End point description:

Assessed symptoms were redness, swelling and pain. The Immunogenicity and Tolerability Subset included 500 subjects coming from Argentina and Panama respectively. This outcome measure concerns solely subjects from the Synflorix Group.

End point type	Secondary

End point timeframe:

Within the 4-days (Days 0–3) follow-up period across the 3 doses of the primary study vaccine administration

End point values	Synflorix Group	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	368	0[4]		
Units: Subjects				
Pain after vaccination with Synflorix	275			
Pain after vaccination with Infanrix Hexa	270			
Redness after vaccination with Synflorix	182			
Redness after vaccination with Infanrix Hexa	171			
Swelling after vaccination with Synflorix	141			
Swelling after vaccination with Infanrix Hexa	143			

Notes:

[4] - The endpoint solely concerns the Synflorix Group.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with solicited local symptoms post booster vaccination in the Immunogenicity and Tolerability Subset

End point title	Number of subjects with solicited local symptoms post booster vaccination in the Immunogenicity and Tolerability Subset

End point description:

Assessed symptoms were redness, swelling and pain. The Immunogenicity and Tolerability Subset included 500 subjects coming from Argentina and Panama respectively. This outcome measure concerns solely subjects from the Synflorix Group.

End point type	Secondary

End point timeframe:

Within the 4-days (Days 0–3) follow-up period following the booster vaccine administration

End point values	Synflorix Group	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	317	0[5]		
Units: Subjects				
Pain after vaccination with Synflorix	129			
Pain after vaccination with Infanrix-IPV/Hib	131			
Redness after vaccination with Synflorix	104			
Redness after vaccination with Infanrix-IPV/Hib	98			
Swelling after vaccination with Synflorix	74			
Swelling after vaccination with Infanrix-IPV/Hib	69			

Notes:

[5] - The endpoint solely concerns the Synflorix Group.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with solicited local symptoms post primary vaccination in the Immunogenicity and Tolerability Subset

End point title	Number of subjects with solicited local symptoms post primary vaccination in the Immunogenicity and Tolerability Subset

End point description:

Assessed symptoms were redness, swelling and pain. The Immunogenicity and Tolerability Subset included 500 subjects coming from Argentina and Panama respectively. This outcome measure concerns solely subjects from the Control Group.

End point type	Secondary

End point timeframe:

Within the 4-days (Days 0–3) follow-up period across the 3 doses of the primary study vaccine administration

End point values	Synflorix Group	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[6]	357		
Units: Subjects				
Pain after vaccination with Infanrix-IPV/Hib		169		
Pain after vaccination with Engerix		165		
Redness after vaccination with Infanrix-IPV/Hib		118		
Redness after vaccination with Engerix		109		
Swelling after vaccination with Infanrix-IPV/Hib		98		
Swelling after vaccination with Engerix		91		

Notes:

[6] - The endpoint solely concerns the Control Group.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with solicited local symptoms post booster vaccination in the Immunogenicity and Tolerability Subset, for the Control Group

End point title	Number of subjects with solicited local symptoms post booster vaccination in the Immunogenicity and Tolerability Subset, for the Control Group

End point description:

Assessed symptoms were redness, swelling and pain. The Immunogenicity and Safety Tolerability Subset included 500 subjects coming from Argentina and Panama respectively. This outcome measure concerns solely subjects from the Control Group.

End point type	Secondary

End point timeframe:

Within the 4-days (Days 0–3) follow-up period following the booster vaccine administration.

End point values	Synflorix Group	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[7]	303		
Units: Subjects				
Pain after vaccination with Infanrix-IPV/Hib		81		
Pain after vaccination with Havrix		89		
Redness after vaccination with Infanrix-IPV/Hib		81		
Redness after vaccination with Havrix		73		
Swelling after vaccination with Infanrix-IPV/Hib		70		
Swelling after vaccination with Havrix		55		

Notes:

[7] - The endpoint solely concerns the Control Group.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with solicited general symptoms post primary vaccination in the Immunogenicity and Tolerability Subset

End point title	Number of subjects with solicited general symptoms post primary vaccination in the Immunogenicity and Tolerability Subset

End point description:

Assessed symptoms were fever (defined as rectal temperature equal or higher than [>=] 38 degrees Celsius [°C]). irritability/fussiness, drowsiness, and loss of appetite. The Immunogenicity and Tolerability Subset included 500 subjects coming from Argentina and Panama respectively.

End point type	Secondary

End point timeframe:

Within the 4-days (Days 0–3) follow-up period across the 3 doses of the primary study vaccine administration

End point values	Synflorix Group	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	368	357		
Units: Subjects				
Drowsiness	236	168		
Fever (rectal temperature >= 38°C)	247	125		
Irritability	289	206		
Loss of appetite	133	80		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with solicited general symptoms post booster vaccination in the Immunogenicity and Tolerability Subset

End point title	Number of subjects with solicited general symptoms post booster vaccination in the Immunogenicity and Tolerability Subset

End point description:

Assessed symptoms were fever (defined as rectal temperature equal or higher than [>=] 38 degrees Celsius [°C]). irritability/fussiness, drowsiness, and loss of appetite. The Immunogenicity and Tolerability Subset included 500 subjects coming from Argentina and Panama respectively.

End point type	Secondary

End point timeframe:

Within the 4-days (Days 0–3) follow-up period following the booster vaccine administration

End point values	Synflorix Group	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	317	303		
Units: Subjects				
Drowsiness	74	65		
Fever (rectal temperature >= 38°C)	93	73		
Irritability	121	95		
Loss of appetite	51	46		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with a first episode reported of clinically confirmed acute otitis media (AOM) (C-AOM), in the Panama Subset

End point title	Number of subjects with a first episode reported of clinically confirmed acute otitis media (AOM) (C-AOM), in the Panama Subset

End point description:

The Panama Subset contained all subjects enrolled in Panama.

End point type	Secondary

End point timeframe:

Any time from 2 weeks after Dose 3 to study end at Month 22-25

End point values	Synflorix Group	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3010	2979		
Units: Subjects				
C-AOM	204	239		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with a first episode reported of community acquired pneumoniae (CAP) with alveolar consolidation or pleural effusion on the chest X-ray (CXR) (C-CAP)

End point title	Number of subjects with a first episode reported of community acquired pneumoniae (CAP) with alveolar consolidation or pleural effusion on the chest X-ray (CXR) (C-CAP)

End point description:

CXR alveolar consolidation was defined as CXR with a dense, often homogeneous, confluent alveolar infiltrate that could encompass an entire lobe or segment, or a fluffy, mass-like, cloud-like density that erased heart and diaphragm borders (silhouette sign) and that often contained air bronchograms. CXR pleural effusion was defined as a fluid collecting in the pleural space around the lung, seen radiologically as a dense rim (the same density as the chest-wall muscles) interposed between the lung and the ribs.

End point type	Secondary

End point timeframe:

Any time from 2 weeks post primary vaccination Dose 3 to study end at Month 22-25

End point values	Synflorix Group	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10211	10140		
Units: Subjects				
CAP with alveolar consolidation/pleural effusion	181	231		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with a first episode reported of bacteriologically confirmed acute otitis media (AOM) (B-AOM) due to any bacterial pathogen, in the Panama Subset

End point title	Number of subjects with a first episode reported of bacteriologically confirmed acute otitis media (AOM) (B-AOM) due to any bacterial pathogen, in the Panama Subset

End point description:

The Panama Subset contained all subjects enrolled in Panama.

End point type	Secondary

End point timeframe:

Any time from 2 weeks post primary vaccination Dose 3 to study end at Month 22-25

End point values	Synflorix Group	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3010	2979		
Units: Subjects				
B-AOM	32	45		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with a first episode reported of bacteriologically confirmed acute otitis media (AOM) (B-AOM) due to Streptococcus pneumoniae (S. pn.) vaccine serotypes, in the Panama Subset

End point title	Number of subjects with a first episode reported of bacteriologically confirmed acute otitis media (AOM) (B-AOM) due to Streptococcus pneumoniae (S. pn.) vaccine serotypes, in the Panama Subset

End point description:

The 10 pneumococcal S. pneumoniae vaccine serotypes assessed for this outcome measure were the serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F. The Panama Subset contained all subjects enrolled in Panama.

End point type	Secondary

End point timeframe:

Any time from 2 weeks post primary vaccination Dose 3 to study end at Month 22-25

End point values	Synflorix Group	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3010	2979		
Units: Subjects				
B-AOM caused by S. pn. serotypes	6	18		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with a first episode reported of bacteriologically confirmed acute otitis media (AOM) (B-AOM) due to Streptococcus pneumoniae (S. pn.) cross-reactive serotypes, in the Panama Subset.

End point title	Number of subjects with a first episode reported of bacteriologically confirmed acute otitis media (AOM) (B-AOM) due to Streptococcus pneumoniae (S. pn.) cross-reactive serotypes, in the Panama Subset.

End point description:

The S. pn. cross-reactive serotypes assessed for this outcome measure were the serotypes 6A, 18B, 19A and 23A. The Panama Subset contained all subjects enrolled in Panama.

End point type	Secondary

End point timeframe:

Any time from 2 weeks post primary vaccination Dose 3 to study end at Month 22-25

End point values	Synflorix Group	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3010	2979		
Units: Subjects				
B-AOM caused by S. pn. cross-reactive serotypes	3	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with a first episode reported of bacteriologically confirmed acute otitis media (AOM) (B-AOM) due to other pneumococcal serotypes, in the Panama Subset.

End point title	Number of subjects with a first episode reported of bacteriologically confirmed acute otitis media (AOM) (B-AOM) due to other pneumococcal serotypes, in the Panama Subset.

End point description:

Other pneumococcal serotypes were defined for this outcome measures as non-Streptococcus pneumoniae vaccine and cross-reactive serotypes. The Panama Subset contained all subjects enrolled in Panama.

End point type	Secondary

End point timeframe:

Any time from 2 weeks post primary vaccination Dose 3 to study end at Month 22-25

End point values	Synflorix Group	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3010	2979		
Units: Subjects				
B-AOM caused by other pneumococcal serotypes	3	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with a first episode reported of bacteriologically confirmed acute otitis media (AOM) (B-AOM) due to Haemophilus influenzae (H. influenzae), in the Panama Subset

End point title	Number of subjects with a first episode reported of bacteriologically confirmed acute otitis media (AOM) (B-AOM) due to Haemophilus influenzae (H. influenzae), in the Panama Subset

End point description:

The Panama Subset contained all subjects enrolled in Panama.

End point type	Secondary

End point timeframe:

Any time from 2 weeks post primary vaccination Dose 3 to study end at Month 22-25

End point values	Synflorix Group	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3010	2979		
Units: Subjects				
B-AOM caused by H. influenzae	12	14		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with a first episode reported of bacteriologically confirmed acute otitis media (AOM) (B-AOM) due to non-typeable Haemophilus influenzae (H. influenzae), in the Panama Subset

End point title	Number of subjects with a first episode reported of bacteriologically confirmed acute otitis media (AOM) (B-AOM) due to non-typeable Haemophilus influenzae (H. influenzae), in the Panama Subset

End point description:

The Panama Subset contained all subjects enrolled in Panama

End point type	Secondary

End point timeframe:

Any time from 2 weeks post primary vaccination Dose 3 to study end at Month 22-25

End point values	Synflorix Group	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3010	2979		
Units: Subjects				
B-AOM caused by non-typeable H. influenzae	12	14		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with a first episode reported of bacteriologically confirmed acute otitis media (AOM) (B-AOM) due to other AOM pathogens, in the Panama Subset

End point title	Number of subjects with a first episode reported of bacteriologically confirmed acute otitis media (AOM) (B-AOM) due to other AOM pathogens, in the Panama Subset

End point description:

Other pathogens assessed included among others Moraxella catarrhalis, Group A streptococci, and Staphyloccus aureus. The Panama Subset contained all subjects enrolled in Panama.

End point type	Secondary

End point timeframe:

Any time from 2 weeks post primary vaccination Dose 3 to study end at Month 22-25

End point values	Synflorix Group	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3010	2979		
Units: Subjects				
B-AOM caused by other pathogens	8	7		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with a first episode reported of community acquired pneumoniae (CAP) with alveolar consolidation or pleural effusion on the Chest X-ray (CXR) (C-CAP) with positive respiratory viral test (RVT)

End point title	Number of subjects with a first episode reported of community acquired pneumoniae (CAP) with alveolar consolidation or pleural effusion on the Chest X-ray (CXR) (C-CAP) with positive respiratory viral test (RVT)

End point description:

A CXR with consolidation was defined as a CXR with a dense, often homogeneous, confluent alveolar infiltrate that could encompass an entire lobe or segment, or a fluffy, mass-like, cloud-like density that erased heart and diaphragm borders (silhouette sign) and that often contained air bronchograms. Pleural effusion was defined as a fluid collecting in the pleural space around the lung, seen radiologically as a dense rim (the same density as the chest-wall muscles) interposed between the lung and the ribs.

End point type	Secondary

End point timeframe:

Any time from 2 weeks post primary vaccination Dose 3 to study end at Month 22-25

End point values	Synflorix Group	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10211	10140		
Units: Subjects				
C-CAP associated with positive RVT	21	25		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with a first episode reported of community acquired pneumoniae (CAP) with any abnormal CXR with positive respiratory viral test (RVT)

End point title	Number of subjects with a first episode reported of community acquired pneumoniae (CAP) with any abnormal CXR with positive respiratory viral test (RVT)

End point description:

An “abnormal CXR” was defined as a CXR with either consolidation, pleural effusion and/or abnormal pulmonary alveolar or non-alveolar infiltrates on the digital CXR image. CXR with consolidation was defined as a CXR with a dense, often homogeneous, confluent alveolar infiltrate that could encompass an entire lobe or segment, or a fluffy, mass-like, cloud-like density that erased heart and diaphragm borders (silhouette sign) and that often contained air bronchograms. Pleural effusion was defined as a fluid collecting in the pleural space around the lung, seen radiologically as a dense rim (the same density as the chest-wall muscles) interposed between the lung and the ribs.

End point type	Secondary

End point timeframe:

Any time from 2 weeks post primary vaccination Dose 3 to study end at Month 22-25

End point values	Synflorix Group	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10211	10140		
Units: Subjects				
CAP with abnormal CXR with positive RVT	104	112		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with a first episode reported of bacterial community acquired pneumoniae (B-CAP) with positive respiratory viral test (RVT).

End point title	Number of subjects with a first episode reported of bacterial community acquired pneumoniae (B-CAP) with positive respiratory viral test (RVT).

End point description:

End point type	Secondary

End point timeframe:

Any time from 2 weeks post primary vaccination Dose 3 to study end at Month 22-25

End point values	Synflorix Group	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10211	10140		
Units: Subjects				
B-CAP associated with positive RVT	35	39		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with a first episode reported of suspected community acquired pneumoniae (CAP) (S-CAP)

End point title	Number of subjects with a first episode reported of suspected community acquired pneumoniae (CAP) (S-CAP)

End point description:

An episode of S-CAP involved either any subject who was referred to have a chest X-ray (CXR) performed as part of the clinical assessment of a febrile syndrome or an acute respiratory infection (ARI), or a hospitalized child who had a CXR performed within 2 days prior to, or within the first 3 days after hospital admission, as part of the clinical assessment of a febrile syndrome or an ARI.

End point type	Secondary

End point timeframe:

Any time from 2 weeks post primary vaccination Dose 3 to study end at Month 22-25

End point values	Synflorix Group	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10211	10140		
Units: Subjects				
S-CAP	2108	2237		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with a first episode reported of community acquired pneumoniae (CAP) with any abnormal chest X-ray (CXR)

End point title	Number of subjects with a first episode reported of community acquired pneumoniae (CAP) with any abnormal chest X-ray (CXR)

End point description:

An "abnormal CXR" was defined as a CXR with either consolidation, pleural effusion and/or abnormal pulmonary alveolar or non-alveolar infiltrates on the digital CXR image. CXR with consolidation was defined as a CXR with a dense, often homogeneous, confluent alveolar infiltrate that could encompass an entire lobe or segment, or a fluffy, mass-like, cloud-like density that erased heart and diaphragm borders (silhouette sign) and that often contained air bronchograms. Pleural effusion was defined as a fluid collecting in the pleural space around the lung, seen radiologically as a dense rim (the same density as the chest-wall muscles) interposed between the lung and the ribs.

End point type	Secondary

End point timeframe:

Any time from 2 weeks post primary vaccination Dose 3 to study end at Month 22-25

End point values	Synflorix Group	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10211	10140		
Units: Subjects				
CAP with any abnormal CXR	681	764		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with a first episode reported of suspected community acquired pneumoniae (CAP) (S-CAP) with C reactive protein (CRP) >= cut-off, regardless of chest X-ray (CXR) reading

End point title	Number of subjects with a first episode reported of suspected community acquired pneumoniae (CAP) (S-CAP) with C reactive protein (CRP) >= cut-off, regardless of chest X-ray (CXR) reading

End point description:

A case of S-CAP involved either any subject who was referred to have a CXR performed as part of the clinical assessment of a febrile syndrome or an acute respiratory infection (ARI), or a hospitalized child who had a CXR performed within 2 days prior to, or within the first 3 days after hospital admission, as part of the clinical assessment of a febrile syndrome or an ARI. CRP cut-off values applied for this outcome measure were 40 milligrams per liter (mg/L), 80 mg/L, and 120 mg/L.

End point type	Secondary

End point timeframe:

Any time from 2 weeks post primary vaccination Dose 3 to study end at Month 22-25

End point values	Synflorix Group	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10211	10140		
Units: Subjects				
S-CAP with CRP >= 40 mg/L regardless of CXR exam	425	499		
S-CAP with CRP >= 80 mg/L regardless of CXR exam	175	237		
S-CAP with CRP >= 120 mg/L regardless of CXR exam	85	119		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with a first episode reported of CAP with either alveolar consolidation/pleural effusion on chest X-ray (CXR) (C-CAP) or with non-alveolar infiltrates (NAI-CAP) but with C reactive protein (CRP) >= cut-off.

End point title	Number of subjects with a first episode reported of CAP with either alveolar consolidation/pleural effusion on chest X-ray (CXR) (C-CAP) or with non-alveolar infiltrates (NAI-CAP) but with C reactive protein (CRP) >= cut-off.

End point description:

CRP cut-off values applied for this outcome measure were 80 milligrams per liter (mg/L), and 120 mg/L.

End point type	Secondary

End point timeframe:

Any time from 2 weeks post primary vaccination Dose 3 to study end at Month 22-25

End point values	Synflorix Group	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10211	10140		
Units: Subjects				
C-CAP or NAI-CAP with CRP >= 80 mg/L	208	256		
C-CAP or NAI-CAP with CRP >= 120 mg/L	191	240		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with a first episode reported of vaccine-type invasive pneumococcal disease (VT-IPD).

End point title	Number of subjects with a first episode reported of vaccine-type invasive pneumococcal disease (VT-IPD).

End point description:

A VT-IPD was defined as a bacteriologically culture confirmed invasive pneumococcal disease case caused by any of the 10 pneumococcal Streptococcus pneumoniae vaccine serotypes. The 10 pneumococcal S. pneumoniae vaccine serotypes assessed for this outcome measure were the serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F.

End point type	Secondary

End point timeframe:

Any time from 2 weeks post primary vaccination Dose 3 to study end at Month 22-25

End point values	Synflorix Group	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10211	10140		
Units: Subjects				
VT-IPD	0	16		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with a first episode reported of a bacteriologically confirmed invasive pneumococcal disease (Bact.-conf. ID).

End point title	Number of subjects with a first episode reported of a bacteriologically confirmed invasive pneumococcal disease (Bact.-conf. ID).

End point description:

A Bact.-conf. ID was defined as a bacteriologically culture confirmed invasive pneumococcal disease (ID) cases due to any of the 10 Streptococcus pneumoniae vaccine serotypes as identified through positive culture. The 10 pneumococcal S. pneumoniae vaccine serotypes assessed for this outcome measure were the serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F.

End point type	Secondary

End point timeframe:

Any time from 2 weeks post primary vaccination Dose 3 to study end at Month 22-25

End point values	Synflorix Group	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10211	10140		
Units: Subjects				
Bact.-conf. ID	6	17		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with a first episode reported of pneumococcal invasive disease (Pneumococcal ID)

End point title	Number of subjects with a first episode reported of pneumococcal invasive disease (Pneumococcal ID)

End point description:

A Pneumococcal ID was defined as a bacteriologically culture confirmed invasive pneumococcal disease (ID) cases due to any of the 10 Streptococcus pneumoniae vaccine serotypes. The 10 pneumococcal S. pneumoniae vaccine serotypes assessed for this outcome measure were the serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F. Pneumococcal ID cases were identified through non-culture pneumococcal diagnostic tests with additional non-culture vaccine type serotyping. Tests used included rapid in-vitro diagnostic tests or Latex agglutination.

End point type	Secondary

End point timeframe:

Any time from 2 weeks post primary vaccination Dose 3 to study end at Month 22-25

End point values	Synflorix Group	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10211	10140		
Units: Subjects				
Pneumococcal ID	6	17		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with a first episode reported of Invasive Pneumococcal Disease (IPD) due to Streptococcus (S. pn.) cross-reactive pneumococcal serotypes.

End point title	Number of subjects with a first episode reported of Invasive Pneumococcal Disease (IPD) due to Streptococcus (S. pn.) cross-reactive pneumococcal serotypes.

End point description:

The S. pn. cross-reactive serotypes assessed for this outcome measure were the serotypes 19A, 6A and 9N.

End point type	Secondary

End point timeframe:

Any time from 2 weeks post primary vaccination Dose 3 to study end at Month 22-25

End point values	Synflorix Group	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10211	10140		
Units: Subjects				
IPD due to S. pn. cross-reactive serotypes	2	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with a first episode reported of Invasive Pneumococcal Disease (IPD) due to pneumococcal serotypes other than Streptococcus (S. pn.) vaccine and cross-reactive serotypes.

End point title	Number of subjects with a first episode reported of Invasive Pneumococcal Disease (IPD) due to pneumococcal serotypes other than Streptococcus (S. pn.) vaccine and cross-reactive serotypes.

End point description:

The serotypes assessed for this outcome measure included among others the pneumococcal serotypes 12F, 16F, 24F, 38 and 8.

End point type	Secondary

End point timeframe:

Any time from 2 weeks post primary vaccination Dose 3 to study end at Month 22-25

End point values	Synflorix Group	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10211	10140		
Units: Subjects				
IPD due to other pneumococcal serotypes	3	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with a first episode reported of invasive disease (ID) due to Haemophilus influenzae

End point title	Number of subjects with a first episode reported of invasive disease (ID) due to Haemophilus influenzae

End point description:

End point type	Secondary

End point timeframe:

Any time from 2 weeks post primary vaccination Dose 3 to study end at Month 22-25

End point values	Synflorix Group	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10211	10140		
Units: Subjects				
ID due to Haemophilus influenzae	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with Streptococcus pneumoniae (S. pn.) vaccine serotypes identified in nasopharyngeal swabs, in the Carriage Subset.

End point title	Number of subjects with Streptococcus pneumoniae (S. pn.) vaccine serotypes identified in nasopharyngeal swabs, in the Carriage Subset.

End point description:

The 10 pneumococcal S. pn. vaccine serotypes assessed for this outcome measure were the serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F. S. pn. serotypes were identified using latex agglutination and by quellung reaction with omni serum. The Carriage Subset consisted in a subgroup of 2,000 subjects enrolled in Panama.

End point type	Secondary

End point timeframe:

At Months 5, 10-13, 13-16, 14-17, 16-19 and 22-25

End point values	Synflorix Group	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	814	814		
Units: Subjects				
Month 5 (N=814; 814)	104	123		
Month 10-13 (N=788; 784)	92	123		
Month 13-16 (N=758; 762)	88	109		
Month 14-17 (N=720; 738)	74	103		
Month 16-19 (N=696; 690)	68	98		
Month 22-25 (N=627; 639)	61	86		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with Streptococcus pneumoniae (S. pn.) cross-reactive serotypes identified in nasopharyngeal swabs, in the Carriage Subset.

End point title	Number of subjects with Streptococcus pneumoniae (S. pn.) cross-reactive serotypes identified in nasopharyngeal swabs, in the Carriage Subset.

End point description:

Any serotype belonging to the same serogroup as the Synflorix vaccine serotypes, but different from the vaccine serotypes, was considered for this analysis of carriage S. pn. cross-reactive serotypes. S. pn. serotypes were identified using latex agglutination and by quellung reaction with omni serum. The Carriage Subset consisted in a subgroup of 2,000 subjects enrolled in Panama.

End point type	Secondary

End point timeframe:

At Months 5, 10-13, 13-16, 14-17, 16-19 and 22-25

End point values	Synflorix Group	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	814	814		
Units: Subjects				
Month 5 (N=814; 814)	63	67		
Month 10-13 (N=788; 784)	81	63		
Month 13-16 (N=758; 762)	57	63		
Month 14-17 (N=720; 738)	57	49		
Month 16-19 (N=696; 690)	55	57		
Month 22-25 (N=627; 639)	38	46		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with Streptococcus pneumoniae (S. pn.) serotypes identified in nasopharyngeal swabs other than the Synflorix vaccine and cross-reactive serotypes, in the Carriage Subset

End point title	Number of subjects with Streptococcus pneumoniae (S. pn.) serotypes identified in nasopharyngeal swabs other than the Synflorix vaccine and cross-reactive serotypes, in the Carriage Subset

End point description:

S. pn. serotypes were identified using latex agglutination and by quellung reaction with omni serum. The Carriage Subset consisted in a subgroup of 2,000 subjects enrolled in Panama.

End point type	Secondary

End point timeframe:

At Months 5, 10-13, 13-16, 14-17, 16-19 and 22-25

End point values	Synflorix Group	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	814	814		
Units: Subjects				
Month 5 (N=814; 814)	99	86		
Month 10-13 (N=788; 784)	85	85		
Month 13-16 (N=758; 762)	83	85		
Month 14-17 (N=720; 738)	78	85		
Month 16-19 (N=696; 690)	89	69		
Month 22-25 (N=627; 639)	74	61		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with H. influenzae strains identified in nasopharyngeal swabs, in the Carriage subset

End point title	Number of subjects with H. influenzae strains identified in nasopharyngeal swabs, in the Carriage subset

End point description:

Results included samples confirmed as positive for Haemophilus influenzae (H. influenzae) or non-typeable H. influenzae (NTHi) after differentiation from H. haemolyticus by polymerase chain reaction (PCR) assay. The Carriage Subset contained a subgroup of 2,000 subjects enrolled in Panama.

End point type	Secondary

End point timeframe:

At Months 5, 10-13, 13-16, 14-17, 16-19 and 22-25

End point values	Synflorix Group	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	824	820		
Units: Subjects				
Month 5 (N=824; 820)	36	40		
Month 10-13 (N=788;785)	45	44		
Month 13-16 (N=757;762)	32	39		
Month 14-17 (N=720; 737)	28	34		
Month 16-19 (N=696; 690)	28	38		
Month 22-25 (N=628; 640)	29	33		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with acquisition of new Streptococcus pneumoniae strains identified in nasopharyngeal swabs, in the Carriage Subset

End point title	Number of subjects with acquisition of new Streptococcus pneumoniae strains identified in nasopharyngeal swabs, in the Carriage Subset

End point description:

The Carriage Subset consisted in a subgroup of 2,000 subjects enrolled in Panama.

End point type	Secondary

End point timeframe:

At Months 10-13, 13-16, 14-17, 16-19 and 22-25

End point values	Synflorix Group	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	788	784		
Units: Subjects				
Month 10-13 (N=788;784)	171	175		
Month 13-16 (N=758;762)	145	165		
Month 14-17 (N=720;738)	110	137		
Month 16-19 (N=696;690)	126	137		
Month 22-25;N=627;639)	123	124		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with acquisition of new Haemophilus influenzae strains identified in nasopharyngeal swabs, in the Carriage Subset.

End point title	Number of subjects with acquisition of new Haemophilus influenzae strains identified in nasopharyngeal swabs, in the Carriage Subset.

End point description:

The Carriage Subset consisted in a subgroup of 2,000 subjects enrolled in Panama.

End point type	Secondary

End point timeframe:

At Months 10-13, 13-16, 14-17, 16-19 and 22-25

End point values	Synflorix Group	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	788	785		
Units: Subjects				
Month 10-13 (N=788;785)	39	37		
Month 13-16 (N=757;762)	27	33		
Month 14-17 (N=720;737)	23	28		
Month 16-19 (N=696;690)	22	32		
Month 22-25 (N=628;640)	28	31		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with any antibiotic prescription at least once during the entire study period, in the Carriage Subset.

End point title	Number of subjects with any antibiotic prescription at least once during the entire study period, in the Carriage Subset.

End point description:

The Carriage Subset consisted in a subgroup of 2,000 subjects enrolled in Panama.

End point type	Secondary

End point timeframe:

Throughout the study (Month 0 to Month 22-25)

End point values	Synflorix Group	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	955	966		
Units: Subjects				
Subjects with any antibiotic prescription	611	626		

Statistical analyses

No statistical analyses for this end point

Secondary: Pneumococcal antibody concentrations against pneumococcal vaccine serotypes, in the Immunogenicity and Tolerability Subset.

End point title	Pneumococcal antibody concentrations against pneumococcal vaccine serotypes, in the Immunogenicity and Tolerability Subset.

End point description:

Antibody concentrations were measured by 22F enzyme-linked Immunosorbent Assay (ELISA), expressed as geometric mean concentrations (GMCs), in micrograms per milliliter (µg/mL). Serotypes assessed were the pneumococcal vaccine serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F. The cut-off of the assay was >= 0.05 µg/mL. The Immunogenicity and Tolerability Subset included 500 subjects coming from Argentina and Panama respectively.

End point type	Secondary

End point timeframe:

At Month 5, one month after the third dose of primary vaccination

End point values	Synflorix Group	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	334	331		
Units: µg/mL				
geometric mean (confidence interval 95%)				
ANTI-1 (N=334;312)	2.51 (2.29 to 2.75)	0.04 (0.03 to 0.04)		
ANTI-4 (N=334;328)	3.26 (2.98 to 3.56)	0.03 (0.03 to 0.04)		
ANTI-5 (N=334;324)	4.2 (3.86 to 4.57)	0.05 (0.04 to 0.05)		
ANTI-6B (N=334;322)	1.34 (1.18 to 1.52)	0.03 (0.03 to 0.03)		
ANTI-7F (N=334;330)	3.86 (3.56 to 4.19)	0.04 (0.04 to 0.05)		
ANTI-9V (N=334;331)	3.15 (2.84 to 3.5)	0.04 (0.03 to 0.04)		
ANTI-14 (N=334;330)	4.55 (4.07 to 5.1)	0.09 (0.08 to 0.11)		
ANTI-18C (N=334;328)	5.32 (4.73 to 5.99)	0.04 (0.04 to 0.04)		
ANTI-19F (N=334;327)	5.33 (4.7 to 6.06)	0.06 (0.05 to 0.07)		
ANTI-23F (N=334;331)	1.99 (1.76 to 2.26)	0.04 (0.03 to 0.04)		

Statistical analyses

No statistical analyses for this end point

Secondary: Antibody concentrations against pneumococcal cross-reactive serotypes 6A and 19A, in the Immunogenicity and Tolerability Subset

End point title	Antibody concentrations against pneumococcal cross-reactive serotypes 6A and 19A, in the Immunogenicity and Tolerability Subset

End point description:

Antibody concentrations were measured by 22F enzyme-linked immunosorbent assay (ELISA), expressed as geometric mean concentrations (GMCs), in micrograms per milliliter (µg/mL). The cut-off of the assay was >= 0.05 µg/mL. The Immunogenicity and Tolerability Subset included 500 subjects coming from Argentina and Panama respectively.

End point type	Secondary

End point timeframe:

At Month 5, one month after the third dose of primary vaccination

End point values	Synflorix Group	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	334	326		
Units: µg/mL				
geometric mean (confidence interval 95%)				

ANTI-6A (N=334;321)	0.32 (0.27 to 0.37)	0.03 (0.03 to 0.04)		
ANTI-19A (N=334;326)	0.29 (0.25 to 0.33)	0.04 (0.04 to 0.05)		

Statistical analyses

No statistical analyses for this end point

Secondary: Antibody concentrations against pneumococcal vaccine serotypes, in the Immunogenicity and Tolerability Subset.

End point title	Antibody concentrations against pneumococcal vaccine serotypes, in the Immunogenicity and Tolerability Subset.

End point description:

Antibody concentrations were measured by 22F enzyme-linked immunosorbent assay (ELISA), expressed as geometric mean concentrations (GMCs), in micrograms per milliliter (µg/mL). Serotypes assessed were the pneumococcal vaccine serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F. The cut-off of the assay was >= 0.05 µg/mL. The Immunogenicity and Tolerability Subset included 500 subjects coming from Argentina and Panama respectively.

End point type	Secondary

End point timeframe:

Before the administration of booster vaccination (PRE), and 1 month and 9 months post booster vaccination (M1 POST-BST and M9 POST-BST)

End point values	Synflorix Group	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	231	214		
Units: µg/mL				
geometric mean (confidence interval 95%)				
ANTI-1, PRE (N=231;203)	0.35 (0.31 to 0.39)	0.05 (0.04 to 0.06)		
ANTI-1, M1 POST-BST (N=219;196)	3.58 (3.15 to 4.07)	0.06 (0.05 to 0.06)		
ANTI-1, M9 POST-BST (N=206;181)	0.65 (0.56 to 0.75)	0.06 (0.05 to 0.06)		
ANTI-4, PRE (N=231;214)	0.48 (0.42 to 0.55)	0.04 (0.04 to 0.05)		
ANTI-4, M1 POST-BST (N=217;204)	6.55 (5.81 to 7.38)	0.05 (0.04 to 0.05)		
ANTI-4, M9 POST-BST (N=206;183)	0.87 (0.77 to 0.99)	0.04 (0.04 to 0.05)		
ANTI-5, PRE (N=231;209)	0.9 (0.8 to 1.01)	0.07 (0.07 to 0.09)		
ANTI-5, M1 POST-BST (N=219;199)	5.73 (5.04 to 6.5)	0.07 (0.06 to 0.08)		
ANTI-5, M9 POST-BST (N=206;182)	1.19 (1.05 to 1.36)	0.09 (0.08 to 0.1)		
ANTI-6B, PRE (N=229;212)	0.55 (0.47 to 0.64)	0.04 (0.03 to 0.04)		
ANTI-6B, M1 POST-BST (N=217;198)	3.32 (2.92 to 3.77)	0.04 (0.03 to 0.04)		

ANTI-6B, M9 POST-BST (N=206;182)	0.83 (0.71 to 0.96)	0.05 (0.04 to 0.06)		
ANTI-7F, PRE (N=231;210)	0.94 (0.84 to 1.04)	0.06 (0.05 to 0.07)		
ANTI-7F, M1 POST-BST (N=218;198)	5.77 (5.23 to 6.36)	0.06 (0.05 to 0.07)		
ANTI-7F, M9 POST-BST (N=206;182)	1.32 (1.19 to 1.45)	0.07 (0.05 to 0.08)		
ANTI-9V, PRE (N=230;214)	1.14 (1 to 1.31)	0.04 (0.04 to 0.05)		
ANTI-9V, M1 POST-BST (N=218;203)	7.34 (6.51 to 8.27)	0.04 (0.04 to 0.05)		
ANTI-9V, M9 POST-BST (N=206;182)	1.8 (1.59 to 2.03)	0.05 (0.04 to 0.06)		
ANTI-14, PRE (N=231;214)	1.15 (1.15 to 1.35)	0.11 (0.09 to 0.13)		
ANTI-14, M1 POST-BST (N=219;200)	9.31 (8.18 to 10.6)	0.12 (0.1 to 0.14)		
ANTI-14, M9 POST-BST (N=206;183)	1.98 (1.74 to 2.26)	0.17 (0.14 to 0.21)		
ANTI-18C, PRE (N=231;210)	0.9 (0.79 to 1.03)	0.05 (0.04 to 0.06)		
ANTI-18C, M1 POST-BST (N=219;203)	16.38 (14.47 to 18.55)	0.05 (0.04 to 0.05)		
ANTI-18C, M9 POST-BST (N=206;181)	2.5 (2.21 to 2.83)	0.05 (0.04 to 0.06)		
ANTI-19F, PRE (N=231;206)	1.27 (1.09 to 1.48)	0.06 (0.05 to 0.07)		
ANTI-19F, M1 POST-BST (N=219;198)	9.4 (8.4 to 10.52)	0.07 (0.05 to 0.08)		
ANTI-19F, M9 POST-BST (N=205;181)	2.47 (2.16 to 2.84)	0.1 (0.08 to 0.12)		
ANTI-23F, PRE (N=229;204)	0.62 (0.53 to 0.72)	0.04 (0.03 to 0.05)		
ANTI-23F, M1 POST-BST (N=218;201)	4.02 (3.49 to 4.62)	0.04 (0.03 to 0.04)		
ANTI-23F, M9 POST-BST (N=206;179)	0.92 (0.8 to 1.06)	0.05 (0.04 to 0.06)		

Statistical analyses

No statistical analyses for this end point

Secondary: Antibody concentrations against pneumococcal cross-reactive serotypes 6A and 19A, in the Immunogenicity and Tolerability Subset

End point title	Antibody concentrations against pneumococcal cross-reactive serotypes 6A and 19A, in the Immunogenicity and Tolerability Subset

End point description:

Antibody concentrations were measured by 22F enzyme-linked immunosorbent assay (ELISA), expressed as geometric mean concentrations (GMCs), in micrograms per milliliter (µg/mL). The cut-off of the assay was >= 0.05 µg/mL. The Immunogenicity and Tolerability Subset included 500 subjects coming from Argentina and Panama respectively.

End point type	Secondary

End point timeframe:

Before the administration of booster vaccination (PRE), and 1 month and 9 months post booster vaccination (M1 POST-BST and M9 POST-BST)

End point values	Synflorix Group	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	231	214		
Units: µg/mL				
geometric mean (confidence interval 95%)				
ANTI-6A, PRE (N=231;214)	0.22 (0.18 to 0.26)	0.04 (0.04 to 0.05)		
ANTI-6A, M1 POST-BST (N=219;204)	1.14 (0.93 to 1.4)	0.04 (0.03 to 0.04)		
ANTI-6A, M9 POST-BST (N=206;183)	0.31 (0.26 to 0.37)	0.05 (0.04 to 0.06)		
ANTI-19A, PRE (N=229;212)	0.25 (0.21 to 0.3)	0.05 (0.05 to 0.07)		
ANTI-19A, M1 POST-BST (N=218;201)	1.34 (1.11 to 1.62)	0.06 (0.05 to 0.07)		
ANTI-19A, M9 POST-BST (N=206;181)	0.54 (0.46 to 0.65)	0.09 (0.07 to 0.11)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with antibody concentrations against pneumococcal vaccine serotypes >= 0.20 micrograms per milliliter (µg/mL), in the Immunogenicity and Tolerability Subset

End point title	Number of subjects with antibody concentrations against pneumococcal vaccine serotypes >= 0.20 micrograms per milliliter (µg/mL), in the Immunogenicity and Tolerability Subset

End point description:

Antibody concentrations were measured by 22F enzyme-linked immunosorbent assay (ELISA). Serotypes assessed were the pneumococcal vaccine serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F. The Immunogenicity and Tolerability Subset included 500 subjects coming from Argentina and Panama respectively.

End point type	Secondary

End point timeframe:

At Month 5, one month after the third dose of primary vaccination

End point values	Synflorix Group	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	334	331		
Units: Subjects				
ANTI-1 (N=334;312)	333	13		
ANTI-4 (N=334;328)	332	11		
ANTI-5 (N=334;324)	333	22		

ANTI-6B (N=334;322)	311	8		
ANTI-7F (N=334;330)	333	28		
ANTI-9V (N=334;331)	330	19		
ANTI-14 (N=334;330)	328	77		
ANTI-18C (N=334;328)	330	21		
ANTI-19F (N=334;327)	325	40		
ANTI-23F (N=334;331)	321	15		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with antibody concentrations against pneumococcal cross-reactive serotypes 6A and 19A >= 0.20 micrograms per milliliter (µg/mL), in the Immunogenicity and Tolerability Subset

End point title	Number of subjects with antibody concentrations against pneumococcal cross-reactive serotypes 6A and 19A >= 0.20 micrograms per milliliter (µg/mL), in the Immunogenicity and Tolerability Subset

End point description:

Antibody concentrations were measured by 22F enzyme-linked immunosorbent assay (ELISA). The Immunogenicity and Tolerability Subset included 500 subjects coming from Argentina and Panama respectively.

End point type	Secondary

End point timeframe:

At Month 5, one month after the third dose of primary vaccination

End point values	Synflorix Group	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	334	326		
Units: Subjects				
ANTI-6A (N=334;321)	215	5		
ANTI-19A (N=334;326)	204	18		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with antibody concentrations against pneumococcal vaccine serotypes >= 0.20 micrograms per milliliter (µg/mL), in the Immunogenicity and Tolerability Subset

End point title	Number of subjects with antibody concentrations against pneumococcal vaccine serotypes >= 0.20 micrograms per milliliter (µg/mL), in the Immunogenicity and Tolerability Subset

End point description:

Antibody concentrations were measured by 22F enzyme-linked immunosorbent assay (ELISA). Serotypes assessed with the pneumococcal vaccine serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F. The Immunogenicity and Tolerability Subset included 500 subjects coming from Argentina and Panama respectively.

End point type	Secondary

End point timeframe:

Before the administration of booster vaccination (PRE), and 1 month and 9 months post booster vaccination (M1 POST-BST and M9 POST-BST)

End point values	Synflorix Group	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	231	214		
Units: Subjects				
ANTI-1, PRE (N=231;203)	164	14		
ANTI-1, M1 POST-BST (N=219;196)	219	19		
ANTI-1, M9 POST-BST (N=206;181)	186	14		
ANTI-4, PRE (N=231;214)	190	26		
ANTI-4, M1 POST-BST (N=217;204)	217	24		
ANTI-4, M9 POST-BST (N=206;183)	198	15		
ANTI-5, PRE (N=231;209)	218	27		
ANTI-5, M1 POST-BST (N=219;199)	219	30		
ANTI-5, M9 POST-BST (N=206;182)	200	34		
ANTI-6B, PRE (N=229;212)	182	12		
ANTI-6B, M1 POST-BST (N=217;198)	215	13		
ANTI-6B, M9 POST-BST (N=206;182)	192	21		
ANTI-7F, PRE (N=231;210)	222	34		
ANTI-7F, M1 POST-BST (N=218;198)	218	36		
ANTI-7F, M9 POST-BST (N=206;182)	205	31		
ANTI-9V, PRE (N=230;214)	221	22		
ANTI-9V, M1 POST-BST (N=218;203)	218	14		
ANTI-9V, M9 POST-BST (N=206;182)	206	26		
ANTI-14, PRE (N=231;214)	217	51		
ANTI-14, M1 POST-BST (N=219;200)	219	52		
ANTI-14, M9 POST-BST (N=206;183)	204	68		
ANTI-18C, PRE (N=231;210)	217	22		
ANTI-18C, M1 POST-BST (N=219;203)	219	21		
ANTI-18C, M9 POST-BST (N=206;181)	205	18		
ANTI-19F, PRE (N=231;206)	221	35		
ANTI-19F, M1 POST-BST (N=219;198)	218	39		
ANTI-19F, M9 POST-BST (N=205;181)	204	52		
ANTI-23F, PRE (N=229;204)	198	15		
ANTI-23F, M1 POST-BST (N=218;201)	216	14		
ANTI-23F, M9 POST-BST (N=206;179)	196	25		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with pneumococcal antibody concentrations against cross-reactive serotypes 6A and 19A higher >= 0.20 micrograms per milliliter (µg/mL), in the Immunogenicity and Tolerability Subset

End point title	Number of subjects with pneumococcal antibody concentrations against cross-reactive serotypes 6A and 19A higher >= 0.20 micrograms per milliliter (µg/mL), in the Immunogenicity and Tolerability Subset

End point description:

Antibody concentrations were measured by 22F enzyme-linked immunosorbent assay (ELISA). The Immunogenicity and Tolerability Subset included 500 subjects coming from Argentina and Panama respectively.

End point type	Secondary

End point timeframe:

Before the administration of booster vaccination (PRE), and 1 month and 9 months post booster vaccination (M1 POST-BST and M9 POST-BST)

End point values	Synflorix Group	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	231	214		
Units: Subjects				
ANTI-6A, PRE (N=231;214)	119	14		
ANTI-6A, M1 POST-BST (N=219;204)	187	12		
ANTI-6A, M9 POST-BST (N=206;183)	129	24		
ANTI-19A, PRE (N=229;212)	131	28		
ANTI-19A, M1 POST-BST (N=218;201)	197	27		
ANTI-19A, M9 POST-BST (N=206;181)	165	47		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with antibody concentrations against vaccine pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F >= 0.05 microgram per milliliter (µg/mL), in the Immunogenicity and Tolerability Subset

End point title	Number of subjects with antibody concentrations against vaccine pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F >= 0.05 microgram per milliliter (µg/mL), in the Immunogenicity and Tolerability Subset

End point description:

A seropositive subject was defined as a subject with antibody concentrations against vaccine pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F => 0.05 µg/mL. The Immunogenicity and Tolerability Subset included 500 subjects coming from Argentina and Panama respectively.

End point type	Secondary

End point timeframe:

At Month 5, one month after the third dose of primary vaccination

End point values	Synflorix Group	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	334	331		
Units: Subjects				
ANTI-1 (N=334;312)	333	88		
ANTI-4 (N=334;328)	333	48		
ANTI-5 (N=334;324)	334	153		
ANTI-6B (N=334;322)	324	48		
ANTI-7F (N=334;330)	333	116		
ANTI-9V (N=334;331)	331	68		
ANTI-14 (N=334;330)	333	234		
ANTI-18C (N=334;328)	333	92		
ANTI-19F (N=334;327)	331	176		
ANTI-23F (N=334;331)	328	78		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with pneumococcal antibody concentrations against serotypes 6A and 19A >= 0.05 µg/mL, in the Immunogenicity and Tolerability Subset

End point title	Number of subjects with pneumococcal antibody concentrations against serotypes 6A and 19A >= 0.05 µg/mL, in the Immunogenicity and Tolerability Subset

End point description:

A seropositive subject was defined as a subject with antibody concentrations against cross-reactive pneumococcal serotypes 6A and 19A>= 0.05 µg/mL. The Immunogenicity and Tolerability Subset included 500 subjects coming from Argentina and Panama respectively.

End point type	Secondary

End point timeframe:

At Month 5, one month after the third dose of primary vaccination

End point values	Synflorix Group	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	334	326		
Units: Subjects				
ANTI-6A (N=334;321)	306	77		
ANTI-19A (N=334;326)	303	120		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with antibody concentrations against vaccine pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F >= 0.05 microgram per milliliter (µg/mL), in the Immunogenicity and Tolerability Subset

End point title	Number of subjects with antibody concentrations against vaccine pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F >= 0.05 microgram per milliliter (µg/mL), in the Immunogenicity and Tolerability Subset

End point description:

A seropositive subject was defined as a subject with antibody concentrations against vaccine pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F => 0.05 µg/mL. The Immunogenicity and Tolerability Subset included 500 subjects coming from Argentina and Panama respectively.

End point type	Secondary

End point timeframe:

Before the administration of booster vaccination (PRE), and 1 month and 9 months post booster vaccination (M1 POST-BST and M9 POST-BST

End point values	Synflorix Group	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	231	214		
Units: Subjects				
ANTI-1, PRE (N=231;203)	231	87		
ANTI-1, M1 POST-BST (N=219;196)	219	101		
ANTI-1, M9 POST-BST (N=206;181)	206	95		
ANTI-4, PRE (N=231;214)	231	52		
ANTI-4, M1 POST-BST (N=217;204)	217	65		
ANTI-4, M9 POST-BST (N=206;183)	206	58		
ANTI-5, PRE (N=231;209)	231	150		
ANTI-5, M1 POST-BST (N=219;199)	219	142		
ANTI-5, M9 POST-BST (N=206;182)	206	133		
ANTI-6B, PRE (N=229;212)	226	60		
ANTI-6B, M1 POST-BST (N=217;198)	216	54		
ANTI-6B, M9 POST-BST (N=206;182)	206	72		
ANTI-7F, PRE (N=231;210)	231	79		
ANTI-7F, M1 POST-BST (N=218;198)	218	79		
ANTI-7F, M9 POST-BST (N=206;182)	206	87		
ANTI-9V, PRE (N=230;214)	230	51		
ANTI-9V, M1 POST-BST (N=218;203)	218	58		
ANTI-9V, M9 POST-BST (N=206;182)	206	68		
ANTI-14, PRE (N=231;214)	231	157		
ANTI-14, M1 POST-BST (N=219;200)	219	160		
ANTI-14, M9 POST-BST (N=206;183)	206	154		
ANTI-18C, PRE (N=231;210)	230	72		
ANTI-18C, M1 POST-BST (N=219;203)	219	71		
ANTI-18C, M9 POST-BST (N=206;181)	206	73		
ANTI-19F, PRE (N=231;206)	231	71		
ANTI-19F, M1 POST-BST (N=219;198)	219	85		
ANTI-19F, M9 POST-BST (N=205;181)	205	93		

ANTI-23F, PRE (N=229;204)	223	44		
ANTI-23F, M1 POST-BST (N=218;201)	216	44		
ANTI-23F, M9 POST-BST (N=206;179)	206	62		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with pneumococcal antibody concentrations against serotypes 6A and 19A >= 0.05 µg/mL, in the Immunogenicity and Tolerability Subset

End point title	Number of subjects with pneumococcal antibody concentrations against serotypes 6A and 19A >= 0.05 µg/mL, in the Immunogenicity and Tolerability Subset

End point description:

A seropositive subject was defined as a subject with antibody concentrations against cross-reactive pneumococcal serotypes 6A and 19A>= 0.05 µg/mL. The Immunogenicity and Tolerability Subset included 500 subjects coming from Argentina and Panama respectively.

End point type	Secondary

End point timeframe:

Before the administration of booster vaccination (PRE), and 1 month and 9 months post booster vaccination (M1 POST-BST and M9 POST-BST) .

End point values	Synflorix Group	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	231	214		
Units: Subjects				
ANTI-6A, PRE (N=231;214)	210	61		
ANTI-6A, M1 POST-BST (N=219;204)	214	61		
ANTI-6A, M9 POST-BST (N=206;183)	196	69		
ANTI-19A, PRE (N=229;212)	208	76		
ANTI-19A, M1 POST-BST (N=218;201)	212	83		
ANTI-19A, M9 POST-BST (N=206;181)	201	89		

Statistical analyses

No statistical analyses for this end point

Secondary: Titers for opsonophagocytic activity against vaccine pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F, in the Immunogenicity and Tolerability Subset

End point title	Titers for opsonophagocytic activity against vaccine pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F, in the Immunogenicity and Tolerability Subset

End point description:

The cut-off of the assay was >= 8. The Immunogenicity and Tolerability Subset included 500 subjects coming from Argentina and Panama respectively.

End point type	Secondary

End point timeframe:

At Month 5, one month after the third dose of primary vaccination

End point values	Synflorix Group	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	317	317		
Units: Titers				
geometric mean (confidence interval 95%)				
OPSONO-1 (N=306;305)	139.5 (116.8 to 166.5)	4.8 (4.5 to 5.3)		
OPSONO-4 (N=310;299)	771.7 (686.5 to 867.6)	5.1 (4.5 to 5.8)		
OPSONO-5 (N=313;314)	224.8 (196 to 257.8)	4.5 (4.2 to 4.8)		
OPSONO-6B (N=315;309)	689.7 (553.2 to 859.7)	5.4 (4.6 to 6.2)		
OPSONO-7F (N=302;266)	4656.7 (4175.6 to 5193.3)	110.4 (78.8 to 154.7)		
OPSONO-9V (N=312;302)	1690.4 (1489.4 to 1918.7)	14.6 (11.6 to 18.2)		
OPSONO-14 (N=308;273)	908.5 (795.2 to 1038.1)	16.5 (12.9 to 21.1)		
OPSONO-18C (N=308;317)	310.9 (259.4 to 372.6)	4.4 (4.1 to 4.7)		
OPSONO-19F (N=304;314)	383 (308.5 to 475.5)	4.7 (4.3 to 5.2)		
OPSONO-23F (N=317;282)	2167.4 (1863.4 to 2521.1)	14.5 (11 to 19.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Titers for opsonophagocytic activity against cross-reactive pneumococcal serotypes 6A and 19A, in the Immunogenicity and Tolerability Subset

End point title	Titers for opsonophagocytic activity against cross-reactive pneumococcal serotypes 6A and 19A, in the Immunogenicity and Tolerability Subset

End point description:

The cut-off of the assay was >= 8. The Immunogenicity and Tolerability Subset included 500 subjects coming from Argentina and Panama respectively.

End point type	Secondary

End point timeframe:

At Month 5, one month after the third dose of primary vaccination

End point values	Synflorix Group	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	302	309		
Units: Titers				
geometric mean (confidence interval 95%)				
OPSONO-6A (N=297;305)	156.9 (121.8 to 202.1)	5 (4.5 to 5.5)		
OPSONO-19A (N=302;309)	18.2 (14.5 to 22.9)	4.1 (4 to 4.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Titers for opsonophagocytic activity against vaccine pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F, in the Immunogenicity and Tolerability Subset

End point title	Titers for opsonophagocytic activity against vaccine pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F, in the Immunogenicity and Tolerability Subset

End point description:

The cut-off of the assay was >= 8. The Immunogenicity and Tolerability Subset included 500 subjects coming from Argentina and Panama respectively.

End point type	Secondary

End point timeframe:

Before the administration of booster vaccination (PRE), and 1 month and 9 months post booster vaccination (M1 POST-BST and M9 POST-BST)

End point values	Synflorix Group	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	221	210		
Units: Titers				
geometric mean (confidence interval 95%)				
OPSONO-1, PRE (N=221;210)	9 (7.4 to 10.9)	4.6 (4.2 to 5)		
OPSONO-1, M1 POST-BST (N=209;200)	357.5 (281.8 to 453.5)	4.8 (4.4 to 5.4)		
OPSONO-1, M9 POST-BST (N=196;176)	34.4 (26.6 to 44.7)	4.6 (4.2 to 5.1)		
OPSONO-4, PRE (N=208;193)	29.2 (21.2 to 40.2)	8.6 (6.4 to 11.5)		
OPSONO-4, M1 POST-BST (N=207;193)	2853.5 (2365.5 to 3442.1)	8.3 (6.3 to 10.9)		
OPSONO-4, M9 POST-BST (N=192;173)	165.6 (115.3 to 237.9)	8.1 (6.1 to 10.8)		

OPSONO-5, PRE (N=205;204)	18.5 (15.4 to 22.3)	4.3 (4.1 to 4.6)		
OPSONO-5, M1 POST-BST (N=196;187)	306.1 (252 to 371.8)	4.4 (4.1 to 4.7)		
OPSONO-5, M9 POST-BST (N=192;173)	44.1 (35.5 to 54.7)	4.2 (4 to 4.4)		
OPSONO-6B, PRE (N=209;197)	95.5 (70.1 to 130.1)	7.6 (6 to 9.8)		
OPSONO-6B, M1 POST-BST (N=203;190)	1123.4 (939.2 to 1343.9)	7.1 (5.6 to 8.9)		
OPSONO-6B, M9 POST-BST (N=178;165)	128.9 (92.7 to 179.2)	11.4 (8.3 to 15.8)		
OPSONO-7F, PRE (N=217;202)	1522.8 (1338.5 to 1732.6)	979.5 (821.2 to 1168.5)		
OPSONO-7F, M1 POST-BST (N=205;196)	4336.3 (3607.9 to 5211.8)	746.4 (590.7 to 943.1)		
OPSONO-7F, M9 POST-BST (N=192;172)	2598 (2232 to 3024.1)	1214.3 (1011.4 to 1458)		
OPSONO-9V, PRE (N=213;188)	709.4 (601.7 to 836.3)	233.7 (175.3 to 311.4)		
OPSONO-9V, M1 POST-BST (N=200;189)	3763 (3317.5 to 4268.3)	250.9 (186.1 to 338.4)		
OPSONO-9V, M9 POST-BST (N=194;168)	1320.3 (1153.1 to 1511.7)	337.4 (252.4 to 451)		
OPSONO-14, PRE (N=205;192)	121.2 (89.7 to 163.8)	27 (18.9 to 38.5)		
OPSONO-14, M1 POST-BST (N=209;188)	2659.6 (2266.2 to 3121.3)	21.7 (15 to 31.2)		
OPSONO-14, M9 POST-BST (N=185;159)	330.6 (242.7 to 450.5)	27.6 (18.3 to 41.8)		
OPSONO-18C, PRE (N=204;191)	15 (11.5 to 19.6)	4.8 (4.2 to 5.4)		
OPSONO-18C, M1 POST-BST (N=188;187)	2426 (2041.8 to 2882.5)	5.2 (4.4 to 6)		
OPSONO-18C, M9 POST-BST (N=170;164)	722 (553.6 to 941.6)	5.3 (4.4 to 6.5)		
OPSONO-19F, PRE (N=218;205)	24.3 (19.6 to 30.1)	5 (4.4 to 5.7)		
OPSONO-19F, M1 POST-BST (N=199;200)	657.5 (497.4 to 869.1)	5 (4.4 to 5.7)		
OPSONO-19F, M9 POST-BST (N=194;170)	118 (90.6 to 153.7)	4.8 (4.3 to 5.4)		
OPSONO-23F, PRE (N=215;199)	679.3 (494.3 to 933.6)	76.9 (49 to 120.6)		
OPSONO-23F, M1 POST-BST (N=206;190)	4278.3 (3609.3 to 5071.3)	99.7 (62.7 to 158.6)		
OPSONO-23F, M9 POST-BST (N=187;167)	999.6 (711.8 to 1403.9)	109.4 (65.7 to 182.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Titers for Opsonophagocytic activity against pneumococcal serotypes 6A and 19A in the Immunogenicity and Tolerability Subset

End point title	Titers for Opsonophagocytic activity against pneumococcal serotypes 6A and 19A in the Immunogenicity and Tolerability Subset

End point description:

The cut-off of the assay was >= 8. The Immunogenicity and Tolerability Subset included 500 subjects coming from Argentina and Panama respectively.

End point type	Secondary

End point timeframe:

Before the administration of booster vaccination (PRE), and 1 month and 9 months post booster vaccination (M1 POST-BST and M9 POST-BST)

End point values	Synflorix Group	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	217	204		
Units: Titers				
geometric mean (confidence interval 95%)				
OPSONO-6A, PRE (N=189;194)	43.8 (31 to 62)	7.1 (5.7 to 8.9)		
OPSONO-6A, M1 POST BST (N=185;185)	277.2 (198.7 to 386.7)	7.6 (6 to 9.7)		
OPSONO-6A, M9 POST-BST (N=175;156)	63.9 (44.3 to 92)	17.2 (12.1 to 24.4)		
OPSONO-19A, PRE (N=217;204)	6.3 (5.3 to 7.4)	5 (4.4 to 5.6)		
OPSONO-19A, M1 POST-BST (N=200;197)	132.8 (97.5 to 180.8)	5.4 (4.7 to 6.2)		
OPSONO-19A, M9 POST-BST (N=187;171)	26.1 (19.5 to 35.1)	6.3 (5.3 to 7.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with titers for opsonophagocytic activity against vaccine pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F => 8, in the Immunogenicity and Tolerability Subset

End point title	Number of subjects with titers for opsonophagocytic activity against vaccine pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F => 8, in the Immunogenicity and Tolerability Subset

End point description:

A seropositive subject was defined as a subject with titers for opsonophagocytic activity against vaccine pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F >= 8. The Immunogenicity and Tolerability Subset included 500 subjects coming from Argentina and Panama respectively.

End point type	Secondary

End point timeframe:

At Month 5, one month after the third dose of primary vaccination

End point values	Synflorix Group	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	317	317		
Units: Subjects				
OPSONO-1 (N=306;305)	280	25		
OPSONO-4 (N=310;299)	306	15		
OPSONO-5 (N=313;314)	303	13		
OPSONO-6B (N=315;309)	286	16		
OPSONO-7F (N=302;266)	302	162		
OPSONO-9V (N=312;302)	311	98		
OPSONO-14 (N=308;273)	306	95		
OPSONO-18C (N=308;317)	290	8		
OPSONO-19F (N=304;314)	277	16		
OPSONO-23F (N=317;282)	311	68		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with titers for opsonophagocytic activity against cross-reactive pneumococcal serotypes 6A and 19A >= 8, in the Immunogenicity and Tolerability Subset

End point title	Number of subjects with titers for opsonophagocytic activity against cross-reactive pneumococcal serotypes 6A and 19A >= 8, in the Immunogenicity and Tolerability Subset

End point description:

A seropositive subject was defined as a subject with titers for opsonophagocytic activity against cross-reactive pneumococcal serotypes 6A and 19A >= 8. The Immunogenicity and Tolerability Subset included 500 subjects coming from Argentina and Panama respectively.

End point type	Secondary

End point timeframe:

At Month 5, one month after the third dose of primary vaccination

End point values	Synflorix Group	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	302	309		
Units: Subjects				
OPSONO-6A (N=297;305)	232	16		
OPSONO-19A (N=302;309)	121	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with titers for opsonophagocytic activity against vaccine pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F >= 8, in the Immunogenicity and Tolerability Subset

End point title	Number of subjects with titers for opsonophagocytic activity against vaccine pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F >= 8, in the Immunogenicity and Tolerability Subset

End point description:

A seropositive subject was defined as a subject with titers for opsonophagocytic activity against vaccine pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F >= 8. The Immunogenicity and Tolerability Subset included 500 subjects coming from Argentina and Panama respectively.

End point type	Secondary

End point timeframe:

Before the administration of booster vaccination (PRE), and 1 month and 9 months post booster vaccination (M1 POST-BST and M9 POST-BST)

End point values	Synflorix Group	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	221	210		
Units: Subjects				
OPSONO-1, PRE (N=221;210)	58	9		
OPSONO-1, M1 POST-BST (N=209;200)	195	14		
OPSONO-1, M9 POST-BST (N=196;176)	127	10		
OPSONO-4, PRE (N=208;193)	108	25		
OPSONO-4, M1 POST-BST (N=207;193)	206	26		
OPSONO-4, M9 POST-BST (N=192;173)	147	22		
OPSONO-5, PRE (N=205;204)	138	7		
OPSONO-5, M1 POST-BST (N=196;187)	194	10		
OPSONO-5, M9 POST-BST (N=192;173)	157	3		
OPSONO-6B, PRE (N=209;197)	162	27		
OPSONO-6B, M1 POST-BST (N=203;190)	200	23		
OPSONO-6B, M9 POST-BST (N=178;165)	146	35		
OPSONO-7F, PRE (N=217;202)	217	197		
OPSONO-7F, M1 POST-BST (N=205;196)	203	185		
OPSONO-7F, M9 POST-BST (N=192;172)	192	169		
OPSONO-9V, PRE (N=213;188)	212	159		
OPSONO-9V, M1 POST-BST (N=200;189)	200	157		
OPSONO-9V, M9 POST-BST (N=194;168)	194	148		
OPSONO-14, PRE (N=205;192)	158	73		
OPSONO-14, M1 POST-BST (N=209;188)	208	61		
OPSONO-14, M9 POST-BST (N=185;159)	160	57		

OPSONO-18C, PRE (N=204;191)	86	8		
OPSONO-18C, M1 POST-BST (N=188;187)	187	11		
OPSONO-18C, M9 POST-BST (N=170;164)	165	10		
OPSONO-19F, PRE (N=218;205)	150	14		
OPSONO-19F, M1 POST-BST (N=199;200)	186	13		
OPSONO-19F, M9 POST-BST (N=194;170)	168	11		
OPSONO-23F, PRE (N=215;199)	190	94		
OPSONO-23F, M1 POST-BST (N=206;190)	205	97		
OPSONO-23F, M9 POST-BST (N=187;167)	167	85		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with titers for opsonophagocytic activity against pneumococcal cross-reactive serotypes 6A and 19A >= 8, in the Immunogenicity and Tolerability Subset

End point title	Number of subjects with titers for opsonophagocytic activity against pneumococcal cross-reactive serotypes 6A and 19A >= 8, in the Immunogenicity and Tolerability Subset

End point description:

A seropositive subject was a subject with titers for opsonophagocytic activity against pneumococcal cross-reactive serotypes 6A and 19A >= 8. The Immunogenicity and Tolerability Subset included 500 subjects coming from Argentina and Panama respectively.

End point type	Secondary

End point timeframe:

Before the administration of booster vaccination (PRE), and 1 month and 9 months post booster vaccination (M1 POST-BST and M9 POST-BST).

End point values	Synflorix Group	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	217	204		
Units: Subjects				
OPSONO-6A, PRE (N=189;194)	99	24		
OPSONO-6A, M1 POST BST (N=185;185)	150	26		
OPSONO-6A, M9 POST-BST (N=175;156)	104	50		
OPSONO-19A, PRE (N=217;204)	32	14		
OPSONO-19A, M1 POST-BST (N=200;197)	161	20		
OPSONO-19A, M9 POST-BST (N=187;171)	108	32		

Statistical analyses

No statistical analyses for this end point

Secondary: Concentrations of antibodies against protein D (ANTI-PD), in the Immunogenicity and Tolerability Subset

End point title	Concentrations of antibodies against protein D (ANTI-PD), in the Immunogenicity and Tolerability Subset

End point description:

ANTI-PD concentrations are expressed as geometric mean concentrations (GMCs), in enzyme-linked immunosorbent assay (ELISA) unit per milliliter (EL.U/mL). The Immunogenicity and Tolerability Subset included 500 subjects coming from Argentina and Panama respectively.

End point type	Secondary

End point timeframe:

At Month 5, one month after the third dose of primary vaccination

End point values	Synflorix Group	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	334	325		
Units: EL.U/mL				
geometric mean (confidence interval 95%)				
ANTI-PD	2455.2 (2248.3 to 2681.1)	101.2 (91.3 to 112.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Concentrations of antibodies against protein D (ANTI-PD), in the Immunogenicity and Tolerability Subset

End point title	Concentrations of antibodies against protein D (ANTI-PD), in the Immunogenicity and Tolerability Subset

End point description:

ANTI-PD concentrations are expressed as geometric mean concentrations (GMCs), in enzyme-linked immunosorbent assay (ELISA) unit per milliliter (EL.U/mL). The Immunogenicity and Tolerability Subset included 500 subjects coming from Argentina and Panama respectively.

End point type	Secondary

End point timeframe:

Before the administration of booster vaccination (PRE), and 1 month and 9 months post booster vaccination (M1 Post-BST and M9 POST-BST)

End point values	Synflorix Group	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	230	211		
Units: EL.U/mL				
geometric mean (confidence interval 95%)				
ANTI-PD, PRE (N=230;211)	638.6 (556.2 to 733.2)	103.1 (90.5 to 117.5)		
ANTI-PD, M1 POST BST (N=218;195)	2787 (2435.9 to 3188.7)	92.4 (82.6 to 103.3)		
ANTI-PD, M9 POST-BST (N=206;182)	824.1 (704.2 to 964.4)	94.5 (84.4 to 105.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with anti-protein D (ANTI-PD) antibody concentrations >= 100 enzyme-linked immunosorbent assay units per milliliter (EL.U/mL), in the Immunogenicity and Tolerability Subset

End point title	Number of subjects with anti-protein D (ANTI-PD) antibody concentrations >= 100 enzyme-linked immunosorbent assay units per milliliter (EL.U/mL), in the Immunogenicity and Tolerability Subset

End point description:

A seropositive subject was defined as a subject with ANTI-PD antibody concentrations >= 100 EL.U/mL. The Immunogenicity and Tolerability Subset included 500 subjects coming from Argentina and Panama respectively.

End point type	Secondary

End point timeframe:

At Month 5, one month after the third dose of primary vaccination

End point values	Synflorix Group	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	334	325		
Units: Subjects				
ANTI-PD	333	141		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with anti-protein D (ANTI-PD) antibody concentrations >= 100 enzyme-linked immunosorbent assay units per milliliter (EL.U/mL), in the Immunogenicity and Tolerability Subset.

End point title	Number of subjects with anti-protein D (ANTI-PD) antibody concentrations >= 100 enzyme-linked immunosorbent assay units per milliliter (EL.U/mL), in the Immunogenicity and Tolerability Subset.

End point description:

A seropositive subject was defined as a subject with ANTI-PD antibody concentrations >= 100 EL.U/mL. The Immunogenicity and Tolerability Subset included 500 subjects coming from Argentina and Panama respectively.

End point type	Secondary

End point timeframe:

Before the administration of booster vaccination (PRE), and 1 month and 9 months post booster vaccination (M1 Post-BST and M9 Post-BST)

End point values	Synflorix Group	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	230	211		
Units: Subjects				
ANTI-PD, PRE (N=230;211)	223	96		
ANTI-PD, M1 POST BST (N=218;195)	218	83		
ANTI-PD, M9 POST-BST (N=206;182)	198	84		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

SAEs and unsolicited AEs: Throughout the study (Months 0 to 22-25). Solicited symptoms: 4-day (Days 0–3) follow-up period across the 3 doses of primary study vaccine course/ 4-day (Days 0–3) follow-up period post booster vaccination

Adverse event reporting additional description:

SAEs reports were collected based on the Total Vaccinated cohort. Reports for unsolicited and solicited AEs were collected based on the TVC, from the Panama Subset and from the Immunogenicity and Tolerability Subset, respectively. Occurrences of AEs (all/related) was not available and is encoded as equal to the number of subjects affected.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups

Reporting group title	Synflorix Group

Reporting group description:

Subjects received 3 primary doses of Synflorix at 2, 4 and 6 months of age co-administered with Infanrix-hexa and booster dose of Synflorix at 15-18 months of age co-administered with Infanrix-IPV/Hib. All vaccines were administered intramuscularly in the right (Synflorix) or the left (Infanrix-hexa, Infanrix-IPV/Hib) thigh (primary dose) or deltoid (booster dose).

Reporting group title	Control Group

Reporting group description:

Subjects received 3 doses of Engerix at 2,4 and 6 months of age co-administered with Infanrix-IPV/Hib and 1 dose of Havrix co-administered with Infanrix-IPV/Hib at 15-18 months of age. All vaccine were administered in the right (Engerix, Havrix) or the left (Infanrix-IPV/Hib) thigh.

Serious adverse events	Synflorix Group	Control Group	
Total subjects affected by serious adverse events			
subjects affected / exposed	2534 / 11798 (21.48%)	2668 / 11799 (22.61%)	
number of deaths (all causes)	19	26	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute lymphocytic leukaemia			
subjects affected / exposed	1 / 11798 (0.01%)	2 / 11799 (0.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myeloid leukaemia			
subjects affected / exposed	1 / 11798 (0.01%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Brain neoplasm			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hepatoblastoma			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Histiocytosis haematophagic			
subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephroblastoma			
subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuroblastoma			
subjects affected / exposed	0 / 11798 (0.00%)	2 / 11799 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinoblastoma bilateral			
subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Capillary fragility			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extremity necrosis			
subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flushing			

subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	0 / 11798 (0.00%)	2 / 11799 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemic shock			
subjects affected / exposed	3 / 11798 (0.03%)	3 / 11799 (0.03%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Kawasaki’s disease			
subjects affected / exposed	9 / 11798 (0.08%)	3 / 11799 (0.03%)	
occurrences causally related to treatment / all	0 / 9	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Phlebitis			
subjects affected / exposed	1 / 11798 (0.01%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock			
subjects affected / exposed	2 / 11798 (0.02%)	4 / 11799 (0.03%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 0	
Surgical and medical procedures			
Finger amputation			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Therapeutic hypothermia			

subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toe amputation			
subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Cephalhaematoma			
subjects affected / exposed	1 / 11798 (0.01%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Crying			
subjects affected / exposed	1 / 11798 (0.01%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Effusion			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocution			
subjects affected / exposed	2 / 11798 (0.02%)	2 / 11799 (0.02%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 0	
Hypothermia			
subjects affected / exposed	1 / 11798 (0.01%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	24 / 11798 (0.20%)	31 / 11799 (0.26%)	
occurrences causally related to treatment / all	0 / 24	0 / 31	
deaths causally related to treatment / all	0 / 0	0 / 0	

Sudden death			
subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sudden infant death syndrome			
subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Systemic inflammatory response syndrome			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	2 / 11798 (0.02%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Food allergy			
subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity			
subjects affected / exposed	5 / 11798 (0.04%)	6 / 11799 (0.05%)	
occurrences causally related to treatment / all	0 / 5	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immunodeficiency			
subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Milk allergy			
subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Selective iga immunodeficiency			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Social circumstances			
Alcohol use			
subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Physical abuse			
subjects affected / exposed	1 / 11798 (0.01%)	2 / 11799 (0.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Balanoposthitis			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Genital lesion			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute lung injury			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Acute pulmonary oedema			
subjects affected / exposed	1 / 11798 (0.01%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Acute respiratory failure			

subjects affected / exposed	0 / 11798 (0.00%)	2 / 11799 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Allergic bronchitis			
subjects affected / exposed	1 / 11798 (0.01%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Apnoea			
subjects affected / exposed	3 / 11798 (0.03%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Apnoeic attack			
subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Apparent life threatening event			
subjects affected / exposed	4 / 11798 (0.03%)	3 / 11799 (0.03%)	
occurrences causally related to treatment / all	0 / 4	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asphyxia			
subjects affected / exposed	2 / 11798 (0.02%)	3 / 11799 (0.03%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 2	0 / 2	
Aspiration			
subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Asthma			
subjects affected / exposed	82 / 11798 (0.70%)	83 / 11799 (0.70%)	
occurrences causally related to treatment / all	0 / 82	0 / 83	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthmatic crisis			

subjects affected / exposed	192 / 11798 (1.63%)	210 / 11799 (1.78%)
occurrences causally related to treatment / all	0 / 192	0 / 210
deaths causally related to treatment / all	0 / 0	0 / 0
Atelectasis		
subjects affected / exposed	10 / 11798 (0.08%)	5 / 11799 (0.04%)
occurrences causally related to treatment / all	0 / 10	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0
Bronchial hyperreactivity		
subjects affected / exposed	16 / 11798 (0.14%)	14 / 11799 (0.12%)
occurrences causally related to treatment / all	0 / 16	0 / 14
deaths causally related to treatment / all	0 / 0	0 / 0
Bronchial obstruction		
subjects affected / exposed	127 / 11798 (1.08%)	141 / 11799 (1.20%)
occurrences causally related to treatment / all	0 / 127	0 / 141
deaths causally related to treatment / all	0 / 0	0 / 1
Bronchospasm		
subjects affected / exposed	6 / 11798 (0.05%)	9 / 11799 (0.08%)
occurrences causally related to treatment / all	0 / 6	0 / 9
deaths causally related to treatment / all	0 / 0	0 / 0
Dyspnoea		
subjects affected / exposed	1 / 11798 (0.01%)	1 / 11799 (0.01%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Epistaxis		
subjects affected / exposed	1 / 11798 (0.01%)	1 / 11799 (0.01%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Infantile asthma		
subjects affected / exposed	1 / 11798 (0.01%)	1 / 11799 (0.01%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Interstitial lung disease		

subjects affected / exposed	6 / 11798 (0.05%)	4 / 11799 (0.03%)	
occurrences causally related to treatment / all	0 / 6	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 2	
Laryngeal oedema			
subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung disorder			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstructive airways disorder			
subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	8 / 11798 (0.07%)	3 / 11799 (0.03%)	
occurrences causally related to treatment / all	0 / 8	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	3 / 11798 (0.03%)	3 / 11799 (0.03%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	3 / 11798 (0.03%)	4 / 11799 (0.03%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	2 / 11798 (0.02%)	2 / 11799 (0.02%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			

subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory disorder			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	4 / 11798 (0.03%)	6 / 11799 (0.05%)	
occurrences causally related to treatment / all	0 / 4	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 3	
Sleep apnoea syndrome			
subjects affected / exposed	1 / 11798 (0.01%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wheezing			
subjects affected / exposed	48 / 11798 (0.41%)	42 / 11799 (0.36%)	
occurrences causally related to treatment / all	0 / 48	0 / 42	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis allergic			
subjects affected / exposed	2 / 11798 (0.02%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Binge eating			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breath holding			

subjects affected / exposed	2 / 11798 (0.02%)	6 / 11799 (0.05%)	
occurrences causally related to treatment / all	0 / 2	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychomotor retardation			
subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	1 / 11798 (0.01%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hepatitis acute			
subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Acid base balance abnormal			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Aspiration bronchial			
subjects affected / exposed	2 / 11798 (0.02%)	3 / 11799 (0.03%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 2	0 / 3	
Injury, poisoning and procedural			

complications			
Abdominal injury			
subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Accidental exposure			
subjects affected / exposed	10 / 11798 (0.08%)	8 / 11799 (0.07%)	
occurrences causally related to treatment / all	0 / 10	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Accidental overdose			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Accidental poisoning			
subjects affected / exposed	3 / 11798 (0.03%)	3 / 11799 (0.03%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Animal bite			
subjects affected / exposed	5 / 11798 (0.04%)	2 / 11799 (0.02%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthropod bite			
subjects affected / exposed	2 / 11798 (0.02%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthropod sting			
subjects affected / exposed	6 / 11798 (0.05%)	5 / 11799 (0.04%)	
occurrences causally related to treatment / all	0 / 6	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back injury			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Burns first degree			

subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Burns second degree			
subjects affected / exposed	6 / 11798 (0.05%)	8 / 11799 (0.07%)	
occurrences causally related to treatment / all	0 / 6	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 1	
Carbon monoxide poisoning			
subjects affected / exposed	2 / 11798 (0.02%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chemical injury			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chemical poisoning			
subjects affected / exposed	24 / 11798 (0.20%)	21 / 11799 (0.18%)	
occurrences causally related to treatment / all	0 / 24	0 / 21	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest injury			
subjects affected / exposed	1 / 11798 (0.01%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Craniocerebral injury			
subjects affected / exposed	39 / 11798 (0.33%)	36 / 11799 (0.31%)	
occurrences causally related to treatment / all	0 / 39	0 / 36	
deaths causally related to treatment / all	0 / 1	0 / 0	
Electric shock			

subjects affected / exposed	4 / 11798 (0.03%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrical burn			
subjects affected / exposed	1 / 11798 (0.01%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extradural haematoma			
subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye burns			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye injury			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eyelid injury			
subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Face injury			
subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	2 / 11798 (0.02%)	5 / 11799 (0.04%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foreign body			

subjects affected / exposed	16 / 11798 (0.14%)	15 / 11799 (0.13%)	
occurrences causally related to treatment / all	0 / 16	0 / 15	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture			
subjects affected / exposed	1 / 11798 (0.01%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gingival injury			
subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hand fracture			
subjects affected / exposed	2 / 11798 (0.02%)	3 / 11799 (0.03%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	75 / 11798 (0.64%)	74 / 11799 (0.63%)	
occurrences causally related to treatment / all	0 / 75	0 / 74	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herbal toxicity			
subjects affected / exposed	2 / 11798 (0.02%)	2 / 11799 (0.02%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	4 / 11798 (0.03%)	2 / 11799 (0.02%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury			
subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laceration			

subjects affected / exposed	2 / 11798 (0.02%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limb crushing injury			
subjects affected / exposed	0 / 11798 (0.00%)	2 / 11799 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limb traumatic amputation			
subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture			
subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mouth injury			
subjects affected / exposed	1 / 11798 (0.01%)	2 / 11799 (0.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple injuries			
subjects affected / exposed	26 / 11798 (0.22%)	33 / 11799 (0.28%)	
occurrences causally related to treatment / all	0 / 26	0 / 33	
deaths causally related to treatment / all	0 / 0	0 / 1	
Near drowning			
subjects affected / exposed	6 / 11798 (0.05%)	3 / 11799 (0.03%)	
occurrences causally related to treatment / all	0 / 6	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Open fracture			
subjects affected / exposed	0 / 11798 (0.00%)	2 / 11799 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Open wound			

subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis chemical			
subjects affected / exposed	1 / 11798 (0.01%)	3 / 11799 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Poisoning			
subjects affected / exposed	3 / 11798 (0.03%)	2 / 11799 (0.02%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative fever			
subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural haemorrhage			
subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	0 / 11798 (0.00%)	2 / 11799 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Skull fracture			
subjects affected / exposed	6 / 11798 (0.05%)	5 / 11799 (0.04%)	
occurrences causally related to treatment / all	0 / 6	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Tendon injury			

subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thermal burn			
subjects affected / exposed	25 / 11798 (0.21%)	36 / 11799 (0.31%)	
occurrences causally related to treatment / all	0 / 25	0 / 36	
deaths causally related to treatment / all	0 / 1	0 / 0	
Tibia fracture			
subjects affected / exposed	1 / 11798 (0.01%)	2 / 11799 (0.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tongue injury			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth fracture			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			
subjects affected / exposed	12 / 11798 (0.10%)	12 / 11799 (0.10%)	
occurrences causally related to treatment / all	0 / 12	0 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic haematoma			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	3 / 11798 (0.03%)	4 / 11799 (0.03%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vulvovaginal injury			

subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound			
subjects affected / exposed	0 / 11798 (0.00%)	5 / 11799 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound dehiscence			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Cerebral palsy			
subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coarctation of the aorta			
subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital absence of bile ducts			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital oral malformation			
subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital syphilis			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystic fibrosis			

subjects affected / exposed	3 / 11798 (0.03%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermoid cyst			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heart disease congenital			
subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Laryngomalacia			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningomyelocele			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Porencephaly			
subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pyloric stenosis			
subjects affected / exposed	1 / 11798 (0.01%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinoblastoma			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sickle cell anaemia			

subjects affected / exposed	1 / 11798 (0.01%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sickle cell anaemia with crisis			
subjects affected / exposed	0 / 11798 (0.00%)	2 / 11799 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal muscular atrophy			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thalassaemia sickle cell			
subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	1 / 11798 (0.01%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Cardiac failure congestive			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	2 / 11798 (0.02%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Cyanosis			
subjects affected / exposed	1 / 11798 (0.01%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracardiac mass			

subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ventricular arrhythmia			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Ataxia			
subjects affected / exposed	2 / 11798 (0.02%)	2 / 11799 (0.02%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain injury			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain oedema			
subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cerebrospinal fistula			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cns ventriculitis			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Convulsion			
subjects affected / exposed	28 / 11798 (0.24%)	25 / 11799 (0.21%)	
occurrences causally related to treatment / all	0 / 28	0 / 25	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dystonia			

subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	2 / 11798 (0.02%)	2 / 11799 (0.02%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extrapyramidal disorder			
subjects affected / exposed	2 / 11798 (0.02%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile convulsion			
subjects affected / exposed	95 / 11798 (0.81%)	135 / 11799 (1.14%)	
occurrences causally related to treatment / all	0 / 95	0 / 135	
deaths causally related to treatment / all	0 / 0	0 / 0	
Grand mal convulsion			
subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Guillain-barre syndrome			
subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxic-ischaemic encephalopathy			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Infantile spasms			

subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial pressure increased			
subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Myoclonic epilepsy			
subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post-traumatic epilepsy			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Status epilepticus			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 11798 (0.01%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viith nerve paralysis			
subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	5 / 11798 (0.04%)	9 / 11799 (0.08%)	
occurrences causally related to treatment / all	0 / 5	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 1	
Coagulopathy			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	4 / 11798 (0.03%)	4 / 11799 (0.03%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemolysis			
subjects affected / exposed	1 / 11798 (0.01%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disseminated intravascular coagulation			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Haemolytic anaemia			
subjects affected / exposed	1 / 11798 (0.01%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemolytic uraemic syndrome			
subjects affected / exposed	2 / 11798 (0.02%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic disorder			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersplenism			

subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypochromic anaemia			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Idiopathic thrombocytopenic purpura			
subjects affected / exposed	3 / 11798 (0.03%)	2 / 11799 (0.02%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iron deficiency anaemia			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukaemoid reaction			
subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenitis			
subjects affected / exposed	12 / 11798 (0.10%)	19 / 11799 (0.16%)	
occurrences causally related to treatment / all	0 / 12	0 / 19	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenopathy			
subjects affected / exposed	2 / 11798 (0.02%)	2 / 11799 (0.02%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			

subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenic purpura			
subjects affected / exposed	1 / 11798 (0.01%)	2 / 11799 (0.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Conjunctivitis			
subjects affected / exposed	1 / 11798 (0.01%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Conjunctivitis allergic			
subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulcerative keratitis			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal adhesions			
subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal distension			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal mass			

subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	8 / 11798 (0.07%)	5 / 11799 (0.04%)	
occurrences causally related to treatment / all	0 / 8	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute abdomen			
subjects affected / exposed	2 / 11798 (0.02%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendix disorder			
subjects affected / exposed	2 / 11798 (0.02%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	11 / 11798 (0.09%)	10 / 11799 (0.08%)	
occurrences causally related to treatment / all	0 / 11	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	63 / 11798 (0.53%)	53 / 11799 (0.45%)	
occurrences causally related to treatment / all	0 / 63	0 / 53	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea haemorrhagic			
subjects affected / exposed	1 / 11798 (0.01%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspepsia			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			

subjects affected / exposed	15 / 11798 (0.13%)	20 / 11799 (0.17%)	
occurrences causally related to treatment / all	0 / 15	0 / 20	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faecaloma			
subjects affected / exposed	2 / 11798 (0.02%)	3 / 11799 (0.03%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Food poisoning			
subjects affected / exposed	5 / 11798 (0.04%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	1 / 11798 (0.01%)	4 / 11799 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis erosive			
subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorder			
subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 11798 (0.00%)	2 / 11799 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			
subjects affected / exposed	6 / 11798 (0.05%)	3 / 11799 (0.03%)	
occurrences causally related to treatment / all	0 / 6	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gingival bleeding			

subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematochezia			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	4 / 11798 (0.03%)	3 / 11799 (0.03%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus paralytic			
subjects affected / exposed	33 / 11798 (0.28%)	23 / 11799 (0.19%)	
occurrences causally related to treatment / all	0 / 33	0 / 23	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infantile colic			
subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	0 / 11798 (0.00%)	3 / 11799 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia, obstructive			
subjects affected / exposed	5 / 11798 (0.04%)	3 / 11799 (0.03%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal haemorrhage			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			

subjects affected / exposed	2 / 11798 (0.02%)	2 / 11799 (0.02%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intussusception			
subjects affected / exposed	14 / 11798 (0.12%)	11 / 11799 (0.09%)	
occurrences causally related to treatment / all	0 / 14	0 / 11	
deaths causally related to treatment / all	0 / 0	0 / 1	
Malabsorption			
subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mallory-weiss syndrome			
subjects affected / exposed	1 / 11798 (0.01%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	3 / 11798 (0.03%)	6 / 11799 (0.05%)	
occurrences causally related to treatment / all	0 / 3	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	2 / 11798 (0.02%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			

subjects affected / exposed	42 / 11798 (0.36%)	37 / 11799 (0.31%)	
occurrences causally related to treatment / all	0 / 42	0 / 37	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multi-organ failure			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Skin and subcutaneous tissue disorders			
Acute haemorrhagic oedema of infancy			
subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angioedema			
subjects affected / exposed	2 / 11798 (0.02%)	3 / 11799 (0.03%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cutaneous loxoscelism			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis bullous			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis contact			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis diaper			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis exfoliative			

subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatosis			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erythema multiforme			
subjects affected / exposed	0 / 11798 (0.00%)	2 / 11799 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic urticaria			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heat rash			
subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Henoch-schonlein purpura			
subjects affected / exposed	5 / 11798 (0.04%)	3 / 11799 (0.03%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	2 / 11798 (0.02%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash scarlatiniform			
subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin oedema			

subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urticaria			
subjects affected / exposed	10 / 11798 (0.08%)	15 / 11799 (0.13%)	
occurrences causally related to treatment / all	0 / 10	0 / 15	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Glomerulonephritis acute			
subjects affected / exposed	2 / 11798 (0.02%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	3 / 11798 (0.03%)	4 / 11799 (0.03%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrotic syndrome			
subjects affected / exposed	2 / 11798 (0.02%)	3 / 11799 (0.03%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oliguria			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prerenal failure			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelocaliectasis			

subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure acute			
subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hyperadrenalism			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypothyroidism			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Compartment syndrome			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Connective tissue disorder			
subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dactylitis			
subjects affected / exposed	0 / 11798 (0.00%)	2 / 11799 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Muscular weakness			
subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periostitis			
subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sacroiliitis			
subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Synovitis			
subjects affected / exposed	3 / 11798 (0.03%)	2 / 11799 (0.02%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tenosynovitis			
subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Torticollis			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Trigger finger			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal wall abscess			
subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess			

subjects affected / exposed	11 / 11798 (0.09%)	9 / 11799 (0.08%)	
occurrences causally related to treatment / all	0 / 11	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 1	
Abscess limb			
subjects affected / exposed	10 / 11798 (0.08%)	16 / 11799 (0.14%)	
occurrences causally related to treatment / all	0 / 10	0 / 16	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess neck			
subjects affected / exposed	4 / 11798 (0.03%)	8 / 11799 (0.07%)	
occurrences causally related to treatment / all	0 / 4	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess of eyelid			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acarodermatitis			
subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acquired immunodeficiency syndrome			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute sinusitis			
subjects affected / exposed	2 / 11798 (0.02%)	3 / 11799 (0.03%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenoiditis			
subjects affected / exposed	1 / 11798 (0.01%)	4 / 11799 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenovirus infection			

subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Amoebiasis			
subjects affected / exposed	0 / 11798 (0.00%)	2 / 11799 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Amoebic dysentery			
subjects affected / exposed	0 / 11798 (0.00%)	3 / 11799 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal abscess			
subjects affected / exposed	2 / 11798 (0.02%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	3 / 11798 (0.03%)	3 / 11799 (0.03%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis perforated			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis bacterial			
subjects affected / exposed	3 / 11798 (0.03%)	2 / 11799 (0.02%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascariasis			
subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atypical pneumonia			

subjects affected / exposed	14 / 11798 (0.12%)	12 / 11799 (0.10%)	
occurrences causally related to treatment / all	0 / 14	0 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	4 / 11798 (0.03%)	6 / 11799 (0.05%)	
occurrences causally related to treatment / all	0 / 4	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial diarrhoea			
subjects affected / exposed	2 / 11798 (0.02%)	2 / 11799 (0.02%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial infection			
subjects affected / exposed	0 / 11798 (0.00%)	2 / 11799 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast abscess			
subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchiolitis			
subjects affected / exposed	473 / 11798 (4.01%)	518 / 11799 (4.39%)	
occurrences causally related to treatment / all	0 / 473	0 / 518	
deaths causally related to treatment / all	0 / 1	0 / 1	
Bronchitis			
subjects affected / exposed	124 / 11798 (1.05%)	129 / 11799 (1.09%)	
occurrences causally related to treatment / all	0 / 124	0 / 129	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			
subjects affected / exposed	106 / 11798 (0.90%)	95 / 11799 (0.81%)	
occurrences causally related to treatment / all	0 / 106	0 / 95	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bullous impetigo			

subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Burn infection			
subjects affected / exposed	2 / 11798 (0.02%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cat scratch disease			
subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	45 / 11798 (0.38%)	46 / 11799 (0.39%)	
occurrences causally related to treatment / all	0 / 45	0 / 46	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis of male external genital organ			
subjects affected / exposed	1 / 11798 (0.01%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis orbital			
subjects affected / exposed	1 / 11798 (0.01%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colostomy infection			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Conjunctivitis bacterial			
subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Conjunctivitis chlamydial			

subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Conjunctivitis infective			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (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	10 / 11798 (0.08%)	7 / 11799 (0.06%)	
occurrences causally related to treatment / all	0 / 10	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus hepatitis			
subjects affected / exposed	1 / 11798 (0.01%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dengue fever			
subjects affected / exposed	18 / 11798 (0.15%)	15 / 11799 (0.13%)	
occurrences causally related to treatment / all	0 / 18	0 / 15	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea infectious			
subjects affected / exposed	2 / 11798 (0.02%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysentery			
subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear infection			
subjects affected / exposed	1 / 11798 (0.01%)	2 / 11799 (0.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Empyema			

subjects affected / exposed	2 / 11798 (0.02%)	2 / 11799 (0.02%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalitis viral			
subjects affected / exposed	1 / 11798 (0.01%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis infectious			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterococcal sepsis			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection			
subjects affected / exposed	4 / 11798 (0.03%)	2 / 11799 (0.02%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Exanthema subitum			
subjects affected / exposed	4 / 11798 (0.03%)	4 / 11799 (0.03%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
External ear cellulitis			
subjects affected / exposed	2 / 11798 (0.02%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fungal skin infection			

subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	553 / 11798 (4.69%)	497 / 11799 (4.21%)	
occurrences causally related to treatment / all	0 / 553	0 / 497	
deaths causally related to treatment / all	0 / 2	0 / 0	
Gastroenteritis adenovirus			
subjects affected / exposed	1 / 11798 (0.01%)	3 / 11799 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis bacterial			
subjects affected / exposed	8 / 11798 (0.07%)	9 / 11799 (0.08%)	
occurrences causally related to treatment / all	0 / 8	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis rotavirus			
subjects affected / exposed	38 / 11798 (0.32%)	49 / 11799 (0.42%)	
occurrences causally related to treatment / all	0 / 38	0 / 49	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis shigella			
subjects affected / exposed	8 / 11798 (0.07%)	8 / 11799 (0.07%)	
occurrences causally related to treatment / all	0 / 8	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	9 / 11798 (0.08%)	9 / 11799 (0.08%)	
occurrences causally related to treatment / all	0 / 9	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Giardiasis			
subjects affected / exposed	1 / 11798 (0.01%)	3 / 11799 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gingivitis			

subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hantaviral infection			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpangina			
subjects affected / exposed	2 / 11798 (0.02%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes simplex			
subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes virus infection			
subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impetigo			
subjects affected / exposed	10 / 11798 (0.08%)	4 / 11799 (0.03%)	
occurrences causally related to treatment / all	0 / 10	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected bites			
subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected cyst			
subjects affected / exposed	2 / 11798 (0.02%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected fistula			

subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious mononucleosis			
subjects affected / exposed	5 / 11798 (0.04%)	4 / 11799 (0.03%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 11798 (0.01%)	2 / 11799 (0.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella bacteraemia			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella sepsis			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngitis			
subjects affected / exposed	9 / 11798 (0.08%)	14 / 11799 (0.12%)	
occurrences causally related to treatment / all	0 / 9	0 / 14	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lobar pneumonia			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			

subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymph node abscess			
subjects affected / exposed	2 / 11798 (0.02%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mastoiditis			
subjects affected / exposed	2 / 11798 (0.02%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis			
subjects affected / exposed	1 / 11798 (0.01%)	2 / 11799 (0.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis aseptic			
subjects affected / exposed	6 / 11798 (0.05%)	2 / 11799 (0.02%)	
occurrences causally related to treatment / all	0 / 6	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis meningococcal			
subjects affected / exposed	1 / 11798 (0.01%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis pneumococcal			
subjects affected / exposed	0 / 11798 (0.00%)	2 / 11799 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Meningitis viral			
subjects affected / exposed	1 / 11798 (0.01%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myiasis			

subjects affected / exposed	1 / 11798 (0.01%)	4 / 11799 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasal abscess			
subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasopharyngitis			
subjects affected / exposed	6 / 11798 (0.05%)	3 / 11799 (0.03%)	
occurrences causally related to treatment / all	0 / 6	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Necrotising fasciitis			
subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nosocomial infection			
subjects affected / exposed	1 / 11798 (0.01%)	3 / 11799 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Oral candidiasis			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (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	11 / 11798 (0.09%)	2 / 11799 (0.02%)	
occurrences causally related to treatment / all	0 / 11	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis externa			

subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media			
subjects affected / exposed	4 / 11798 (0.03%)	8 / 11799 (0.07%)	
occurrences causally related to treatment / all	0 / 4	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media acute			
subjects affected / exposed	16 / 11798 (0.14%)	16 / 11799 (0.14%)	
occurrences causally related to treatment / all	0 / 16	0 / 16	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paronychia			
subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parotitis			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periorbital cellulitis			
subjects affected / exposed	12 / 11798 (0.10%)	16 / 11799 (0.14%)	
occurrences causally related to treatment / all	0 / 12	0 / 16	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	4 / 11798 (0.03%)	4 / 11799 (0.03%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pertussis			
subjects affected / exposed	19 / 11798 (0.16%)	16 / 11799 (0.14%)	
occurrences causally related to treatment / all	0 / 19	0 / 16	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pharyngeal abscess			

subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	5 / 11798 (0.04%)	13 / 11799 (0.11%)	
occurrences causally related to treatment / all	0 / 5	0 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngotonsillitis			
subjects affected / exposed	4 / 11798 (0.03%)	2 / 11799 (0.02%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumococcal sepsis			
subjects affected / exposed	1 / 11798 (0.01%)	2 / 11799 (0.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jiroveci infection			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	478 / 11798 (4.05%)	557 / 11799 (4.72%)	
occurrences causally related to treatment / all	0 / 478	0 / 557	
deaths causally related to treatment / all	0 / 3	0 / 6	
Pneumonia adenoviral			
subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia influenza			

subjects affected / exposed	1 / 11798 (0.01%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia pneumococcal			
subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia respiratory syncytial viral			
subjects affected / exposed	2 / 11798 (0.02%)	5 / 11799 (0.04%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia viral			
subjects affected / exposed	8 / 11798 (0.07%)	9 / 11799 (0.08%)	
occurrences causally related to treatment / all	0 / 8	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			
subjects affected / exposed	2 / 11798 (0.02%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomembranous colitis			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary sepsis			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pyelonephritis			
subjects affected / exposed	11 / 11798 (0.09%)	6 / 11799 (0.05%)	
occurrences causally related to treatment / all	0 / 11	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			

subjects affected / exposed	2 / 11798 (0.02%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyoderma			
subjects affected / exposed	4 / 11798 (0.03%)	8 / 11799 (0.07%)	
occurrences causally related to treatment / all	0 / 4	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyomyositis			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (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	6 / 11798 (0.05%)	5 / 11799 (0.04%)	
occurrences causally related to treatment / all	0 / 6	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus bronchitis			
subjects affected / exposed	3 / 11798 (0.03%)	6 / 11799 (0.05%)	
occurrences causally related to treatment / all	0 / 3	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus infection			
subjects affected / exposed	0 / 11798 (0.00%)	2 / 11799 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection viral			
subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhinitis			

subjects affected / exposed	5 / 11798 (0.04%)	7 / 11799 (0.06%)	
occurrences causally related to treatment / all	0 / 5	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Roseola			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salmonellosis			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Scarlet fever			
subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	11 / 11798 (0.09%)	14 / 11799 (0.12%)	
occurrences causally related to treatment / all	0 / 11	0 / 14	
deaths causally related to treatment / all	0 / 0	0 / 4	
Sepsis syndrome			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	4 / 11798 (0.03%)	7 / 11799 (0.06%)	
occurrences causally related to treatment / all	0 / 4	0 / 7	
deaths causally related to treatment / all	0 / 3	0 / 5	
Shigella infection			
subjects affected / exposed	1 / 11798 (0.01%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			

subjects affected / exposed	9 / 11798 (0.08%)	5 / 11799 (0.04%)	
occurrences causally related to treatment / all	0 / 9	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin candida			
subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			
subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal bacteraemia			
subjects affected / exposed	2 / 11798 (0.02%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal scalded skin syndrome			
subjects affected / exposed	3 / 11798 (0.03%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	1 / 11798 (0.01%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal skin infection			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal sepsis			
subjects affected / exposed	2 / 11798 (0.02%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			

subjects affected / exposed	8 / 11798 (0.07%)	14 / 11799 (0.12%)	
occurrences causally related to treatment / all	0 / 8	0 / 14	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic candida			
subjects affected / exposed	2 / 11798 (0.02%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Thyroglossal cyst infection			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			
subjects affected / exposed	4 / 11798 (0.03%)	3 / 11799 (0.03%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth abscess			
subjects affected / exposed	2 / 11798 (0.02%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheitis			
subjects affected / exposed	8 / 11798 (0.07%)	7 / 11799 (0.06%)	
occurrences causally related to treatment / all	0 / 8	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Typhoid fever			
subjects affected / exposed	1 / 11798 (0.01%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	15 / 11798 (0.13%)	11 / 11799 (0.09%)	
occurrences causally related to treatment / all	0 / 15	0 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			

subjects affected / exposed	76 / 11798 (0.64%)	93 / 11799 (0.79%)	
occurrences causally related to treatment / all	0 / 76	0 / 93	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicella			
subjects affected / exposed	10 / 11798 (0.08%)	18 / 11799 (0.15%)	
occurrences causally related to treatment / all	0 / 10	0 / 18	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	12 / 11798 (0.10%)	11 / 11799 (0.09%)	
occurrences causally related to treatment / all	0 / 12	0 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral pharyngitis			
subjects affected / exposed	9 / 11798 (0.08%)	7 / 11799 (0.06%)	
occurrences causally related to treatment / all	0 / 9	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral rash			
subjects affected / exposed	3 / 11798 (0.03%)	4 / 11799 (0.03%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral sepsis			
subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral tonsillitis			
subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vulvovaginitis			

subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	0 / 11798 (0.00%)	3 / 11799 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Cow’s milk intolerance			
subjects affected / exposed	1 / 11798 (0.01%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	463 / 11798 (3.92%)	438 / 11799 (3.71%)	
occurrences causally related to treatment / all	0 / 463	0 / 438	
deaths causally related to treatment / all	0 / 2	0 / 1	
Diabetes mellitus			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic ketoacidosis			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrolyte imbalance			
subjects affected / exposed	8 / 11798 (0.07%)	5 / 11799 (0.04%)	
occurrences causally related to treatment / all	0 / 8	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Failure to thrive			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Feeding disorder neonatal			

subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Food intolerance			
subjects affected / exposed	0 / 11798 (0.00%)	3 / 11799 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	3 / 11798 (0.03%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	4 / 11798 (0.03%)	5 / 11799 (0.04%)	
occurrences causally related to treatment / all	0 / 4	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lactose intolerance			
subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			
subjects affected / exposed	3 / 11798 (0.03%)	4 / 11799 (0.03%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic acidosis			

subjects affected / exposed	1 / 11798 (0.01%)	0 / 11799 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 1 diabetes mellitus			
subjects affected / exposed	0 / 11798 (0.00%)	1 / 11799 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Synflorix Group	Control Group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3530 / 11798 (29.92%)	3518 / 11799 (29.82%)	
Injury, poisoning and procedural complications			
Head injury			
subjects affected / exposed[1]	454 / 3602 (12.60%)	406 / 3612 (11.24%)	
occurrences (all)	454	406	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed[2]	1411 / 3602 (39.17%)	1378 / 3612 (38.15%)	
occurrences (all)	1411	1378	
General disorders and administration site conditions			
Injection site pain			
subjects affected / exposed[3]	384 / 3602 (10.66%)	201 / 3612 (5.56%)	
occurrences (all)	384	201	
Pyrexia			
subjects affected / exposed[4]	2272 / 3602 (63.08%)	1916 / 3612 (53.05%)	
occurrences (all)	2272	1916	
Irritability			
subjects affected / exposed[5]	458 / 3602 (12.72%)	372 / 3612 (10.30%)	
occurrences (all)	458	372	
Injection site erythema			

subjects affected / exposed[6]	260 / 3602 (7.22%)	172 / 3612 (4.76%)	
occurrences (all)	260	172	
Drowsiness - Primary vaccination	Additional description: Solicited general AE collected in subjects in the Immunogenicity and Tolerability Subset post primary vaccination, across doses		
alternative assessment type: Systematic			
subjects affected / exposed[7]	236 / 368 (64.13%)	168 / 357 (47.06%)	
occurrences (all)	236	168	
Fever - Primary vaccination	Additional description: Solicited general AE - Fever = rectal temperature >= 38.0°C - collected in subjects in the Immunogenicity and Tolerability Subset post primary vaccination, across doses		
alternative assessment type: Systematic			
subjects affected / exposed[8]	247 / 368 (67.12%)	125 / 357 (35.01%)	
occurrences (all)	247	125	
Irritability - Primary vaccination	Additional description: Solicited general AE collected in subjects in the Immunogenicity and Tolerability Subset post primary vaccination, across doses		
alternative assessment type: Systematic			
subjects affected / exposed[9]	289 / 368 (78.53%)	206 / 357 (57.70%)	
occurrences (all)	289	206	
Loss of appetite - Primary vaccination	Additional description: Solicited general AE collected in subjects in the Immunogenicity and Tolerability Subset post primary vaccination		
alternative assessment type: Systematic			
subjects affected / exposed[10]	133 / 368 (36.14%)	80 / 357 (22.41%)	
occurrences (all)	133	80	
Drowsiness - Booster vaccination	Additional description: Solicited general AE collected in subjects in the Immunogenicity and Tolerability Subset post booster vaccination		
alternative assessment type: Systematic			
subjects affected / exposed[11]	74 / 317 (23.34%)	65 / 303 (21.45%)	
occurrences (all)	74	65	
Fever - Booster vaccination	Additional description: Solicited general AE - Fever = rectal temperature >= 38.0°C - collected in subjects in the Immunogenicity and Tolerability Subset post booster vaccination		
alternative assessment type: Systematic			
subjects affected / exposed[12]	93 / 317 (29.34%)	73 / 303 (24.09%)	
occurrences (all)	93	73	
Irritability - Booster vaccination	Additional description: Solicited general AE collected in subjects in the Immunogenicity and Tolerability Subset post booster vaccination		
alternative assessment type: Systematic			
subjects affected / exposed[13]	121 / 317 (38.17%)	95 / 303 (31.35%)	
occurrences (all)	121	95	
Loss of appetite - Booster vaccination	Additional description: Solicited general AE collected in subjects in the Immunogenicity and Tolerability Subset post booster vaccination		

alternative assessment type: Systematic			
subjects affected / exposed[14]	51 / 317 (16.09%)	46 / 303 (15.18%)	
occurrences (all)	51	46	
Pain – Primary Vaccination	Additional description: Solicited local AE collected in subjects in the Immunogenicity and Tolerability Subset post primary vaccination, across all doses and all vaccines		
alternative assessment type: Systematic			
subjects affected / exposed[15]	282 / 368 (76.63%)	177 / 357 (49.58%)	
occurrences (all)	282	177	
Redness – Primary Vaccination	Additional description: Solicited local AE collected in subjects in the Immunogenicity and Tolerability Subset post primary vaccination, across all doses and all vaccines		
alternative assessment type: Systematic			
subjects affected / exposed[16]	194 / 368 (52.72%)	135 / 357 (37.82%)	
occurrences (all)	194	135	
Swelling – Primary Vaccination	Additional description: Solicited local AE collected in subjects in the Immunogenicity and Tolerability Subset post primary vaccination, across all doses and all vaccines		
alternative assessment type: Systematic			
subjects affected / exposed[17]	158 / 368 (42.93%)	109 / 357 (30.53%)	
occurrences (all)	158	109	
Pain – Booster Vaccination	Additional description: Solicited local AE collected in subjects in the Immunogenicity and Tolerability Subset post booster vaccination, across all doses and all vaccines		
alternative assessment type: Systematic			
subjects affected / exposed[18]	140 / 317 (44.16%)	98 / 303 (32.34%)	
occurrences (all)	140	98	
Redness – Booster Primary Vaccination	Additional description: Solicited local AE collected in subjects in the Immunogenicity and Tolerability Subset post booster vaccination, across all doses and all vaccines		
alternative assessment type: Systematic			
subjects affected / exposed[19]	117 / 317 (36.91%)	102 / 303 (33.66%)	
occurrences (all)	117	102	
Swelling – Booster Primary Vaccination	Additional description: Solicited local AE collected in subjects in the Immunogenicity and Tolerability Subset post primary vaccination, across all doses and all vaccines		
alternative assessment type: Systematic			
subjects affected / exposed[20]	86 / 317 (27.13%)	85 / 303 (28.05%)	
occurrences (all)	86	85	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed[21]	315 / 3602 (8.75%)	328 / 3612 (9.08%)	
occurrences (all)	315	328	

Eye disorders			
Conjunctivitis			
subjects affected / exposed[22]	598 / 3602 (16.60%)	575 / 3612 (15.92%)	
occurrences (all)	598	575	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed[23]	1905 / 3602 (52.89%)	1794 / 3612 (49.67%)	
occurrences (all)	1905	1794	
Vomiting			
subjects affected / exposed[24]	520 / 3602 (14.44%)	506 / 3612 (14.01%)	
occurrences (all)	520	506	
Constipation			
subjects affected / exposed[25]	279 / 3602 (7.75%)	257 / 3612 (7.12%)	
occurrences (all)	279	257	
Stomatitis			
subjects affected / exposed[26]	174 / 3602 (4.83%)	202 / 3612 (5.59%)	
occurrences (all)	174	202	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed[27]	596 / 3602 (16.55%)	582 / 3612 (16.11%)	
occurrences (all)	596	582	
Cough			
subjects affected / exposed[28]	499 / 3602 (13.85%)	510 / 3612 (14.12%)	
occurrences (all)	499	510	
Asthmatic crisis			
subjects affected / exposed[29]	288 / 3602 (8.00%)	313 / 3612 (8.67%)	
occurrences (all)	288	313	
Bronchial hyperreactivity			
subjects affected / exposed[30]	322 / 3602 (8.94%)	297 / 3612 (8.22%)	
occurrences (all)	322	297	
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed[31]	468 / 3602 (12.99%)	464 / 3612 (12.85%)	
occurrences (all)	468	464	
Dermatitis diaper			

subjects affected / exposed[32]	293 / 3602 (8.13%)	316 / 3612 (8.75%)	
occurrences (all)	293	316	
Dermatitis atopic			
subjects affected / exposed[33]	332 / 3602 (9.22%)	296 / 3612 (8.19%)	
occurrences (all)	332	296	
Rash			
subjects affected / exposed[34]	220 / 3602 (6.11%)	220 / 3612 (6.09%)	
occurrences (all)	220	220	
Prurigo			
subjects affected / exposed[35]	179 / 3602 (4.97%)	199 / 3612 (5.51%)	
occurrences (all)	179	199	
Dermatitis allergic			
subjects affected / exposed[36]	163 / 3602 (4.53%)	196 / 3612 (5.43%)	
occurrences (all)	163	196	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed[37]	3338 / 3602 (92.67%)	3326 / 3612 (92.08%)	
occurrences (all)	3338	3326	
Gastroenteritis			
subjects affected / exposed[38]	1310 / 3602 (36.37%)	1281 / 3612 (35.47%)	
occurrences (all)	1310	1281	
Bronchiolitis			
subjects affected / exposed[39]	1119 / 3602 (31.07%)	1123 / 3612 (31.09%)	
occurrences (all)	1119	1123	
Pharyngitis			
subjects affected / exposed[40]	950 / 3602 (26.37%)	958 / 3612 (26.52%)	
occurrences (all)	950	958	
Viral infection			
subjects affected / exposed[41]	714 / 3602 (19.82%)	738 / 3612 (20.43%)	
occurrences (all)	714	738	
Pharyngotonsillitis			
subjects affected / exposed[42]	672 / 3602 (18.66%)	682 / 3612 (18.88%)	
occurrences (all)	672	682	
Rhinitis			

subjects affected / exposed[43]	542 / 3602 (15.05%)	516 / 3612 (14.29%)	
occurrences (all)	542	516	
Impetigo			
subjects affected / exposed[44]	497 / 3602 (13.80%)	474 / 3612 (13.12%)	
occurrences (all)	497	474	
Bronchitis			
subjects affected / exposed[45]	486 / 3602 (13.49%)	410 / 3612 (11.35%)	
occurrences (all)	486	410	
Pyoderma			
subjects affected / exposed[46]	350 / 3602 (9.72%)	368 / 3612 (10.19%)	
occurrences (all)	350	368	
Tonsillitis			
subjects affected / exposed[47]	232 / 3602 (6.44%)	242 / 3612 (6.70%)	
occurrences (all)	232	242	
Pneumonia			
subjects affected / exposed[48]	217 / 3602 (6.02%)	238 / 3612 (6.59%)	
occurrences (all)	217	238	
Urinary tract infection			
subjects affected / exposed[49]	202 / 3602 (5.61%)	228 / 3612 (6.31%)	
occurrences (all)	202	228	
Influenza			
subjects affected / exposed[50]	206 / 3602 (5.72%)	175 / 3612 (4.84%)	
occurrences (all)	206	175	
Metabolism and nutrition disorders			
Malnutrition			
subjects affected / exposed[51]	556 / 3602 (15.44%)	545 / 3612 (15.09%)	
occurrences (all)	556	545	
Overweight			
subjects affected / exposed[52]	416 / 3602 (11.55%)	422 / 3612 (11.68%)	
occurrences (all)	416	422	
Dehydration			
subjects affected / exposed[53]	182 / 3602 (5.05%)	207 / 3612 (5.73%)	
occurrences (all)	182	207	

Notes:

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Justification: Assessment for this event was done in subjects with available results.

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More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 November 2007	The following changes were implemented in this Amendment 1. Firstly, study centres in Colombia were added. Secondly, a new subset ('Additional immuno' subset) of subjects in Panama was added for further exploration after study end of the correlation between protection against of Acute Otitis Media (AOM) episodes caused by (non-typeable) H. influenzae and results of the measurement and characterization of responses induced by the protein D carrier protein. Thirdly, the Reference Laboratory was changed from Instituto Malbrán in Argentina to Eurofins in the United States, which implied adaptations to the laboratory procedures. Fourthly, an appendix was added about the background of AOM severity scales and their application in the study.
20 March 2008	The following changes were implemented in this Amendment 2. Firstly, in Colombia, two doses of HRV (Rotarix) vaccine would be offered to all subjects within the first six months of life to provide additional benefit. Secondly, in Panama, subjects who were part of the 'Carriage' subset were also given the opportunity to participate in the 'Additional immuno' subset. However, subjects who were part of the 'Immunogenicity and Tolerability' subset would not be invited to participate in the 'Additional immuno' subset as already four blood samples were to be collected from these subjects. Thirdly, for preterm infants the gestation period had been defined. Fourth, in case subjects would by mistake receive a vaccine with antigens common to the antigens contained in the study or co-administered vaccines outside of the context of the study, the investigator would need to evaluate whether the subject could still continue participation in the study. Therefore this criterion was added to the exclusion criteria for further study participation. Fifth, for subjects in the 'Additional immuno' subset, a visit was removed from the list of study procedures and the detailed description of study procedures. Sixth, new validated temperature monitoring devices had been provided to the investigational sites. Although the temperature monitoring process described in protocol still covered the use of these new devices, the related section was updated with the mandatory text of the current protocol document standard to avoid confusion. Seventh, the classification of the CXR was aligned throughout the protocol and with the Radiology workbook. Eighth, additional minor changes and clarifications were implemented.
25 November 2008	This protocol amendment - Amendment 3 – was developed in reply to questions from local authorities. Firstly, the recruitment period was extended to 18 months. Secondly, subjects diagnosed to be at high risk for Invasive pneumococcal disease (IPD) were excluded from the study in case a specific local vaccination program was available. Thirdly, the informed consent process for minor parents (<18 years of age) was specified. Fourth, additional minor changes and clarifications were implemented.
11 May 2009	This protocol amendment – Amendment 4 – was developed in reply to questions from local authorities. Additions were, 1) in the exclusion criteria for further study participation the criteria for high risk for pneumococcal disease were specified and 2) clarification on how to proceed in case of diagnosis of a high risk condition for pneumococcal infection was added.
14 December 2009	Changes were implemented in the protocol Amendment 5 towards taking into account that the number of AOM cases reported to that date was much lower than anticipated. To be able to perform the interim analysis to evaluate the efficacy of the 10Pn-PD-DiT/Synflorix vaccine to prevent the first episodes of B-CAP regardless of the number of cases of C-AOM that would be reached, it was decided to evaluate the vaccine efficacy (VE) to prevent the first episodes of B-CAP as the only primary objective, and to evaluate the VE to prevent the first episodes of C-AOM as a secondary objective instead of a co-primary objective. The number of B-CAP cases needed to perform the interim analysis was adjusted accordingly.

09 September 2010	This protocol Amendment 6 was developed for the following reasons. Firstly, as the observed incidence of B-CAP was lower than the expected incidence, the number of cases needed to perform the final analysis would not be reached in the near future and might never be reached based on extrapolation of the accrual of B-CAP cases. As this study had been designed to determine VE against pneumonia, which is a major burden in Latin America and the rest of the world, results should be reported in a timely manner. Therefore GSK Biologicals decided to amend the protocol to re-define the study end based on the outcome of the planned interim analysis. Secondly, in addition, clarifications to the objectives and endpoints were implemented and wordings were corrected to align with the change in the primary objective implemented in previous amendment dated 14 December 2009). Thirdly, contact details for the emergency code break were updated.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported