Clinical trial results:
International Randomized Double Blind Study Evaluating the Efficacy and the Safety of Clopidogrel 0.2 mg/kg Once Daily Versus Placebo in Neonates and Infants With Cyanotic Congenital Heart Disease Palliated With Systemic to Pulmonary Artery Shunt

Summary

EudraCT number	2006-000946-38
Trial protocol	BE GB DE FI SE DK PT FR HU IT NL Outside EU/EEA
Global end of trial date	01 February 2010

Results information

Result version number	v1 (current)
This version publication date	23 May 2016
First version publication date	16 May 2015

Trial information

Trial identification

Sponsor protocol code	EFC5314

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00396877
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Sanofi aventis recherche & developpement
Sponsor organisation address	1 avenue Pierre Brossolette, Chilly-Mazarin , France, 91380
Public contact	Trial transparency team, Sanofi aventis recherche & developpement, Contact-US@sanofi.com
Scientific contact	Trial transparency team, Sanofi aventis recherche & developpement, Contact-US@sanofi.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000049-PIP01-07
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	26 February 2010
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	01 February 2010
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of Clopidogrel 0.2 mg/kg/day for the reduction of all cause mortality and shunt related morbidity in neonates or infants with cyanotic congenital heart disease palliated with a systemic-to-pulmonary artery shunt (e.g. modified Blalock Taussig Shunt [BTS]).

Protection of trial subjects:

The study was conducted by investigators experienced in the treatment of pediatric subjects. The parent(s) or guardian(s) as well as the children were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time. In addition to the consent form for the parent(s)/guardian(s), an assent form in child-appropriate language was provided and explained to the child. Repeated invasive procedures were minimized. The number of blood samples as well as the amount of blood drawn were adjusted according to age and weight. A topical anesthesia may have been used to minimize distress and discomfort.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 November 2006
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: 52
Country: Number of subjects enrolled	Brazil: 65
Country: Number of subjects enrolled	Netherlands: 6
Country: Number of subjects enrolled	Norway: 16
Country: Number of subjects enrolled	Portugal: 20
Country: Number of subjects enrolled	Israel: 7
Country: Number of subjects enrolled	Mexico: 69
Country: Number of subjects enrolled	Poland: 10
Country: Number of subjects enrolled	Russian Federation: 28
Country: Number of subjects enrolled	Singapore: 4
Country: Number of subjects enrolled	South Africa: 26
Country: Number of subjects enrolled	Taiwan: 22
Country: Number of subjects enrolled	Sweden: 11
Country: Number of subjects enrolled	Egypt: 10
Country: Number of subjects enrolled	Finland: 3
Country: Number of subjects enrolled	Germany: 113
Country: Number of subjects enrolled	Belgium: 21

Country: Number of subjects enrolled	Canada: 11
Country: Number of subjects enrolled	China: 21
Country: Number of subjects enrolled	Denmark: 6
Country: Number of subjects enrolled	France: 21
Country: Number of subjects enrolled	Italy: 39
Country: Number of subjects enrolled	Hong Kong: 1
Country: Number of subjects enrolled	Hungary: 18
Country: Number of subjects enrolled	India: 47
Country: Number of subjects enrolled	Korea, Republic of: 5
Country: Number of subjects enrolled	Malaysia: 9
Country: Number of subjects enrolled	Spain: 30
Country: Number of subjects enrolled	Thailand: 5
Country: Number of subjects enrolled	United Kingdom: 32
Country: Number of subjects enrolled	United States: 178
Worldwide total number of subjects	906
EEA total number of subjects	346

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	404
Infants and toddlers (28 days-23 months)	502
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:

Recruitment was initially planned with a minimum of 490 subjects anticipating that it would continue until a total of 172 subjects reaching primary endpoint criteria is achieved. Finally 906 subjects were enrolled and randomized between November 2006 and October 2009 in 134 sites in 31 countries. Actual median follow-up was 5.8 months.

Pre-assignment

Screening details:

A subject was considered randomized when informed consent had been obtained and there was confirmation of successful allocation of a randomization number through the study treatment allocation system (Interactive Voice Response System).

Period 1

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

Blinding implementation details:

Eligible subjects were randomized to receive either Clopidogrel or placebo in a 1:1 ration without the disclosure of assigned treatments to the investigator and to the subject's parents/guardians. Both the Clopidogrel and placebo were reconstituted in the same fashion and were similar in appearance.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Clopidogrel matching placebo until primary endpoint criteria was reached i.e. (shunt thrombosis, the next surgical procedure for correction of the congenital heart disease or death) or one year of age or common study-end-date, whichever came first.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for oral solution
Routes of administration	Gastroenteral use, Oral use

Dosage and administration details:

Placebo to be administered once daily with a graduated syringe in the mouth or via a feeding tube.

Arm title	Clopidogrel 0.2 mg/kg/Day

Arm description:

Clopidogrel until the primary endpoint criteria was reached i.e. (shunt thrombosis, the next surgical procedure for correction of the congenital heart disease or death) or one year of age or the common study-end-date, whichever came first

Arm type	Experimental
Investigational medicinal product name	Clopidogrel
Investigational medicinal product code	SR25990
Other name	Plavix
Pharmaceutical forms	Powder and solvent for oral solution
Routes of administration	Gastroenteral use, Oral use

Dosage and administration details:

Clopidogrel administered once daily with a graduated syringe in the mouth or via a feeding tube.
Dose: daily dose adjusted for weight.

Number of subjects in period 1	Placebo	Clopidogrel 0.2 mg/kg/Day
Started	439	467
Treated	436	464
Completed	433	459
Not completed	6	8
Lost to follow-up	2	1
Parent(s)/guardian(s)'s request	4	7

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Clopidogrel matching placebo until primary endpoint criteria was reached i.e. (shunt thrombosis, the next surgical procedure for correction of the congenital heart disease or death) or one year of age or common study-end-date, whichever came first.	
Reporting group title	Clopidogrel 0.2 mg/kg/Day
Reporting group description:	
Clopidogrel until the primary endpoint criteria was reached i.e. (shunt thrombosis, the next surgical procedure for correction of the congenital heart disease or death) or one year of age or the common study-end-date, whichever came first	

Reporting group values	Placebo	Clopidogrel 0.2 mg/kg/Day	Total
Number of subjects	439	467	906
Age categorical Units: Subjects			
≤ 30 days	223	238	461
30 (<) - 92 days	216	229	445
Age continuous Units: days			
arithmetic mean	36	36.1	
standard deviation	± 22.5	± 22.3	-
Gender categorical Units: Subjects			
Female	185	198	383
Male	254	269	523
Region of Enrollment Units: Subjects			
United States	90	88	178
Portugal	10	10	20
Taiwan	12	10	22
Hong Kong	1	0	1
Thailand	2	3	5
Spain	16	14	30
Israel	3	4	7
Russian Federation	13	15	28
Italy	20	19	39
India	20	27	47
France	11	10	21
Malaysia	5	4	9
Denmark	3	3	6
South Africa	13	13	26
Netherlands	2	4	6
China	10	11	21
Korea, Republic of	3	2	5
Finland	2	1	3
United Kingdom	16	16	32
Egypt	4	6	10

Hungary	9	9	18
Mexico	32	37	69
Canada	5	6	11
Argentina	24	28	52
Brazil	31	34	65
Belgium	9	12	21
Poland	3	7	10
Singapore	2	2	4
Germany	54	59	113
Norway	8	8	16
Sweden	6	5	11
Type of systemic-to-pulmonary artery shunt palliation			
One subject didn't have a systemic-to-pulmonary artery shunt but underwent stenting of the right ventricular outflow track.			
Units: Subjects			
Modified Blalock Taussig Shunt With Norwood	51	62	113
Modified Blalock Taussig Shunt Without Norwood	252	257	509
Sano Procedure With Norwood	54	60	114
Sano Procedure Without Norwood	2	5	7
Central Shunt	38	40	78
Stent of Ductus Arteriosus	42	42	84
Not Applicable	0	1	1
Shunt on cardiopulmonary bypass			
Units: Subjects			
Yes	177	194	371
No	262	273	535
Time from shunt palliation to randomization			
Units: Subjects			
less than or equal to (<=) 1 week	116	113	229
1 (less than [<]) to 2 weeks	105	126	231
2 (<) to 4 weeks	117	119	236
greater than (>) 4 weeks	101	109	210
Weight			
Units: kilograms (kg)			
arithmetic mean	3.5	3.4	
standard deviation	± 0.7	± 0.7	-
Age at shunt palliation			
Units: Days			
arithmetic mean	16	16.2	
standard deviation	± 18.7	± 18.6	-
Height			
Units: Centimeters (cm)			
arithmetic mean	51.8	51.4	
standard deviation	± 4.6	± 4.4	-

End points

End points reporting groups

Reporting group title	Placebo

Reporting group description:

Clopidogrel matching placebo until primary endpoint criteria was reached i.e. (shunt thrombosis, the next surgical procedure for correction of the congenital heart disease or death) or one year of age or common study-end-date, whichever came first.

Reporting group title	Clopidogrel 0.2 mg/kg/Day

Reporting group description:

Clopidogrel until the primary endpoint criteria was reached i.e. (shunt thrombosis, the next surgical procedure for correction of the congenital heart disease or death) or one year of age or the common study-end-date, whichever came first

Primary: Number of Subjects Reaching Primary Endpoint Criteria (First Occurrence of Death / Shunt Thrombosis / Cardiac Procedure < 120 Days Considered of Thrombotic Nature)

End point title	Number of Subjects Reaching Primary Endpoint Criteria (First Occurrence of Death / Shunt Thrombosis / Cardiac Procedure < 120 Days Considered of Thrombotic Nature)

End point description:

The primary endpoint was the first occurrence of any of the following events: Death (including heart transplant); Shunt thrombosis requiring intervention; Hospitalization for bi-directional Glenn procedure or any cardiac related intervention prior to 120 days of age following an event or a shunt narrowing considered being of thrombotic nature by the blinded adjudication committee. Only the first event was counted. The analysis was performed on the intent-to-treat (ITT) population (i.e. all randomized subjects irrespective of whether or not the subject actually received study drug or the subject's compliance with the study protocol). Subjects were included in the treatment group to which they were originally allocated.

End point type	Primary

End point timeframe:

Median follow-up of 5.8 months (up to a maximum of 12 months after randomization)

End point values	Placebo	Clopidogrel 0.2 mg/kg/Day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	439	467		
Units: Subjects				
Death / Shunt Thrombosis / Cardiac Procedure	90	89		
- Death	60	51		
- Shunt thrombosis	21	26		
- Cardiac procedure <120 days of thrombotic nature	9	12		

Statistical analyses

Statistical analysis title	Clopidogrel 0.2 mg/kg/Day vs. Placebo

Statistical analysis description:

Due to the limited knowledge in this population, 3 interim analyses were performed at approximately 40%, 60%, 80% and 100% of maximum number of 172 required primary efficacy events to evaluate the effect of Clopidogrel on endpoint with potential to end trial in case of a clear efficacy advantage for Clopidogrel. Study was designed with 80% power and an overall type I error rate of 5%. Relative Risk Reduction (Clopidogrel vs placebo) and 95% CI estimated using Cox's proportional hazards model

Comparison groups	Placebo v Clopidogrel 0.2 mg/kg/Day
Number of subjects included in analysis	906
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.434 [1]
Method	Logrank
Parameter estimate	Relative Risk Reduction (%)
Point estimate	11.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.2
upper limit	33.6

Notes:

[1] - The a-priori threshold for statistical significance was < 0.035 reflecting the adjustment for interim analyses. No other adjustment for multiplicity was made.

Secondary: Number of Subjects With Bleeding Events

End point title	Number of Subjects With Bleeding Events

End point description:

Bleeding events spanning from signature of the Informed Consent Form up to the last visit were collected as for any Adverse Event.
The 'on-treatment' period was defined as the period from randomization up until 28 days after treatment discontinuation or final follow-up visit, whichever came first, and subjects who experienced bleeding events during that period were counted. The analysis was performed on the exposed population (i.e. all randomized subjects who received at least one dose of study drug regardless of the amount of treatment received). Subjects were included in the treatment group according to the treatment received.

End point type	Secondary

End point timeframe:

From randomization up to 28 days after treatment discontinuation or final follow-up visit, whichever comes first

End point values	Placebo	Clopidogrel 0.2 mg/kg/Day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	436	464		
Units: Subjects				
Any bleeding event	88	87		
- Serious	32	30		
- Serious with an outcome of death	1	1		
- Leading to permanent treatment discontinuation	9	9		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects According to Bleeding Type/Etiology

End point title	Number of Subjects According to Bleeding Type/Etiology

End point description:

For all reported bleeding events, the type and the etiology of the bleeding event were collected. Subjects who experienced bleeding events during the 'on-treatment period' were counted by bleeding type and etiology. Subjects who had multiple bleeding could be counted several times. The analysis was performed on the same population as previously (i.e. exposed population).

End point type	Secondary

End point timeframe:

From randomization up to 28 days after treatment discontinuation or final follow-up visit, whichever comes first

End point values	Placebo	Clopidogrel 0.2 mg/kg/Day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	436	464		
Units: Subjects				
Spontaneous	60	56		
Post-traumatic	6	11		
Puncture (vascular access site)	19	9		
Surgical	10	17		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events (AEs) were collected from signature of the informed consent form up to the last visit regardless of seriousness or relationship to investigational product.

Adverse event reporting additional description:

AEs that developed/worsened and deaths that occurred during 'on treatment period' (from randomization up to 28 days after treatment discontinuation or final follow-up visit, whichever came first) are reported. All-cause deaths include cardiovascular deaths (primary efficacy endpoint) and non-cardiovascular deaths resulting from AEs.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	12.1

Reporting groups

Reporting group title	Placebo

Reporting group description:

Clopidogrel matching placebo until primary endpoint criteria was reached i.e. (shunt thrombosis, the next surgical procedure for correction of the congenital heart disease or death) or one year of age or common study-end-date, whichever came first.

Reporting group title	Clopidogrel 0.2mg/kg/day

Reporting group description:

Clopidogrel until the primary endpoint criteria was reached i.e. (shunt thrombosis, the next surgical procedure for correction of the congenital heart disease or death) or one year of age or the common study-end-date, whichever came first

Serious adverse events	Placebo	Clopidogrel 0.2mg/kg/day	
Total subjects affected by serious adverse events			
subjects affected / exposed	196 / 436 (44.95%)	234 / 464 (50.43%)	
number of deaths (all causes)	56	50	
number of deaths resulting from adverse events			
Vascular disorders			
Aortic Stenosis			
subjects affected / exposed	2 / 436 (0.46%)	2 / 464 (0.43%)	
occurrences causally related to treatment / all	0 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	1 / 436 (0.23%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Circulatory Collapse			

subjects affected / exposed	0 / 436 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	2 / 436 (0.46%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemic Shock			
subjects affected / exposed	1 / 436 (0.23%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Peripheral Ischaemia			
subjects affected / exposed	0 / 436 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral Arterial Occlusive Disease			
subjects affected / exposed	1 / 436 (0.23%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock			
subjects affected / exposed	0 / 436 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular Stenosis			
subjects affected / exposed	0 / 436 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous Thrombosis			
subjects affected / exposed	1 / 436 (0.23%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vena Cava Thrombosis			

subjects affected / exposed	1 / 436 (0.23%)	2 / 464 (0.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Anorectal Operation			
subjects affected / exposed	0 / 436 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteroneocystostomy			
subjects affected / exposed	0 / 436 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiovascular Event Prophylaxis			
subjects affected / exposed	0 / 436 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Catheter Thrombosis			
subjects affected / exposed	1 / 436 (0.23%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter Related Complication			
subjects affected / exposed	1 / 436 (0.23%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter Site Haemorrhage			
subjects affected / exposed	0 / 436 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Feeling Abnormal			
subjects affected / exposed	1 / 436 (0.23%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

General Physical Health Deterioration			
subjects affected / exposed	0 / 436 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Puncture Site Haemorrhage			
subjects affected / exposed	2 / 436 (0.46%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Irritability			
subjects affected / exposed	0 / 436 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	3 / 436 (0.69%)	5 / 464 (1.08%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vessel Puncture Site Haematoma			
subjects affected / exposed	1 / 436 (0.23%)	0 / 464 (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			
Hypogammaglobulinaemia			
subjects affected / exposed	1 / 436 (0.23%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Milk Allergy			
subjects affected / exposed	0 / 436 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute Respiratory Distress Syndrome			
subjects affected / exposed	0 / 436 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Apnoea			
subjects affected / exposed	1 / 436 (0.23%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspiration			
subjects affected / exposed	2 / 436 (0.46%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Atelectasis			
subjects affected / exposed	1 / 436 (0.23%)	2 / 464 (0.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchostenosis			
subjects affected / exposed	0 / 436 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	1 / 436 (0.23%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chylothorax			
subjects affected / exposed	1 / 436 (0.23%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Diaphragmatic Paralysis			
subjects affected / exposed	2 / 436 (0.46%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 436 (0.23%)	2 / 464 (0.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea Exertional			

subjects affected / exposed	0 / 436 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemothorax			
subjects affected / exposed	1 / 436 (0.23%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	1 / 436 (0.23%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	11 / 436 (2.52%)	14 / 464 (3.02%)	
occurrences causally related to treatment / all	0 / 11	0 / 16	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal Oedema			
subjects affected / exposed	1 / 436 (0.23%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal Stenosis			
subjects affected / exposed	1 / 436 (0.23%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Mediastinal Haematoma			
subjects affected / exposed	1 / 436 (0.23%)	0 / 464 (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 / 436 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mediastinal Haemorrhage			

subjects affected / exposed	1 / 436 (0.23%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural Effusion			
subjects affected / exposed	1 / 436 (0.23%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia Aspiration			
subjects affected / exposed	0 / 436 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumothorax			
subjects affected / exposed	2 / 436 (0.46%)	2 / 464 (0.43%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Artery Stenosis			
subjects affected / exposed	2 / 436 (0.46%)	3 / 464 (0.65%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Congestion			
subjects affected / exposed	1 / 436 (0.23%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Embolism			
subjects affected / exposed	1 / 436 (0.23%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Haemorrhage			
subjects affected / exposed	2 / 436 (0.46%)	3 / 464 (0.65%)	
occurrences causally related to treatment / all	1 / 2	3 / 3	
deaths causally related to treatment / all	1 / 1	0 / 0	
Pulmonary Vein Occlusion			

subjects affected / exposed	0 / 436 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Hypertension			
subjects affected / exposed	2 / 436 (0.46%)	2 / 464 (0.43%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Vein Stenosis			
subjects affected / exposed	1 / 436 (0.23%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Oedema			
subjects affected / exposed	0 / 436 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory Arrest			
subjects affected / exposed	1 / 436 (0.23%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory Distress			
subjects affected / exposed	3 / 436 (0.69%)	5 / 464 (1.08%)	
occurrences causally related to treatment / all	0 / 4	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory Failure			
subjects affected / exposed	4 / 436 (0.92%)	5 / 464 (1.08%)	
occurrences causally related to treatment / all	0 / 5	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory Fatigue			
subjects affected / exposed	0 / 436 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachypnoea			

subjects affected / exposed	2 / 436 (0.46%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stridor			
subjects affected / exposed	1 / 436 (0.23%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheal Stenosis			
subjects affected / exposed	1 / 436 (0.23%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheomalacia			
subjects affected / exposed	0 / 436 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper Respiratory Tract Congestion			
subjects affected / exposed	0 / 436 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vocal Cord Thickening			
subjects affected / exposed	1 / 436 (0.23%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Agitation			
subjects affected / exposed	1 / 436 (0.23%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Aspiration Bronchial			
subjects affected / exposed	1 / 436 (0.23%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood Urine Present			

subjects affected / exposed	1 / 436 (0.23%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oxygen Saturation Decreased			
subjects affected / exposed	10 / 436 (2.29%)	11 / 464 (2.37%)	
occurrences causally related to treatment / all	0 / 15	0 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oxygen Saturation Increased			
subjects affected / exposed	1 / 436 (0.23%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Arterial Pressure Decreased			
subjects affected / exposed	0 / 436 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet Count Decreased			
subjects affected / exposed	1 / 436 (0.23%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Arterial Pressure Increased			
subjects affected / exposed	1 / 436 (0.23%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight Increased			
subjects affected / exposed	0 / 436 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Accidental Overdose			
subjects affected / exposed	2 / 436 (0.46%)	3 / 464 (0.65%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Device Breakage			
subjects affected / exposed	1 / 436 (0.23%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug Toxicity			
subjects affected / exposed	1 / 436 (0.23%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	0 / 436 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Feeding Tube Complication			
subjects affected / exposed	0 / 436 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incisional Hernia			
subjects affected / exposed	1 / 436 (0.23%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Graft Thrombosis			
subjects affected / exposed	1 / 436 (0.23%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Operative Haemorrhage			
subjects affected / exposed	3 / 436 (0.69%)	3 / 464 (0.65%)	
occurrences causally related to treatment / all	1 / 3	1 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pneumothorax Traumatic			
subjects affected / exposed	0 / 436 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post Procedural Haematoma			

subjects affected / exposed	0 / 436 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post Procedural Haemorrhage			
subjects affected / exposed	4 / 436 (0.92%)	8 / 464 (1.72%)	
occurrences causally related to treatment / all	1 / 4	6 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post Vaccination Syndrome			
subjects affected / exposed	0 / 436 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative Fever			
subjects affected / exposed	0 / 436 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative Respiratory Distress			
subjects affected / exposed	1 / 436 (0.23%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative Wound Complication			
subjects affected / exposed	1 / 436 (0.23%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural Complication			
subjects affected / exposed	2 / 436 (0.46%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural Site Reaction			
subjects affected / exposed	1 / 436 (0.23%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seroma			

subjects affected / exposed	1 / 436 (0.23%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shunt Blood Flow Excessive			
subjects affected / exposed	0 / 436 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shunt Malfunction			
subjects affected / exposed	3 / 436 (0.69%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shunt Occlusion			
subjects affected / exposed	1 / 436 (0.23%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skull Fracture			
subjects affected / exposed	1 / 436 (0.23%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shunt Stenosis			
subjects affected / exposed	2 / 436 (0.46%)	2 / 464 (0.43%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suture Related Complication			
subjects affected / exposed	0 / 436 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suture Rupture			
subjects affected / exposed	1 / 436 (0.23%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular Pseudoaneurysm			

subjects affected / exposed	1 / 436 (0.23%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound Dehiscence			
subjects affected / exposed	1 / 436 (0.23%)	0 / 464 (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			
Atrial Septal Defect			
subjects affected / exposed	0 / 436 (0.00%)	2 / 464 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coarctation Of The Aorta			
subjects affected / exposed	2 / 436 (0.46%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngomalacia			
subjects affected / exposed	0 / 436 (0.00%)	1 / 464 (0.22%)	
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 / 436 (0.23%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Artery Stenosis Congenital			
subjects affected / exposed	0 / 436 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	0 / 436 (0.00%)	2 / 464 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Atrioventricular Block			
subjects affected / exposed	0 / 436 (0.00%)	2 / 464 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular Block Complete			
subjects affected / exposed	1 / 436 (0.23%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	4 / 436 (0.92%)	3 / 464 (0.65%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Arrest			
subjects affected / exposed	2 / 436 (0.46%)	3 / 464 (0.65%)	
occurrences causally related to treatment / all	0 / 2	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Disorder			
subjects affected / exposed	0 / 436 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Failure			
subjects affected / exposed	5 / 436 (1.15%)	6 / 464 (1.29%)	
occurrences causally related to treatment / all	0 / 5	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Failure Acute			
subjects affected / exposed	0 / 436 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Failure Congestive			
subjects affected / exposed	2 / 436 (0.46%)	4 / 464 (0.86%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Perforation			

subjects affected / exposed	0 / 436 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-Respiratory Arrest			
subjects affected / exposed	1 / 436 (0.23%)	4 / 464 (0.86%)	
occurrences causally related to treatment / all	0 / 1	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Pseudoaneurysm			
subjects affected / exposed	0 / 436 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiogenic Shock			
subjects affected / exposed	2 / 436 (0.46%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiopulmonary Failure			
subjects affected / exposed	0 / 436 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cyanosis			
subjects affected / exposed	9 / 436 (2.06%)	24 / 464 (5.17%)	
occurrences causally related to treatment / all	0 / 9	0 / 26	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dilatation Ventricular			
subjects affected / exposed	0 / 436 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left Ventricular Dysfunction			
subjects affected / exposed	0 / 436 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Low Cardiac Output Syndrome			

subjects affected / exposed	2 / 436 (0.46%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nodal Arrhythmia			
subjects affected / exposed	1 / 436 (0.23%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial Effusion			
subjects affected / exposed	1 / 436 (0.23%)	4 / 464 (0.86%)	
occurrences causally related to treatment / all	0 / 1	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial Haemorrhage			
subjects affected / exposed	1 / 436 (0.23%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Valve Stenosis			
subjects affected / exposed	3 / 436 (0.69%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right Ventricular Dysfunction			
subjects affected / exposed	0 / 436 (0.00%)	2 / 464 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular Extrasystoles			
subjects affected / exposed	0 / 436 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right Ventricular Failure			
subjects affected / exposed	0 / 436 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular Tachycardia			

subjects affected / exposed	2 / 436 (0.46%)	3 / 464 (0.65%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	1 / 436 (0.23%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tricuspid Valve Incompetence			
subjects affected / exposed	3 / 436 (0.69%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular Dysfunction			
subjects affected / exposed	1 / 436 (0.23%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular Arrhythmia			
subjects affected / exposed	0 / 436 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular Fibrillation			
subjects affected / exposed	0 / 436 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral Infarction			
subjects affected / exposed	0 / 436 (0.00%)	2 / 464 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral Ischaemia			
subjects affected / exposed	0 / 436 (0.00%)	2 / 464 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clonic Convulsion			

subjects affected / exposed	0 / 436 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Convulsion			
subjects affected / exposed	2 / 436 (0.46%)	3 / 464 (0.65%)	
occurrences causally related to treatment / all	0 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Convulsions Local			
subjects affected / exposed	1 / 436 (0.23%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyskinesia			
subjects affected / exposed	0 / 436 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalitis			
subjects affected / exposed	0 / 436 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Embolic Stroke			
subjects affected / exposed	0 / 436 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile Convulsion			
subjects affected / exposed	1 / 436 (0.23%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hydrocephalus			
subjects affected / exposed	1 / 436 (0.23%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hypoglycaemic Encephalopathy			

subjects affected / exposed	0 / 436 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ischaemic Stroke			
subjects affected / exposed	0 / 436 (0.00%)	3 / 464 (0.65%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic Cerebral Infarction			
subjects affected / exposed	0 / 436 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lethargy			
subjects affected / exposed	0 / 436 (0.00%)	2 / 464 (0.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Partial Seizures			
subjects affected / exposed	0 / 436 (0.00%)	3 / 464 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Phrenic Nerve Paralysis			
subjects affected / exposed	0 / 436 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid Haemorrhage Neonatal			
subjects affected / exposed	0 / 436 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Poor Sucking Reflex			
subjects affected / exposed	0 / 436 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vocal Cord Paralysis			

subjects affected / exposed	0 / 436 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vocal Cord Paresis			
subjects affected / exposed	0 / 436 (0.00%)	1 / 464 (0.22%)	
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			
Deficiency Anaemia			
subjects affected / exposed	0 / 436 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	3 / 436 (0.69%)	2 / 464 (0.43%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disseminated Intravascular Coagulation			
subjects affected / exposed	1 / 436 (0.23%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic Anaemia			
subjects affected / exposed	1 / 436 (0.23%)	0 / 464 (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 / 436 (0.23%)	2 / 464 (0.43%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Middle Ear Inflammation			
subjects affected / exposed	0 / 436 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastrointestinal disorders			
Abdominal Discomfort			
subjects affected / exposed	0 / 436 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal Pain			
subjects affected / exposed	0 / 436 (0.00%)	2 / 464 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal Pain Upper			
subjects affected / exposed	0 / 436 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 436 (0.23%)	5 / 464 (1.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal Stenosis			
subjects affected / exposed	1 / 436 (0.23%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal Fissure			
subjects affected / exposed	1 / 436 (0.23%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	2 / 436 (0.46%)	3 / 464 (0.65%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			
subjects affected / exposed	1 / 436 (0.23%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis Haemorrhagic			

subjects affected / exposed	0 / 436 (0.00%)	2 / 464 (0.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	2 / 436 (0.46%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	0 / 436 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal Reflux Disease			
subjects affected / exposed	4 / 436 (0.92%)	6 / 464 (1.29%)	
occurrences causally related to treatment / all	0 / 4	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal Haemorrhage			
subjects affected / exposed	2 / 436 (0.46%)	4 / 464 (0.86%)	
occurrences causally related to treatment / all	1 / 3	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	1 / 436 (0.23%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematochezia			
subjects affected / exposed	7 / 436 (1.61%)	2 / 464 (0.43%)	
occurrences causally related to treatment / all	4 / 7	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal Hernia			
subjects affected / exposed	1 / 436 (0.23%)	0 / 464 (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	1 / 436 (0.23%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Necrotising Colitis			
subjects affected / exposed	1 / 436 (0.23%)	6 / 464 (1.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 1	
Intestinal Perforation			
subjects affected / exposed	1 / 436 (0.23%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower Gastrointestinal Haemorrhage			
subjects affected / exposed	3 / 436 (0.69%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	4 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumatosis Intestinalis			
subjects affected / exposed	1 / 436 (0.23%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post-Tussive Vomiting			
subjects affected / exposed	0 / 436 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal Haemorrhage			
subjects affected / exposed	1 / 436 (0.23%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small Intestinal Obstruction			
subjects affected / exposed	1 / 436 (0.23%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			

subjects affected / exposed	5 / 436 (1.15%)	5 / 464 (1.08%)	
occurrences causally related to treatment / all	0 / 6	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Acute Hepatic Failure			
subjects affected / exposed	0 / 436 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Dermatitis Allergic			
subjects affected / exposed	0 / 436 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis Diaper			
subjects affected / exposed	0 / 436 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous Emphysema			
subjects affected / exposed	0 / 436 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash Papular			
subjects affected / exposed	0 / 436 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute Prerenal Failure			
subjects affected / exposed	1 / 436 (0.23%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Bladder Prolapse			
subjects affected / exposed	1 / 436 (0.23%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Haematuria			
subjects affected / exposed	0 / 436 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal Failure			
subjects affected / exposed	1 / 436 (0.23%)	2 / 464 (0.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vesicoureteric Reflux			
subjects affected / exposed	1 / 436 (0.23%)	0 / 464 (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 Sepsis			
subjects affected / exposed	0 / 436 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenovirus Infection			
subjects affected / exposed	1 / 436 (0.23%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial Sepsis			
subjects affected / exposed	2 / 436 (0.46%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial Infection			
subjects affected / exposed	0 / 436 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchiolitis			
subjects affected / exposed	12 / 436 (2.75%)	15 / 464 (3.23%)	
occurrences causally related to treatment / all	0 / 13	0 / 15	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			

subjects affected / exposed	1 / 436 (0.23%)	4 / 464 (0.86%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis Bacterial			
subjects affected / exposed	0 / 436 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis Viral			
subjects affected / exposed	0 / 436 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			
subjects affected / exposed	4 / 436 (0.92%)	4 / 464 (0.86%)	
occurrences causally related to treatment / all	0 / 6	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 436 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter Sepsis			
subjects affected / exposed	4 / 436 (0.92%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Candida Sepsis			
subjects affected / exposed	1 / 436 (0.23%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium Difficile Colitis			
subjects affected / exposed	1 / 436 (0.23%)	2 / 464 (0.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis			

subjects affected / exposed	1 / 436 (0.23%)	4 / 464 (0.86%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear Infection			
subjects affected / exposed	0 / 436 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterococcal Bacteraemia			
subjects affected / exposed	2 / 436 (0.46%)	2 / 464 (0.43%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterobacter Sepsis			
subjects affected / exposed	1 / 436 (0.23%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterococcal Infection			
subjects affected / exposed	1 / 436 (0.23%)	0 / 464 (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 / 436 (0.23%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia Sepsis			
subjects affected / exposed	0 / 436 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia Urinary Tract Infection			
subjects affected / exposed	0 / 436 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fungal Sepsis			

subjects affected / exposed	0 / 436 (0.00%)	2 / 464 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastroenteritis Adenovirus			
subjects affected / exposed	1 / 436 (0.23%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	14 / 436 (3.21%)	24 / 464 (5.17%)	
occurrences causally related to treatment / all	0 / 15	0 / 28	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastroenteritis Caliciviral			
subjects affected / exposed	1 / 436 (0.23%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis Rotavirus			
subjects affected / exposed	3 / 436 (0.69%)	2 / 464 (0.43%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal Infection			
subjects affected / exposed	1 / 436 (0.23%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastroenteritis Viral			
subjects affected / exposed	4 / 436 (0.92%)	5 / 464 (1.08%)	
occurrences causally related to treatment / all	0 / 4	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemophilus Infection			
subjects affected / exposed	0 / 436 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impetigo			

subjects affected / exposed	0 / 436 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incision Site Infection			
subjects affected / exposed	2 / 436 (0.46%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	5 / 436 (1.15%)	6 / 464 (1.29%)	
occurrences causally related to treatment / all	0 / 6	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella Bacteraemia			
subjects affected / exposed	0 / 436 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella Sepsis			
subjects affected / exposed	1 / 436 (0.23%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lobar Pneumonia			
subjects affected / exposed	1 / 436 (0.23%)	0 / 464 (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	0 / 436 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised Infection			
subjects affected / exposed	1 / 436 (0.23%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower Respiratory Tract Infection			

subjects affected / exposed	2 / 436 (0.46%)	3 / 464 (0.65%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower Respiratory Tract Infection Viral			
subjects affected / exposed	0 / 436 (0.00%)	2 / 464 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung Infection			
subjects affected / exposed	2 / 436 (0.46%)	3 / 464 (0.65%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mediastinal Abscess			
subjects affected / exposed	0 / 436 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mediastinitis			
subjects affected / exposed	3 / 436 (0.69%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis Aseptic			
subjects affected / exposed	1 / 436 (0.23%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis Pneumococcal			
subjects affected / exposed	1 / 436 (0.23%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nosocomial Infection			
subjects affected / exposed	0 / 436 (0.00%)	2 / 464 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis Media			

subjects affected / exposed	1 / 436 (0.23%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis Media Acute			
subjects affected / exposed	2 / 436 (0.46%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parainfluenzae Virus Infection			
subjects affected / exposed	1 / 436 (0.23%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis Bacterial			
subjects affected / exposed	1 / 436 (0.23%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumococcal Sepsis			
subjects affected / exposed	1 / 436 (0.23%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonia			
subjects affected / exposed	9 / 436 (2.06%)	21 / 464 (4.53%)	
occurrences causally related to treatment / all	0 / 11	0 / 24	
deaths causally related to treatment / all	0 / 1	0 / 1	
Pneumonia Bacterial			
subjects affected / exposed	0 / 436 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonia Escherichia			
subjects affected / exposed	0 / 436 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia Influenzal			

subjects affected / exposed	1 / 436 (0.23%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia Pneumococcal			
subjects affected / exposed	2 / 436 (0.46%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia Respiratory Syncytial Viral			
subjects affected / exposed	0 / 436 (0.00%)	2 / 464 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia Viral			
subjects affected / exposed	0 / 436 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post Procedural Cellulitis			
subjects affected / exposed	1 / 436 (0.23%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post Procedural Infection			
subjects affected / exposed	1 / 436 (0.23%)	2 / 464 (0.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative Wound Infection			
subjects affected / exposed	2 / 436 (0.46%)	7 / 464 (1.51%)	
occurrences causally related to treatment / all	0 / 2	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonal Sepsis			
subjects affected / exposed	1 / 436 (0.23%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			

subjects affected / exposed	2 / 436 (0.46%)	2 / 464 (0.43%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Sepsis			
subjects affected / exposed	3 / 436 (0.69%)	5 / 464 (1.08%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 2	0 / 1	
Pyelonephritis Acute			
subjects affected / exposed	1 / 436 (0.23%)	0 / 464 (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	1 / 436 (0.23%)	2 / 464 (0.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory Tract Infection			
subjects affected / exposed	3 / 436 (0.69%)	3 / 464 (0.65%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory Syncytial Virus Infection			
subjects affected / exposed	3 / 436 (0.69%)	4 / 464 (0.86%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory Tract Infection Bacterial			
subjects affected / exposed	1 / 436 (0.23%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory Tract Infection Viral			
subjects affected / exposed	0 / 436 (0.00%)	3 / 464 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhinitis			

subjects affected / exposed	0 / 436 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rotavirus Infection			
subjects affected / exposed	1 / 436 (0.23%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	4 / 436 (0.92%)	8 / 464 (1.72%)	
occurrences causally related to treatment / all	0 / 4	0 / 8	
deaths causally related to treatment / all	0 / 1	0 / 2	
Sepsis Syndrome			
subjects affected / exposed	0 / 436 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic Shock			
subjects affected / exposed	0 / 436 (0.00%)	2 / 464 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin Infection			
subjects affected / exposed	0 / 436 (0.00%)	2 / 464 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal Bacteraemia			
subjects affected / exposed	0 / 436 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal Sepsis			
subjects affected / exposed	0 / 436 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal Sepsis			

subjects affected / exposed	1 / 436 (0.23%)	4 / 464 (0.86%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Upper Respiratory Tract Infection			
subjects affected / exposed	13 / 436 (2.98%)	11 / 464 (2.37%)	
occurrences causally related to treatment / all	0 / 13	0 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Tract Infection			
subjects affected / exposed	6 / 436 (1.38%)	6 / 464 (1.29%)	
occurrences causally related to treatment / all	0 / 6	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral Diarrhoea			
subjects affected / exposed	1 / 436 (0.23%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 436 (0.23%)	2 / 464 (0.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral Infection			
subjects affected / exposed	6 / 436 (1.38%)	7 / 464 (1.51%)	
occurrences causally related to treatment / all	0 / 6	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral Rash			
subjects affected / exposed	0 / 436 (0.00%)	2 / 464 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral Upper Respiratory Tract Infection			
subjects affected / exposed	1 / 436 (0.23%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound Abscess			

subjects affected / exposed	2 / 436 (0.46%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound Infection			
subjects affected / exposed	2 / 436 (0.46%)	3 / 464 (0.65%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound Sepsis			
subjects affected / exposed	1 / 436 (0.23%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 436 (0.23%)	6 / 464 (1.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Failure To Thrive			
subjects affected / exposed	6 / 436 (1.38%)	3 / 464 (0.65%)	
occurrences causally related to treatment / all	0 / 7	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Feeding Disorder Of Infancy Or Early Childhood			
subjects affected / exposed	5 / 436 (1.15%)	2 / 464 (0.43%)	
occurrences causally related to treatment / all	0 / 6	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Food Intolerance			
subjects affected / exposed	3 / 436 (0.69%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	0 / 436 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemic Seizure			

subjects affected / exposed	1 / 436 (0.23%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcaemia			
subjects affected / exposed	0 / 436 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	1 / 436 (0.23%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoproteinaemia			
subjects affected / exposed	0 / 436 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 436 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			
subjects affected / exposed	0 / 436 (0.00%)	1 / 464 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic Acidosis			
subjects affected / exposed	2 / 436 (0.46%)	2 / 464 (0.43%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight Gain Poor			
subjects affected / exposed	3 / 436 (0.69%)	0 / 464 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	Clopidogrel 0.2mg/kg/day	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	96 / 436 (22.02%)	107 / 464 (23.06%)	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	20 / 436 (4.59%)	24 / 464 (5.17%)	
occurrences (all)	26	27	
Vomiting			
subjects affected / exposed	18 / 436 (4.13%)	32 / 464 (6.90%)	
occurrences (all)	21	35	
Infections and infestations			
Upper Respiratory Tract Infection			
subjects affected / exposed	53 / 436 (12.16%)	60 / 464 (12.93%)	
occurrences (all)	69	72	
Nasopharyngitis			
subjects affected / exposed	24 / 436 (5.50%)	21 / 464 (4.53%)	
occurrences (all)	28	31	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 September 2008	Following the FDA comments that stopping the trial for futility could reduce the chance of having interpretable results (especially if the benefit is lower than the 30% assumption of the protocol) or the possibility to have meaningful information in the label, it had been decided to remove the futility stopping boundaries for the 3 planned interim analyses of the protocol. This decision was endorsed by the Data Monitoring Committee of the study prior to performing the first interim analysis. Since the efficacy and futility boundaries were computed considering both boundaries simultaneously, the removal of the futility boundary resulted in minor changes to the previously proposed efficacy boundary. Consequently, the EFC5314/CLARINET protocol was amended to remove the futility stopping boundaries and to make subsequent changes to the efficacy stopping boundaries, final significance level, and required number of primary events. The required number of primary events needed for this event driven trial decreased slightly from 174 to 172, and the final significance level changed from 0.037 to 0.035.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/23782178