Clinical trial results:
Prophylactic treatment of the ductus arteriosus in preterm infants by acetaminophen

Summary

EudraCT number	2019-004297-26
Trial protocol	FR EE IE FI BE PT SE HU DK GB NO AT GR PL IT
Global end of trial date	20 June 2024

Results information

Result version number	v1 (current)
This version publication date	23 October 2025
First version publication date	23 October 2025
Summary attachment (see zip file)	SUMMARY_PROTOCOL (2019-004297-26_RESUME_V6_20231104_clean_C19-29.pdf)

Trial information

Trial identification

Sponsor protocol code	C19-29

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04459117
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Inserm
Sponsor organisation address	8 rue de la Croix Jarry, Paris, France, 75013
Public contact	Sandrine COUFFIN-CADIERGUES, Inserm, 33 144 23 64 16, rqrc.siege@inserm.fr
Scientific contact	Sandrine COUFFIN-CADIERGUES, Inserm, 33 144 23 64 16, rqrc.siege@inserm.fr

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	13 February 2025
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 June 2024
Global end of trial reached?	Yes
Global end of trial date	20 June 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary objectives :
Phase II: The objective of Phase II is to define the minimum effective dose of acetaminophen to close the ductus arteriosus before or at day 7 in preterm infants of 23-26 weeks of gestation

Phase III: The primary objective is an increase in surviving without severe morbidity at 36 weeks of post menstrual age (or at discharge if it occurs before) from 50% (placebo group) to 60% in group receiving a prophylactic treatment by acetaminophen during the first 5 days of life.

Protection of trial subjects:

Adverse events—including serious adverse events, deaths, and events related to the underlying disease—are recorded and reported in accordance with the Safety Management Plan and applicable ICH-GCP/EU requirements. Independent oversight is ensured through the following bodies, which convene regularly: Inserm Pharmacovigilance, National Hub Pharmacovigilance Responsible Person (NH PVRP), Data and Safety Monitoring Board (DSMB), Trial Management Group (TMG), and Trial Steering Committee (TSC).
Emergency code-break (unblinding) procedures are available and restricted to situations where knowledge of treatment allocation is essential for subject management; all instances are documented. Predefined criteria for treatment discontinuation are in place.
For blood sampling, in Phase II up to six tubes per subject will be collected in line with routine clinical practice. In Phase III, two samples are taken during routine care; additional tubes will be collected in a subset of 50 patients only.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 May 2020
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Scientific research, Safety
Long term follow-up duration	3 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Norway: 10
Country: Number of subjects enrolled	Portugal: 30
Country: Number of subjects enrolled	Spain: 12
Country: Number of subjects enrolled	Sweden: 15
Country: Number of subjects enrolled	Austria: 16
Country: Number of subjects enrolled	Belgium: 11
Country: Number of subjects enrolled	Denmark: 16
Country: Number of subjects enrolled	Estonia: 33

Country: Number of subjects enrolled	Finland: 58
Country: Number of subjects enrolled	France: 457
Country: Number of subjects enrolled	Ireland: 19
Country: Number of subjects enrolled	Italy: 8
Country: Number of subjects enrolled	Switzerland: 85
Country: Number of subjects enrolled	Greece: 34
Worldwide total number of subjects	804
EEA total number of subjects	719

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	804
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 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

First inclusion on October, the 29th 2020. End of study on June, the 20th 2024. Database lock on January, the 15th 2025. Parents/guardians approached, written consent before randomisation. Central IWRS 1:1, acetaminophen vs placebo, stratified by Gestational Age and centre.

Pre-assignment

Screening details:

Screening in NICU within hours of birth. Inclusion: Birth between 23-26 W for Phase II, between 23-28 W for Phase III, Post natal age < 12 hours, Parental or Legal Authority Consent, Parents with a social security or health insurance. Exclusion: Birth defect/Congenital anomaly, Twin-to-twin transfusion syndrome not cured...

Pre-assignment period milestones

Number of subjects started	804
Number of subjects completed	778

Pre-assignment subject non-completion reasons

Reason: Number of subjects	No parental authorisation: 1
Reason: Number of subjects	IMP not available in time: 6
Reason: Number of subjects	Clinical instability that can lead to rapid death: 2
Reason: Number of subjects	Suspicion of pulmonary hypoplasia: 1
Reason: Number of subjects	infants with congenital anomaly: 3
Reason: Number of subjects	Withdrawal before primary outcome: 4
Reason: Number of subjects	Missing Primary outcome: 5
Reason: Number of subjects	Impossibility to start IMP before 12h: 4

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Polyethylene ampoule of 10ml of NaCL 0.9%
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Phase II :
The first level will be 20 mg/kg loading dose within 12 hours after birth followed by 7.5 mg/kg/ 6 hours during 5 days (total = 20 doses). The 2nd, 3rd and 4th level doses will stand for 25%, 50%, and 75% increase of the first level:

- 25 mg/kg loading dose within 12 hours after birth followed by 10 mg/kg/ 6 hours during 5 days (total = 20 doses)
- 30 mg/kg loading dose within 12 hours after birth followed by 12 mg/kg/ 6 hours during 5 days (total = 20 doses)
- 35 mg/kg loading dose within 12 hours after birth followed by 15 mg/kg/ 6 hours during 5 days (total = 20 doses)

Phase III:
- In the 27-28 weeks gestational age group, the dosage is 20 mg/kg loading dose within 12 hours after birth followed by 7.5 mg/kg/ 6 hours (+/-15min) during 5 days
(total = 20 doses).
- In the 23-26 weeks gestational age group, the dosage will be minimum effective dose of acetaminophen to close the ductus arteriosus before or at day 7, found
during the phase II.

Arm title	Investigational Medicinal Product
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Acetaminophen 100 mg per 10 mL
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

In the 27-28 weeks gestational age group, the dosage is 20 mg/kg loading dose within 12 hours after birth followed by 7.5 mg/kg/ 6 hours (+/- 15 min) during 5 days (total = 20 doses).
o In the 23-26 weeks gestational age group, the dosage will be minimum effective dose of acetaminophen to close the ductus arteriosus before or at day 7, found during the phase II.

Number of subjects in period 1[1]	Placebo	Investigational Medicinal Product
Started	387	391
Completed	387	391

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: The baseline period counts only subjects who started Phase III treatment (Modified intention-to-treat (mITT) N=778). The ‘worldwide number enrolled’ (804) includes consented but not randomised infants, therefore totals differ.

Baseline characteristics

Reporting groups

Reporting group title	Phase III - Treatment

Reporting group description:

Modified intention-to-treat (mITT) analysis set: 778 infants (acetaminophen n=391; placebo n=387).

Reporting group values	Phase III - Treatment	Total	
Number of subjects	778	778	
Age categorical Units: Subjects			
23 weeks	23	23	
24 weeks	85	85	
25 weeks	119	119	
26 weeks	173	173	
27 weeks	186	186	
28 weeks	192	192	
Gender categorical Units: Subjects			
Female	375	375	
Male	403	403	

Subject analysis sets

Subject analysis set title	Full Analysis Set – Phase III (ITT)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All randomised infants in Phase III, analysed as assigned (intention-to-treat). Baseline characteristics are those collected at/just before randomisation. Phase II dose-finding subjects are not included in this analysis set.

Reporting group values	Full Analysis Set – Phase III (ITT)		
Number of subjects	778		
Age categorical Units: Subjects			
23 weeks	23		
24 weeks	85		
25 weeks	119		
26 weeks	173		
27 weeks	186		
28 weeks	192		
Gender categorical Units: Subjects			
Female	375		
Male	403		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Investigational Medicinal Product
Reporting group description: -	
Subject analysis set title	Full Analysis Set – Phase III (ITT)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All randomised infants in Phase III, analysed as assigned (intention-to-treat). Baseline characteristics are those collected at/just before randomisation. Phase II dose-finding subjects are not included in this analysis set.

Primary: Death or severe morbidity at 36 wk of postmenstrual age

End point title	Death or severe morbidity at 36 wk of postmenstrual age

End point description:

End point type	Primary

End point timeframe:

at 36 wk of postmenstrual age

End point values	Placebo	Investigational Medicinal Product		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	387	391		
Units: Participants				
Death	57	48		
Survival with severe bronchopulmonary dysplasia	40	44		
Intraventricular hemorrhage Grade III or IV	45	40		
Cystic periventricular leukomalacia	17	20		
Severe necrotizing enterocolitis	43	34		

Statistical analyses

Statistical analysis title	Primary analysis - modified ITT

Statistical analysis description:

Two-arm superiority comparison (paracetamol vs placebo) on survival without severe morbidity at 36 weeks PMA. Analysis set: modified ITT. Group-sequential O'Brien–Fleming design with interim looks at N=397 and N=595 (z-bounds ±2.86; ±2.34) and final bound ±2.02 at N≈793. Effect measure: risk ratio with two-sided 95% CI; α=0.05 overall. Test based on Z statistic for a binary endpoint (final p-value from normalized Z). Missing data: complete-case (no imputation)

Comparison groups	Placebo v Investigational Medicinal Product

Number of subjects included in analysis	778
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk ratio (RR)
Point estimate	1.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.94
upper limit	1.16

Secondary: Pulmonary hemorrhage (before day8)

End point title	Pulmonary hemorrhage (before day8)
End point description:	

End point type	Secondary
End point timeframe:	
Before day 8	

End point values	Placebo	Investigational Medicinal Product		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	387	391		
Units: Participants	20	15		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of days with enteral feeding during first week

End point title	Number of days with enteral feeding during first week
End point description:	

End point type	Secondary
End point timeframe:	
at 7 days of postnatal age	

End point values	Placebo	Investigational Medicinal Product		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	387	391		
Units: day				
median (inter-quartile range (Q1-Q3))	8 (6 to 8)	8 (7 to 8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Median volume of enteral nutrition at day 7, ml/kg, (IQR)

End point title	Median volume of enteral nutrition at day 7, ml/kg, (IQR)

End point description:

End point type	Secondary

End point timeframe:

Day 7 of life

End point values	Placebo	Investigational Medicinal Product		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	365	369		
Units: ml/kg				
median (inter-quartile range (Q1-Q3))	65 (22 to 112)	64 (22.5 to 112)		

Statistical analyses

No statistical analyses for this end point

Secondary: Median maximal Weight loss during first week after birth

End point title	Median maximal Weight loss during first week after birth

End point description:

End point type	Secondary

End point timeframe:

First 7 days after birth.

End point values	Placebo	Investigational Medicinal Product		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	387	390		
Units: % (of birth weight)				
median (inter-quartile range (Q1-Q3))	8.08 (4.14 to 11.36)	5.5 (2.51 to 8.91)		

Statistical analyses

No statistical analyses for this end point

Secondary: Respiratory support at day 7

End point title	Respiratory support at day 7

End point description:

End point type	Secondary

End point timeframe:

Day 7 of life.

End point values	Placebo	Investigational Medicinal Product		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	367	370		
Units: Participants				
No support	13	19		
Noninvasive respiratory support	241	257		
Invasive respiratory support	113	94		

Statistical analyses

No statistical analyses for this end point

Secondary: At least one catecholamine support

End point title	At least one catecholamine support

End point description:

End point type	Secondary

End point timeframe:

Birth to day 7 inclusive.

End point values	Placebo	Investigational Medicinal Product		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	387	391		
Units: Participants	89	79		

Statistical analyses

No statistical analyses for this end point

Secondary: At least one sedation/analgesia

End point title	At least one sedation/analgesia

End point description:

End point type	Secondary

End point timeframe:

Birth to day 7 inclusive.

End point values	Placebo	Investigational Medicinal Product		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	387	391		
Units: Participants	159	159		

Statistical analyses

No statistical analyses for this end point

Secondary: At least one steroid

End point title	At least one steroid

End point description:

End point type	Secondary

End point timeframe:

Birth to day 7 inclusive.

End point values	Placebo	Investigational Medicinal Product		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	387	391		
Units: Participants	134	117		

Statistical analyses

No statistical analyses for this end point

Secondary: Any retinopathy of prematurity (ROP)

End point title	Any retinopathy of prematurity (ROP)

End point description:

End point type	Secondary

End point timeframe:

at 36 weeks of postmenstrual age

End point values	Placebo	Investigational Medicinal Product		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	310	322		
Units: Participants	132	131		

Statistical analyses

No statistical analyses for this end point

Secondary: Retinopathy of prematurity in at least one eye requiring treatment

End point title	Retinopathy of prematurity in at least one eye requiring treatment

End point description:

End point type	Secondary

End point timeframe:

at 36 weeks of postmenstrual age

End point values	Placebo	Investigational Medicinal Product		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	310	322		
Units: Participants	19	18		

Statistical analyses

No statistical analyses for this end point

Secondary: Survival with any ventilatory support at 36 weeks PMA

End point title	Survival with any ventilatory support at 36 weeks PMA

End point description:

End point type	Secondary

End point timeframe:

at 36 weeks of postmenstrual age

End point values	Placebo	Investigational Medicinal Product		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	330	343		
Units: Participants	169	177		

Statistical analyses

No statistical analyses for this end point

Secondary: Weight gain measured by change in z score

End point title	Weight gain measured by change in z score

End point description:

End point type	Secondary

End point timeframe:

at 36 weeks of postmenstrual age

End point values	Placebo	Investigational Medicinal Product		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	361	371		
Units: z score				
arithmetic mean (standard deviation)	-0.73 (± 0.84)	-0.79 (± 0.84)		

Statistical analyses

No statistical analyses for this end point

Secondary: Head circumference gain measured by change in z score

End point title	Head circumference gain measured by change in z score

End point description:

End point type	Secondary

End point timeframe:

at 36 weeks of postmenstrual age

End point values	Placebo	Investigational Medicinal Product		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	311	318		
Units: z score				
arithmetic mean (standard deviation)	0.14 (± 2.75)	0.08 (± 2.69)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From 29-10-2020 (first inclusion) to 15-01-2025 (database lock)	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	28.0

Reporting groups	
Reporting group title	Acetaminophen phase II
Reporting group description:	
The active product is a 10 ml polyethylene ampoule of acetaminophen containing 100 mg of acetaminophen, solution for infusion, B BRAUN.	
Reporting group title	Acetaminophen phase III
Reporting group description: -	
Reporting group title	Placebo
Reporting group description:	
The placebo product is a polyethylene ampoule of 10ml of NaCL 0.9%, B BRAUN. Polyethylene ampoule of active and placebo products are with the same appearance, in accordance with Good Manufacturing Practices Drugs for Clinical Trials.	

Serious adverse events	Acetaminophen phase II	Acetaminophen phase III	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 31 (41.94%)	121 / 396 (30.56%)	114 / 387 (29.46%)
number of deaths (all causes)	4	51	59
number of deaths resulting from adverse events	4	51	59
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	0 / 31 (0.00%)	3 / 396 (0.76%)	0 / 387 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Haemodynamic instability			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	1 / 387 (0.26%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	0 / 31 (0.00%)	0 / 396 (0.00%)	2 / 387 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Peripheral vein thrombosis			
subjects affected / exposed	0 / 31 (0.00%)	0 / 396 (0.00%)	1 / 387 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Shock haemorrhagic			
subjects affected / exposed	0 / 31 (0.00%)	2 / 396 (0.51%)	2 / 387 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Complication associated with device			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	1 / 387 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 31 (3.23%)	8 / 396 (2.02%)	9 / 387 (2.33%)
occurrences causally related to treatment / all	0 / 1	1 / 8	0 / 9
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 6
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	2 / 387 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Acute respiratory failure			
subjects affected / exposed	0 / 31 (0.00%)	2 / 396 (0.51%)	0 / 387 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Apnoea			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	2 / 387 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchopulmonary dysplasia			

subjects affected / exposed	0 / 31 (0.00%)	2 / 396 (0.51%)	1 / 387 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 1
Emphysema			
subjects affected / exposed	0 / 31 (0.00%)	0 / 396 (0.00%)	1 / 387 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydrothorax			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	0 / 387 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	0 / 31 (0.00%)	7 / 396 (1.77%)	6 / 387 (1.55%)
occurrences causally related to treatment / all	0 / 0	1 / 7	0 / 6
deaths causally related to treatment / all	0 / 0	1 / 4	0 / 4
Laryngeal cyst			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	0 / 387 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngeal oedema			
subjects affected / exposed	0 / 31 (0.00%)	0 / 396 (0.00%)	1 / 387 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung disorder			
subjects affected / exposed	0 / 31 (0.00%)	0 / 396 (0.00%)	1 / 387 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neonatal respiratory distress syndrome			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	0 / 387 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pneumothorax			

subjects affected / exposed	0 / 31 (0.00%)	7 / 396 (1.77%)	6 / 387 (1.55%)
occurrences causally related to treatment / all	0 / 0	0 / 7	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pulmonary arterial hypertension			
subjects affected / exposed	0 / 31 (0.00%)	5 / 396 (1.26%)	1 / 387 (0.26%)
occurrences causally related to treatment / all	0 / 0	1 / 5	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pulmonary haemorrhage			
subjects affected / exposed	0 / 31 (0.00%)	3 / 396 (0.76%)	9 / 387 (2.33%)
occurrences causally related to treatment / all	0 / 0	2 / 3	0 / 9
deaths causally related to treatment / all	0 / 0	1 / 2	0 / 4
Pulmonary hypertension			
subjects affected / exposed	0 / 31 (0.00%)	10 / 396 (2.53%)	9 / 387 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 10	0 / 9
deaths causally related to treatment / all	0 / 0	0 / 3	0 / 1
Respiratory acidosis			
subjects affected / exposed	2 / 31 (6.45%)	1 / 396 (0.25%)	2 / 387 (0.52%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	1 / 31 (3.23%)	4 / 396 (1.01%)	2 / 387 (0.52%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 1
Tracheomalacia			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	0 / 387 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	0 / 387 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Red blood cell count decreased			

subjects affected / exposed	0 / 31 (0.00%)	0 / 396 (0.00%)	1 / 387 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transaminases increased			
subjects affected / exposed	0 / 31 (0.00%)	0 / 396 (0.00%)	3 / 387 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	0 / 387 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Congenital diaphragmatic hernia			
subjects affected / exposed	1 / 31 (3.23%)	0 / 396 (0.00%)	0 / 387 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital small intestinal atresia			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	0 / 387 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertrophic cardiomyopathy			
subjects affected / exposed	0 / 31 (0.00%)	0 / 396 (0.00%)	1 / 387 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal atresia			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	0 / 387 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Newborn persistent pulmonary hypertension			

subjects affected / exposed	0 / 31 (0.00%)	2 / 396 (0.51%)	0 / 387 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Patent ductus arteriosus			
subjects affected / exposed	0 / 31 (0.00%)	0 / 396 (0.00%)	1 / 387 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary hypoplasia			
subjects affected / exposed	0 / 31 (0.00%)	0 / 396 (0.00%)	1 / 387 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Sickle cell disease			
subjects affected / exposed	0 / 31 (0.00%)	2 / 396 (0.51%)	0 / 387 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Bradycardia			
subjects affected / exposed	1 / 31 (3.23%)	3 / 396 (0.76%)	2 / 387 (0.52%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	1 / 31 (3.23%)	1 / 396 (0.25%)	1 / 387 (0.26%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac tamponade			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	1 / 387 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiogenic shock			
subjects affected / exposed	0 / 31 (0.00%)	2 / 396 (0.51%)	2 / 387 (0.52%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 2
Pericardial effusion			

subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	0 / 387 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Brain injury			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	0 / 387 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral haemorrhage			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	1 / 387 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Cerebral ischaemia			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	0 / 387 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic cerebral infarction			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	0 / 387 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydrocephalus			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	0 / 387 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intracranial pressure increased			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	0 / 387 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Intraventricular haemorrhage			
subjects affected / exposed	1 / 31 (3.23%)	16 / 396 (4.04%)	9 / 387 (2.33%)
occurrences causally related to treatment / all	0 / 1	1 / 16	0 / 9
deaths causally related to treatment / all	0 / 1	1 / 12	0 / 7
Nervous system cyst			

subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	0 / 387 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Periventricular leukomalacia			
subjects affected / exposed	0 / 31 (0.00%)	0 / 396 (0.00%)	1 / 387 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Posthaemorrhagic hydrocephalus			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	0 / 387 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	0 / 387 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Haemorrhagic disorder			
subjects affected / exposed	0 / 31 (0.00%)	0 / 396 (0.00%)	1 / 387 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Thrombocytopenia			
subjects affected / exposed	0 / 31 (0.00%)	3 / 396 (0.76%)	2 / 387 (0.52%)
occurrences causally related to treatment / all	0 / 0	1 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaemia			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	1 / 387 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Thrombocytosis			
subjects affected / exposed	0 / 31 (0.00%)	0 / 396 (0.00%)	1 / 387 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			

Mouth haemorrhage			
subjects affected / exposed	0 / 31 (0.00%)	0 / 396 (0.00%)	1 / 387 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine perforation			
subjects affected / exposed	0 / 31 (0.00%)	0 / 396 (0.00%)	1 / 387 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal perforation			
subjects affected / exposed	0 / 31 (0.00%)	0 / 396 (0.00%)	1 / 387 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	0 / 387 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal obstruction			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	0 / 387 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal perforation			
subjects affected / exposed	3 / 31 (9.68%)	13 / 396 (3.28%)	8 / 387 (2.07%)
occurrences causally related to treatment / all	3 / 3	3 / 14	0 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Ascites			
subjects affected / exposed	0 / 31 (0.00%)	0 / 396 (0.00%)	1 / 387 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal stenosis			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	0 / 387 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileal perforation			

subjects affected / exposed	0 / 31 (0.00%)	2 / 396 (0.51%)	0 / 387 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	0 / 387 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Inguinal hernia			
subjects affected / exposed	1 / 31 (3.23%)	0 / 396 (0.00%)	0 / 387 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meconium ileus			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	0 / 387 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Necrotising enterocolitis neonatal			
subjects affected / exposed	4 / 31 (12.90%)	31 / 396 (7.83%)	40 / 387 (10.34%)
occurrences causally related to treatment / all	0 / 4	4 / 31	0 / 41
deaths causally related to treatment / all	0 / 1	2 / 10	0 / 11
Neonatal intestinal obstruction			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	0 / 387 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	0 / 31 (0.00%)	0 / 396 (0.00%)	1 / 387 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal perforation			
subjects affected / exposed	1 / 31 (3.23%)	0 / 396 (0.00%)	0 / 387 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			

subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	0 / 387 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Volvulus			
subjects affected / exposed	0 / 31 (0.00%)	0 / 396 (0.00%)	1 / 387 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholestasis			
subjects affected / exposed	1 / 31 (3.23%)	3 / 396 (0.76%)	1 / 387 (0.26%)
occurrences causally related to treatment / all	1 / 1	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic failure			
subjects affected / exposed	0 / 31 (0.00%)	3 / 396 (0.76%)	0 / 387 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver injury			
subjects affected / exposed	0 / 31 (0.00%)	0 / 396 (0.00%)	1 / 387 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subcapsular hepatic haematoma			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	0 / 387 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 31 (6.45%)	2 / 396 (0.51%)	2 / 387 (0.52%)
occurrences causally related to treatment / all	0 / 2	1 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anuria			
subjects affected / exposed	0 / 31 (0.00%)	2 / 396 (0.51%)	1 / 387 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oliguria			

subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	4 / 387 (1.03%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	0 / 31 (0.00%)	2 / 396 (0.51%)	0 / 387 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal tubular disorder			
subjects affected / exposed	1 / 31 (3.23%)	0 / 396 (0.00%)	1 / 387 (0.26%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal vein thrombosis			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	0 / 387 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Pathological fracture			
subjects affected / exposed	0 / 31 (0.00%)	0 / 396 (0.00%)	1 / 387 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Septic shock			
subjects affected / exposed	1 / 31 (3.23%)	11 / 396 (2.78%)	12 / 387 (3.10%)
occurrences causally related to treatment / all	0 / 1	1 / 12	0 / 12
deaths causally related to treatment / all	0 / 1	1 / 6	0 / 8
Candida sepsis			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	0 / 387 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cytomegalovirus infection			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	0 / 387 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Sepsis neonatal			
subjects affected / exposed	0 / 31 (0.00%)	0 / 396 (0.00%)	2 / 387 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Enterococcal sepsis			
subjects affected / exposed	0 / 31 (0.00%)	0 / 396 (0.00%)	1 / 387 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalitis			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	0 / 387 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Escherichia sepsis			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	0 / 387 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Klebsiella sepsis			
subjects affected / exposed	0 / 31 (0.00%)	0 / 396 (0.00%)	1 / 387 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis bacterial			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	0 / 387 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 31 (0.00%)	3 / 396 (0.76%)	6 / 387 (1.55%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 2
Serratia sepsis			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	0 / 387 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Staphylococcal sepsis			

subjects affected / exposed	0 / 31 (0.00%)	3 / 396 (0.76%)	0 / 387 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Systemic mycosis			
subjects affected / exposed	0 / 31 (0.00%)	0 / 396 (0.00%)	1 / 387 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	1 / 31 (3.23%)	4 / 396 (1.01%)	1 / 387 (0.26%)
occurrences causally related to treatment / all	0 / 1	1 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypernatraemia			
subjects affected / exposed	1 / 31 (3.23%)	0 / 396 (0.00%)	0 / 387 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperphosphataemia			
subjects affected / exposed	1 / 31 (3.23%)	0 / 396 (0.00%)	0 / 387 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	0 / 31 (0.00%)	0 / 396 (0.00%)	1 / 387 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	2 / 31 (6.45%)	0 / 396 (0.00%)	2 / 387 (0.52%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lactic acidosis			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	0 / 387 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolic acidosis			

subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	4 / 387 (1.03%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Acetaminophen phase II	Acetaminophen phase III	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 31 (41.94%)	152 / 396 (38.38%)	145 / 387 (37.47%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Haemangioma of liver			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	0 / 387 (0.00%)
occurrences (all)	0	1	0
Vascular disorders			
Aortic thrombosis			
subjects affected / exposed	0 / 31 (0.00%)	0 / 396 (0.00%)	1 / 387 (0.26%)
occurrences (all)	0	0	1
Hypotension			
subjects affected / exposed	0 / 31 (0.00%)	4 / 396 (1.01%)	2 / 387 (0.52%)
occurrences (all)	0	4	2
Hypertension			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	0 / 387 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Extravasation			
subjects affected / exposed	0 / 31 (0.00%)	0 / 396 (0.00%)	1 / 387 (0.26%)
occurrences (all)	0	0	1
Face oedema			
subjects affected / exposed	0 / 31 (0.00%)	0 / 396 (0.00%)	1 / 387 (0.26%)
occurrences (all)	0	0	1
Hypothermia			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	0 / 387 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			

Atelectasis			
subjects affected / exposed	0 / 31 (0.00%)	0 / 396 (0.00%)	1 / 387 (0.26%)
occurrences (all)	0	0	1
Bronchopulmonary dysplasia			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	3 / 387 (0.78%)
occurrences (all)	0	1	3
Chronic respiratory disease			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	2 / 387 (0.52%)
occurrences (all)	0	1	2
Epiglottic cyst			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	0 / 387 (0.00%)
occurrences (all)	0	1	0
Hypoxia			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	0 / 387 (0.00%)
occurrences (all)	0	1	0
Pneumothorax			
subjects affected / exposed	0 / 31 (0.00%)	2 / 396 (0.51%)	4 / 387 (1.03%)
occurrences (all)	0	2	4
Pulmonary arterial hypertension			
subjects affected / exposed	1 / 31 (3.23%)	6 / 396 (1.52%)	2 / 387 (0.52%)
occurrences (all)	1	8	2
Pulmonary artery stenosis			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	0 / 387 (0.00%)
occurrences (all)	0	1	0
Pulmonary haemorrhage			
subjects affected / exposed	0 / 31 (0.00%)	0 / 396 (0.00%)	1 / 387 (0.26%)
occurrences (all)	0	0	1
Pulmonary hypertension			
subjects affected / exposed	0 / 31 (0.00%)	9 / 396 (2.27%)	8 / 387 (2.07%)
occurrences (all)	0	9	8
Pulmonary interstitial emphysema syndrome			
subjects affected / exposed	0 / 31 (0.00%)	2 / 396 (0.51%)	1 / 387 (0.26%)
occurrences (all)	0	2	1
Pulmonary oedema			

subjects affected / exposed	0 / 31 (0.00%)	0 / 396 (0.00%)	1 / 387 (0.26%)
occurrences (all)	0	0	1
Respiratory acidosis			
subjects affected / exposed	1 / 31 (3.23%)	0 / 396 (0.00%)	0 / 387 (0.00%)
occurrences (all)	1	0	0
Respiratory failure			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	0 / 387 (0.00%)
occurrences (all)	0	1	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	0 / 387 (0.00%)
occurrences (all)	0	1	0
Analgesic drug level above therapeutic			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	0 / 387 (0.00%)
occurrences (all)	0	1	0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 31 (0.00%)	3 / 396 (0.76%)	7 / 387 (1.81%)
occurrences (all)	0	3	7
Blood urea increased			
subjects affected / exposed	0 / 31 (0.00%)	0 / 396 (0.00%)	1 / 387 (0.26%)
occurrences (all)	0	0	1
Blood creatinine increased			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	0 / 387 (0.00%)
occurrences (all)	0	1	0
Hepatic enzyme increased			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	0 / 387 (0.00%)
occurrences (all)	0	1	0
Blood lactic acid increased			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	0 / 387 (0.00%)
occurrences (all)	0	1	0
Transaminases increased			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	0 / 387 (0.00%)
occurrences (all)	0	1	0
Ultrasound liver abnormal			

subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	0 / 387 (0.00%)
occurrences (all)	0	1	0
White blood cell count increased			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	0 / 387 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Overdose			
subjects affected / exposed	0 / 31 (0.00%)	0 / 396 (0.00%)	1 / 387 (0.26%)
occurrences (all)	0	0	1
Congenital, familial and genetic disorders			
Atrial septal defect			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	1 / 387 (0.26%)
occurrences (all)	0	1	1
Cerebellar hypoplasia			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	0 / 387 (0.00%)
occurrences (all)	0	1	0
Congenital choroid plexus cyst			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	0 / 387 (0.00%)
occurrences (all)	0	1	0
Endocardial fibroelastosis			
subjects affected / exposed	0 / 31 (0.00%)	0 / 396 (0.00%)	1 / 387 (0.26%)
occurrences (all)	0	0	1
Epidermolysis bullosa			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	0 / 387 (0.00%)
occurrences (all)	0	1	0
Patent ductus arteriosus			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	3 / 387 (0.78%)
occurrences (all)	0	1	4
Pulmonary artery stenosis congenital			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	1 / 387 (0.26%)
occurrences (all)	0	1	1
Re-opening of ductus arteriosus			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	0 / 387 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			

Bradycardia			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	0 / 387 (0.00%)
occurrences (all)	0	2	0
Pericardial effusion			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	0 / 387 (0.00%)
occurrences (all)	0	1	0
Pulmonary valve stenosis			
subjects affected / exposed	0 / 31 (0.00%)	0 / 396 (0.00%)	1 / 387 (0.26%)
occurrences (all)	0	0	1
Supraventricular tachycardia			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	0 / 387 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Cerebellar haematoma			
subjects affected / exposed	1 / 31 (3.23%)	0 / 396 (0.00%)	0 / 387 (0.00%)
occurrences (all)	1	0	0
Cerebellar haemorrhage			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	0 / 387 (0.00%)
occurrences (all)	0	1	0
Cerebral disorder			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	0 / 387 (0.00%)
occurrences (all)	0	1	0
Cerebral haemorrhage			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	0 / 387 (0.00%)
occurrences (all)	0	1	0
Haemorrhage intracranial			
subjects affected / exposed	0 / 31 (0.00%)	0 / 396 (0.00%)	1 / 387 (0.26%)
occurrences (all)	0	0	1
Intraventricular haemorrhage			
subjects affected / exposed	0 / 31 (0.00%)	3 / 396 (0.76%)	3 / 387 (0.78%)
occurrences (all)	0	3	3
Lenticulostriatal vasculopathy			
subjects affected / exposed	0 / 31 (0.00%)	2 / 396 (0.51%)	0 / 387 (0.00%)
occurrences (all)	0	2	0
Monoplegia			

subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	0 / 387 (0.00%)
occurrences (all)	0	1	0
Neonatal seizure			
subjects affected / exposed	0 / 31 (0.00%)	0 / 396 (0.00%)	1 / 387 (0.26%)
occurrences (all)	0	0	1
Periventricular leukomalacia			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	1 / 387 (0.26%)
occurrences (all)	0	1	1
Seizure			
subjects affected / exposed	1 / 31 (3.23%)	0 / 396 (0.00%)	1 / 387 (0.26%)
occurrences (all)	1	0	1
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	0 / 387 (0.00%)
occurrences (all)	0	1	0
Transverse sinus thrombosis			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	0 / 387 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 31 (0.00%)	0 / 396 (0.00%)	3 / 387 (0.78%)
occurrences (all)	0	0	4
Erythroblastosis			
subjects affected / exposed	0 / 31 (0.00%)	0 / 396 (0.00%)	2 / 387 (0.52%)
occurrences (all)	0	0	2
Leukocytosis			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	0 / 387 (0.00%)
occurrences (all)	0	1	0
Leukopenia			
subjects affected / exposed	0 / 31 (0.00%)	2 / 396 (0.51%)	0 / 387 (0.00%)
occurrences (all)	0	2	0
Lymphadenopathy			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	1 / 387 (0.26%)
occurrences (all)	0	1	1
Neutropenia			
subjects affected / exposed	0 / 31 (0.00%)	6 / 396 (1.52%)	4 / 387 (1.03%)
occurrences (all)	0	6	4

Nucleated red cells			
subjects affected / exposed	0 / 31 (0.00%)	4 / 396 (1.01%)	2 / 387 (0.52%)
occurrences (all)	0	4	3
Sickle cell anaemia			
subjects affected / exposed	0 / 31 (0.00%)	0 / 396 (0.00%)	1 / 387 (0.26%)
occurrences (all)	0	0	1
Thrombocytopenia			
subjects affected / exposed	2 / 31 (6.45%)	30 / 396 (7.58%)	25 / 387 (6.46%)
occurrences (all)	2	32	27
Thrombocytosis			
subjects affected / exposed	1 / 31 (3.23%)	8 / 396 (2.02%)	12 / 387 (3.10%)
occurrences (all)	1	9	13
Eye disorders			
Retinopathy of prematurity			
subjects affected / exposed	0 / 31 (0.00%)	0 / 396 (0.00%)	1 / 387 (0.26%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	0 / 387 (0.00%)
occurrences (all)	0	1	0
Enterocolitis			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	0 / 387 (0.00%)
occurrences (all)	0	1	0
Food protein-induced enteropathy			
subjects affected / exposed	0 / 31 (0.00%)	0 / 396 (0.00%)	1 / 387 (0.26%)
occurrences (all)	0	0	1
Gastrointestinal disorder			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	1 / 387 (0.26%)
occurrences (all)	0	1	1
Haematochezia			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	1 / 387 (0.26%)
occurrences (all)	0	1	1
Inguinal hernia			
subjects affected / exposed	1 / 31 (3.23%)	0 / 396 (0.00%)	1 / 387 (0.26%)
occurrences (all)	1	0	1
Melaena			

subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	0 / 387 (0.00%)
occurrences (all)	0	1	0
Necrotising enterocolitis neonatal			
subjects affected / exposed	0 / 31 (0.00%)	3 / 396 (0.76%)	2 / 387 (0.52%)
occurrences (all)	0	3	2
Neonatal intestinal obstruction			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	0 / 387 (0.00%)
occurrences (all)	0	1	0
Oesophageal perforation			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	0 / 387 (0.00%)
occurrences (all)	0	1	0
Pneumatosis intestinalis			
subjects affected / exposed	0 / 31 (0.00%)	0 / 396 (0.00%)	1 / 387 (0.26%)
occurrences (all)	0	0	1
Rectal haemorrhage			
subjects affected / exposed	0 / 31 (0.00%)	16 / 396 (4.04%)	20 / 387 (5.17%)
occurrences (all)	0	17	23
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	0 / 387 (0.00%)
occurrences (all)	0	1	0
Hepatobiliary disorders			
Cholestasis			
subjects affected / exposed	0 / 31 (0.00%)	22 / 396 (5.56%)	9 / 387 (2.33%)
occurrences (all)	0	22	10
Hydrocholecystis			
subjects affected / exposed	0 / 31 (0.00%)	0 / 396 (0.00%)	1 / 387 (0.26%)
occurrences (all)	0	0	1
Hyperbilirubinaemia			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	1 / 387 (0.26%)
occurrences (all)	0	1	1
Skin and subcutaneous tissue disorders			
Skin lesion			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	1 / 387 (0.26%)
occurrences (all)	0	1	1
Renal and urinary disorders			

Acute kidney injury			
subjects affected / exposed	1 / 31 (3.23%)	14 / 396 (3.54%)	7 / 387 (1.81%)
occurrences (all)	1	14	7
Anuria			
subjects affected / exposed	0 / 31 (0.00%)	3 / 396 (0.76%)	2 / 387 (0.52%)
occurrences (all)	0	3	2
Nephrocalcinosis			
subjects affected / exposed	0 / 31 (0.00%)	4 / 396 (1.01%)	3 / 387 (0.78%)
occurrences (all)	0	4	3
Oliguria			
subjects affected / exposed	0 / 31 (0.00%)	3 / 396 (0.76%)	4 / 387 (1.03%)
occurrences (all)	0	3	4
Renal failure			
subjects affected / exposed	1 / 31 (3.23%)	10 / 396 (2.53%)	8 / 387 (2.07%)
occurrences (all)	1	10	8
Renal tubular disorder			
subjects affected / exposed	0 / 31 (0.00%)	0 / 396 (0.00%)	1 / 387 (0.26%)
occurrences (all)	0	0	1
Endocrine disorders			
Central hypothyroidism			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	0 / 387 (0.00%)
occurrences (all)	0	1	0
Hyperparathyroidism			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	0 / 387 (0.00%)
occurrences (all)	0	1	0
Hypothyroidism			
subjects affected / exposed	0 / 31 (0.00%)	2 / 396 (0.51%)	0 / 387 (0.00%)
occurrences (all)	0	2	0
Immune-mediated hypothyroidism			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	0 / 387 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Osteomalacia			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	0 / 387 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			

Bacillus infection			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	0 / 387 (0.00%)
occurrences (all)	0	1	0
Candida infection			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	1 / 387 (0.26%)
occurrences (all)	0	1	1
Cytomegalovirus infection			
subjects affected / exposed	0 / 31 (0.00%)	0 / 396 (0.00%)	1 / 387 (0.26%)
occurrences (all)	0	0	1
Enterovirus infection			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	0 / 387 (0.00%)
occurrences (all)	0	1	0
Escherichia infection			
subjects affected / exposed	0 / 31 (0.00%)	0 / 396 (0.00%)	1 / 387 (0.26%)
occurrences (all)	0	0	1
Escherichia sepsis			
subjects affected / exposed	0 / 31 (0.00%)	0 / 396 (0.00%)	1 / 387 (0.26%)
occurrences (all)	0	0	1
Meningitis bacterial			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	0 / 387 (0.00%)
occurrences (all)	0	1	0
Urinary tract infection			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	0 / 387 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Acidosis			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	1 / 387 (0.26%)
occurrences (all)	0	1	1
Blood potassium increased			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	0 / 387 (0.00%)
occurrences (all)	0	1	0
Carbohydrate intolerance			
subjects affected / exposed	0 / 31 (0.00%)	0 / 396 (0.00%)	1 / 387 (0.26%)
occurrences (all)	0	0	1
Cell death			

subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	0 / 387 (0.00%)
occurrences (all)	0	1	0
Hypercalcaemia			
subjects affected / exposed	1 / 31 (3.23%)	1 / 396 (0.25%)	1 / 387 (0.26%)
occurrences (all)	1	1	1
Hyperferritinaemia			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	0 / 387 (0.00%)
occurrences (all)	0	1	0
Hyperglycaemia			
subjects affected / exposed	4 / 31 (12.90%)	15 / 396 (3.79%)	19 / 387 (4.91%)
occurrences (all)	8	15	22
Hyperkalaemia			
subjects affected / exposed	2 / 31 (6.45%)	4 / 396 (1.01%)	3 / 387 (0.78%)
occurrences (all)	2	4	3
Hypernatraemia			
subjects affected / exposed	3 / 31 (9.68%)	23 / 396 (5.81%)	25 / 387 (6.46%)
occurrences (all)	3	23	25
Hyperphosphataemia			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	3 / 387 (0.78%)
occurrences (all)	0	1	3
Hypocalcaemia			
subjects affected / exposed	0 / 31 (0.00%)	3 / 396 (0.76%)	1 / 387 (0.26%)
occurrences (all)	0	3	1
Hypoglycaemia			
subjects affected / exposed	0 / 31 (0.00%)	5 / 396 (1.26%)	3 / 387 (0.78%)
occurrences (all)	0	5	3
Hypokalaemia			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	3 / 387 (0.78%)
occurrences (all)	0	1	3
Hyponatraemia			
subjects affected / exposed	1 / 31 (3.23%)	5 / 396 (1.26%)	3 / 387 (0.78%)
occurrences (all)	1	5	3
Hypophosphataemia			
subjects affected / exposed	0 / 31 (0.00%)	1 / 396 (0.25%)	1 / 387 (0.26%)
occurrences (all)	0	1	1
Lactic acidosis			

subjects affected / exposed	0 / 31 (0.00%)	0 / 396 (0.00%)	1 / 387 (0.26%)
occurrences (all)	0	0	1
Metabolic acidosis			
subjects affected / exposed	0 / 31 (0.00%)	2 / 396 (0.51%)	4 / 387 (1.03%)
occurrences (all)	0	2	4

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 March 2020	On 12 Feb 2021, recruitment was paused after an alert of 4 gastrointestinal perforations among 21 participants. The DSMB met on 16 Feb 2021 and, after reviewing all available data, found no evidence of a causal relationship with paracetamol (no imbalance between arms). Given that the rate of intestinal perforation in the cohort appeared higher than expected (acknowledging the small sample size), the DSMB recommended enhanced monitoring of intestinal complications and continuation of the trial. On 25 Feb 2021, the Trial Steering Committee implemented these safety recommendations by introducing closer surveillance: necrotising enterocolitis (NEC) and focal intestinal perforation were reclassified as 'Other notable events' and made subject to 24-hour reporting to the Pharmacovigilance Team to enable real-time review. No changes were made to the study objectives, primary endpoint or randomisation.
31 January 2022	Following a Swiss authority inspection, the protocol was clarified for AE reporting and concomitant medication reporting. Sections were updated and a new Appendix 20.9 (AE reporting tool) was added as requested by Switzerland. We also incorporated prior country-specific requests and editorial clarifications to harmonise versions. No changes to objectives, endpoints, randomisation, IMP or sample size.
22 November 2022	Update to harmonise protocol across countries. (1) Recruitment window extended from 28 to 42 months to reach target N; associated milestones updated (primary endpoint observation ends July 2024; last patient last visit July 2024; final monitoring Nov 2024). (2) Rescue treatment for PDA: criteria clarified per McNamara staging (C4/E3 or C3/E4 combination); recommendation wording aligned to allow local practice. (3) Disease-related events: list expanded to include all retinopathies (not only retinal surgery) recorded in the eCRF; no immediate SAE form required unless specified.
22 November 2023	This global operational amendment clarifies timing and data handling in busy neonatal intensive care units. IMP administration: a ±15-minute administration window is introduced to reflect real-life NICU conditions; a minimum interval of 5 hours 30 minutes between two administrations is specified. Both are compatible with the pharmacokinetic model and supported by the SmPC for paracetamol 10 mg/mL solution for infusion (B. Braun, 07/2022). Assessments: for Visit 3, a ±1-week window is defined for anthropometric measurements (head circumference, length, weight) to align with routine practice in which these are typically recorded weekly. Transfers between hospitals: the protocol now recognises standard-of-care transfers from tertiary NICUs to level IIA/IIB units and adds a new paragraph referring to a dedicated procedure. This standardises the process and clarifies responsibilities when a participant is transferred before completing participation: the receiving hospital must transmit Visit 2 and Visit 3 assessments and all safety data to the recruiting investigational site within the specified timelines and using agreed communication routes. Impact: these changes harmonise operations and ensure data completeness. There is no change to study objectives, endpoints, randomisation scheme, IMP composition/dose, or overall subject burden beyond the defined windows.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
12 March 2021	Based on the unexpectedly high incidence of gastrointestinal perforation, the sponsor decided on the following precautionary measures: - Convening the DSMB as soon as possible for an extraordinary meeting; the DSMB met on 16/02/2021 - Informing the investigating sites to suspend new enrolments. - Inform the trial steering committee in order to implement future recommendations published by the DSMB - Temporary suspension of the study	12 March 2021

Notes:

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/39948605