Clinical trial results:
Dose-Ranging Pharmacodynamic Assessment Of Platelet Aggregation Inhibition With Clopidogrel In Children Of Blalock-Taussing Shunt Age Categories (Neonates And Infants/Toddlers)

Summary

EudraCT number	2004-001841-14
Trial protocol	IT BE Outside EU/EEA
Global end of trial date	15 April 2006

Results information

Result version number	v1
This version publication date	22 June 2016
First version publication date	03 June 2015

Trial information

Trial identification

Sponsor protocol code	PDY4422

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00115375
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Sanofi aventis recherche & développement
Sponsor organisation address	1 avenue Pierre Brossolette, Chilly-Mazarin, France, 91380
Public contact	Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.com
Scientific contact	Trial Transparency Team, Sanofi aventis recherche & développement, 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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	16 May 2006
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	15 April 2006
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to determine the dose of clopidogrel to achieve a mean 30 to 50% inhibition of 5 micromole adenosine diphosphate (ADP)-induced platelet aggregation (that is, to provide inhibition of platelet aggregation similar to that observed with 75 mg in adults) in neonates and infants/Toddlers at risk for thrombosis.

Protection of trial subjects:

The study was conducted by investigators experienced in the treatment of pediatric subjects. The parent(s) or guardian(s) 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), was provided and explained. Repeated invasive procedures were minimized. The number of blood samples as well as the amount of blood drawn was 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	13 January 2004
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	Italy: 2
Country: Number of subjects enrolled	Belgium: 8
Country: Number of subjects enrolled	United States: 42
Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	France: 12
Country: Number of subjects enrolled	Germany: 26
Worldwide total number of subjects	92
EEA total number of subjects	48

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0

Newborns (0-27 days)	42
Infants and toddlers (28 days-23 months)	50
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:

The study was conducted at 22 centers in 6 countries between 13 January 2004 and 15 April 2006.

Pre-assignment

Screening details:

After written informed consent was obtained from the parent or guardian, subjects were randomly assigned to clopidogrel versus placebo in a 3:1 ratio in 4 sequential groups (0.01, 0.10, 0.20, and 0.15 mg/kg). Subjects were also stratified by age: neonates <=30 days old and infant/toddlers >30 days to 24 months old.

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:

The clopidogrel and placebo (mannitol powder) were identical in appearance and consistency and both were reconstituted in the same fashion thus there was no way of identifying the treatment.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Placebo once daily for at least 7 consecutive days (up to a maximum of 28 days).

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	Oral use

Dosage and administration details:

Oral solution administered with a syringe orally or via enteric administration.

Arm title	Clopidogrel 0.01 mg/kg

Arm description:

Clopidogrel 0.01 mg/kg once daily for at least 7 consecutive days (up to a maximum of 28 days).

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

Dosage and administration details:

0.01 mg/kg in oral solution administered with a syringe orally or via enteric administration.

Arm title	Clopidogrel 0.1 mg/kg

Arm description:

Clopidogrel 0.1 mg/kg once daily for at least 7 consecutive days (up to a maximum of 28 days).

Arm type	Experimental

Investigational medicinal product name	Clopidogrel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for oral solution
Routes of administration	Oral use

Dosage and administration details:

0.1 mg/kg in oral solution administered with a syringe orally or via enteric administration.

Arm title	Clopidogrel 0.15 mg/kg

Arm description:

Clopidogrel 0.15 mg/kg once daily for at least 7 consecutive days (up to a maximum of 28 days).

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

Dosage and administration details:

0.15 mg/kg in oral solution administered with a syringe orally or via enteric administration.

Arm title	Clopidogrel 0.2 mg/kg

Arm description:

Clopidogrel 0.2 mg/kg once daily for at least 7 consecutive days (up to a maximum of 28 days).

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

Dosage and administration details:

0.2 mg/kg in oral solution administered with a syringe orally or via enteric administration.

Number of subjects in period 1	Placebo	Clopidogrel 0.01 mg/kg	Clopidogrel 0.1 mg/kg
Started	23	12	21
Treated	21	10	21
Completed	16	9	19
Not completed	7	3	2
Randomized but not treated	2	2	-
Adverse event	2	-	1
Bleeding	1	1	-
Unspecified	2	-	1

Number of subjects in period 1	Clopidogrel 0.15 mg/kg	Clopidogrel 0.2 mg/kg
Started	10	26
Treated	8	26
Completed	7	25
Not completed	3	1

Randomized but not treated	2	-
Adverse event	-	-
Bleeding	-	-
Unspecified	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Placebo once daily for at least 7 consecutive days (up to a maximum of 28 days).	
Reporting group title	Clopidogrel 0.01 mg/kg
Reporting group description:	
Clopidogrel 0.01 mg/kg once daily for at least 7 consecutive days (up to a maximum of 28 days).	
Reporting group title	Clopidogrel 0.1 mg/kg
Reporting group description:	
Clopidogrel 0.1 mg/kg once daily for at least 7 consecutive days (up to a maximum of 28 days).	
Reporting group title	Clopidogrel 0.15 mg/kg
Reporting group description:	
Clopidogrel 0.15 mg/kg once daily for at least 7 consecutive days (up to a maximum of 28 days).	
Reporting group title	Clopidogrel 0.2 mg/kg
Reporting group description:	
Clopidogrel 0.2 mg/kg once daily for at least 7 consecutive days (up to a maximum of 28 days).	

Reporting group values	Placebo	Clopidogrel 0.01 mg/kg	Clopidogrel 0.1 mg/kg
Number of subjects	23	12	21
Age categorical Units: Subjects			
Neonates (<= 30 days)	11	5	10
Infant/Toddler (1 - 24 months)	12	7	11
Gender categorical Units: Subjects			
Female	7	7	5
Male	16	5	16

Reporting group values	Clopidogrel 0.15 mg/kg	Clopidogrel 0.2 mg/kg	Total
Number of subjects	10	26	92
Age categorical Units: Subjects			
Neonates (<= 30 days)	10	9	45
Infant/Toddler (1 - 24 months)	0	17	47
Gender categorical Units: Subjects			
Female	4	12	35
Male	6	14	57

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Placebo once daily for at least 7 consecutive days (up to a maximum of 28 days).	
Reporting group title	Clopidogrel 0.01 mg/kg
Reporting group description:	
Clopidogrel 0.01 mg/kg once daily for at least 7 consecutive days (up to a maximum of 28 days).	
Reporting group title	Clopidogrel 0.1 mg/kg
Reporting group description:	
Clopidogrel 0.1 mg/kg once daily for at least 7 consecutive days (up to a maximum of 28 days).	
Reporting group title	Clopidogrel 0.15 mg/kg
Reporting group description:	
Clopidogrel 0.15 mg/kg once daily for at least 7 consecutive days (up to a maximum of 28 days).	
Reporting group title	Clopidogrel 0.2 mg/kg
Reporting group description:	
Clopidogrel 0.2 mg/kg once daily for at least 7 consecutive days (up to a maximum of 28 days).	

Primary: Percent Inhibition of Maximum Extent of 5 µmol/L ADP-Induced Platelet Aggregation

End point title	Percent Inhibition of Maximum Extent of 5 µmol/L ADP-Induced Platelet Aggregation
End point description:	
Analysis was carried out on per protocol (PP) population defined as all randomized and treated subjects who had a baseline and a steady state assessment of platelet aggregation.	
End point type	Primary
End point timeframe:	
Baseline, Steady State (Day 7-28)	

End point values	Placebo	Clopidogrel 0.01 mg/kg	Clopidogrel 0.1 mg/kg	Clopidogrel 0.15 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16[1]	8[2]	18[3]	6[4]
Units: percent inhibition				
arithmetic mean (standard deviation)	0.8 (± 48)	-12.8 (± 46.2)	18.9 (± 40.4)	36.4 (± 27.5)

Notes:

[1] - 7 neonates and 9 infants/toddlers

[2] - 3 neonates and 5 infants/toddlers

[3] - 8 neonates and 10 infants/toddlers

[4] - 6 neonates only (no infant/toddler)

End point values	Clopidogrel 0.2 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	25[5]			
Units: percent inhibition				

arithmetic mean (standard deviation)	49.3 (± 27.2)			

Notes:

[5] - 10 neonates and 15 infants/toddlers

Statistical analyses

Statistical analysis title	Clopidogrel 0.01 mg/kg vs Placebo

Statistical analysis description:

ANOVA was performed on percent inhibition of maximum extent of aggregation with model terms for treatment group, age group, and the treatment group–by–age group interaction. The differences between active-dose level and placebo were estimated within the ANOVA framework with 95% confidence intervals.

Comparison groups	Placebo v Clopidogrel 0.01 mg/kg
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4445 [6]
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	-12.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	-44.16
upper limit	19.59

Notes:

[6] - Statistical significance was claimed if the computed p-value was ≤0.05.

Statistical analysis title	Clopidogrel 0.1 mg/kg vs Placebo
Comparison groups	Placebo v Clopidogrel 0.1 mg/kg
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1602 [7]
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	17.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.29
upper limit	43.26

Notes:

[7] - Statistical significance was claimed if the computed p-value was ≤0.05.

Statistical analysis title	Clopidogrel 0.15 mg/kg vs Placebo
Comparison groups	Placebo v Clopidogrel 0.15 mg/kg

Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2139 [8]
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	20.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.76
upper limit	54.65

Notes:

[8] - Statistical significance was claimed if the computed p-value was ≤0.05.

Statistical analysis title	Clopidogrel 0.2 mg/kg vs Placebo
Comparison groups	Placebo v Clopidogrel 0.2 mg/kg
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001 [9]
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	49.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	25.7
upper limit	72.82

Notes:

[9] - Statistical significance was claimed if the computed p-value was ≤0.05.

Primary: Percent Inhibition of Rate of 5 µmol/L ADP-Induced Platelet Aggregation

End point title	Percent Inhibition of Rate of 5 µmol/L ADP-Induced Platelet Aggregation

End point description:

Analysis was performed on PP population as previously defined.

End point type	Primary

End point timeframe:

Baseline, Steady State (Day 7-28)

End point values	Placebo	Clopidogrel 0.01 mg/kg	Clopidogrel 0.1 mg/kg	Clopidogrel 0.15 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16[10]	8[11]	18[12]	6[13]
Units: percent inhibition				
arithmetic mean (standard deviation)	-9.6 (± 35)	-1.6 (± 28)	0.8 (± 57.7)	33.7 (± 28.2)

Notes:

[10] - 7 neonates and 9 infants/toddlers

[11] - 3 neonates and 5 infants/toddlers

[12] - 8 neonates and 10 infants/toddlers

[13] - 6 neonates only (no infant/toddler)

End point values	Clopidogrel 0.2 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	25[14]			
Units: percent inhibition				
arithmetic mean (standard deviation)	33.8 (± 31.6)			

Notes:

[14] - 10 neonates and 15 infants/toddlers

Statistical analyses

Statistical analysis title	Clopidogrel 0.01 mg/kg vs Placebo

Statistical analysis description:

ANOVA was performed on percent inhibition of rate of aggregation with model terms for treatment group, age group, and the treatment group–by–age group interaction. The differences between active-dose level and placebo were estimated within the ANOVA framework with 95% confidence intervals.

Comparison groups	Placebo v Clopidogrel 0.01 mg/kg
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.61 [15]
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	8.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-25.47
upper limit	43.07

Notes:

[15] - Statistical significance was claimed if the computed p-value was ≤0.05.

Statistical analysis title	Clopidogrel 0.1 mg/kg vs Placebo
Comparison groups	Placebo v Clopidogrel 0.1 mg/kg
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.455 [16]
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	10.23

Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.94
upper limit	37.4

Notes:

[16] - Statistical significance was claimed if the computed p-value was ≤0.05.

Statistical analysis title	Clopidogrel 0.15 mg/kg vs Placebo
Comparison groups	Placebo v Clopidogrel 0.15 mg/kg
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1063 [17]
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	36.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.28
upper limit	81.27

Notes:

[17] - Statistical significance was claimed if the computed p-value was ≤0.05.

Statistical analysis title	Clopidogrel 0.2 mg/kg vs Placebo
Comparison groups	Placebo v Clopidogrel 0.2 mg/kg
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0009 [18]
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	43.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	18.56
upper limit	69.22

Notes:

[18] - Statistical significance was claimed if the computed p-value was ≤0.05.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events (AE) were collected from signature of the informed consent form up to the final visit (Day 7-28) regardless of seriousness or relationship to investigational product.

Adverse event reporting additional description:

Reported adverse events and deaths are treatment-emergent that is AEs that developed/worsened and deaths that occurred during the 'on treatment period' (from first study drug administration up to final visit)."

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	8.1

Reporting groups

Reporting group title	Clopidogrel 0.1 mg/kg

Reporting group description:

Subjects exposed to clopidogrel 0.1 mg/kg

Reporting group title	Placebo

Reporting group description:

Subjects exposed to placebo.

Reporting group title	Clopidogrel 0.2 mg/kg

Reporting group description:

Subjects exposed to clopidogrel 0.2 mg/kg.

Reporting group title	Clopidogrel 0.01 mg/kg

Reporting group description:

Subjects exposed to clopidogrel 0.01 mg/kg.

Reporting group title	Clopidogrel 0.15 mg/kg

Reporting group description:

Subjects exposed to clopidogrel 0.15 mg/kg.

Serious adverse events	Clopidogrel 0.1 mg/kg	Placebo	Clopidogrel 0.2 mg/kg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 21 (0.00%)	2 / 21 (9.52%)	1 / 26 (3.85%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Investigations			
Desaturation			
subjects affected / exposed	0 / 21 (0.00%)	0 / 21 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Desaturations			

subjects affected / exposed	0 / 21 (0.00%)	0 / 21 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Low Platelet Count			
subjects affected / exposed	0 / 21 (0.00%)	0 / 21 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Shunt Thrombosis			
subjects affected / exposed	0 / 21 (0.00%)	1 / 21 (4.76%)	0 / 26 (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
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 21 (0.00%)	0 / 21 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Bradycardia			
subjects affected / exposed	0 / 21 (0.00%)	0 / 21 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Heart Failure (Worsening)			
subjects affected / exposed	0 / 21 (0.00%)	1 / 21 (4.76%)	0 / 26 (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
Infections and infestations			
Sepsis (Suspicion)			
subjects affected / exposed	0 / 21 (0.00%)	1 / 21 (4.76%)	0 / 26 (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

Serious adverse events	Clopidogrel 0.01 mg/kg	Clopidogrel 0.15 mg/kg	
Total subjects affected by serious adverse events			

subjects affected / exposed	1 / 10 (10.00%)	1 / 8 (12.50%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events			
Investigations			
Desaturation			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Desaturations			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Low Platelet Count			
subjects affected / exposed	1 / 10 (10.00%)	0 / 8 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Shunt Thrombosis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac disorders			
Bradycardia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Heart Failure (Worsening)			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infections and infestations			
Sepsis (Suspicion)			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	
occurrences causally related to treatment / all	0 / 0	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	Clopidogrel 0.1 mg/kg	Placebo	Clopidogrel 0.2 mg/kg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 21 (19.05%)	3 / 21 (14.29%)	1 / 26 (3.85%)
Investigations			
Desaturation Without Hemodynamic Change			
subjects affected / exposed	0 / 21 (0.00%)	0 / 21 (0.00%)	0 / 26 (0.00%)
occurrences (all)	0	0	0
Symmetric Pulmonary Opacity			
subjects affected / exposed	0 / 21 (0.00%)	0 / 21 (0.00%)	0 / 26 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Overdose Of Study Medication			
subjects affected / exposed	0 / 21 (0.00%)	0 / 21 (0.00%)	0 / 26 (0.00%)
occurrences (all)	0	0	0
Study Drug Overdosage			
subjects affected / exposed	0 / 21 (0.00%)	0 / 21 (0.00%)	0 / 26 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Fever			
subjects affected / exposed	0 / 21 (0.00%)	0 / 21 (0.00%)	0 / 26 (0.00%)
occurrences (all)	0	0	0
Irritability			
subjects affected / exposed	0 / 21 (0.00%)	0 / 21 (0.00%)	0 / 26 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Diarrhea			

subjects affected / exposed	2 / 21 (9.52%)	1 / 21 (4.76%)	0 / 26 (0.00%)
occurrences (all)	2	1	0
Emesis			
subjects affected / exposed	2 / 21 (9.52%)	2 / 21 (9.52%)	1 / 26 (3.85%)
occurrences (all)	2	2	1
Emesis - Intermittent			
subjects affected / exposed	0 / 21 (0.00%)	0 / 21 (0.00%)	0 / 26 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal Bleeding			
subjects affected / exposed	0 / 21 (0.00%)	1 / 21 (4.76%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Stomach Ache			
subjects affected / exposed	0 / 21 (0.00%)	1 / 21 (4.76%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 21 (0.00%)	0 / 21 (0.00%)	0 / 26 (0.00%)
occurrences (all)	0	0	0
Hypoxia			
subjects affected / exposed	0 / 21 (0.00%)	0 / 21 (0.00%)	0 / 26 (0.00%)
occurrences (all)	0	0	0
Upper Airway Congestion			
subjects affected / exposed	0 / 21 (0.00%)	0 / 21 (0.00%)	0 / 26 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Exacerbation Of Diaper Rash			
subjects affected / exposed	0 / 21 (0.00%)	0 / 21 (0.00%)	0 / 26 (0.00%)
occurrences (all)	0	0	0
Rash			
subjects affected / exposed	0 / 21 (0.00%)	0 / 21 (0.00%)	0 / 26 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Hematuria Bleeding			
subjects affected / exposed	0 / 21 (0.00%)	0 / 21 (0.00%)	0 / 26 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			

Thrush			
subjects affected / exposed	0 / 21 (0.00%)	0 / 21 (0.00%)	0 / 26 (0.00%)
occurrences (all)	0	0	0
Urinary Tract Infection			
subjects affected / exposed	0 / 21 (0.00%)	0 / 21 (0.00%)	0 / 26 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Clopidogrel 0.01 mg/kg	Clopidogrel 0.15 mg/kg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 10 (60.00%)	6 / 8 (75.00%)	
Investigations			
Desaturation Without Hemodynamic Change			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Symmetric Pulmonary Opacity			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Overdose Of Study Medication			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Study Drug Overdosage			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Fever			
subjects affected / exposed	1 / 10 (10.00%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Irritability			
subjects affected / exposed	1 / 10 (10.00%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Diarrhea			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Emesis			

subjects affected / exposed	2 / 10 (20.00%)	0 / 8 (0.00%)	
occurrences (all)	2	0	
Emesis - Intermittent			
subjects affected / exposed	1 / 10 (10.00%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal Bleeding			
subjects affected / exposed	1 / 10 (10.00%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Stomach Ache			
subjects affected / exposed	1 / 10 (10.00%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Hypoxia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Upper Airway Congestion			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Exacerbation Of Diaper Rash			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Rash			
subjects affected / exposed	1 / 10 (10.00%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Hematuria Bleeding			
subjects affected / exposed	1 / 10 (10.00%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Thrush			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	

Urinary Tract Infection subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 8 (12.50%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 May 2003	Stepwise approach for blood sampling extended to subjects of 3 to 5 kg body weight according to Investigator's judgment. Eligibility of enrollment of any subject with systemic to pulmonary artery shunts in addition to the Blalock-Taussig shunt subject populations. Update of "introduction and rationale" with results of the Phase 1 bioavailability study of the liquid formulation. Shunt replacement was recorded in addition to other clinical outcomes in event rate documentation for planning the Phase 3 efficacy and safety study. Since this information was collected in an anonymous fashion, no informed consent was required for this type of data collection. Update of instructions for platelet aggregation testing and pharmacokinetic blood sample handling as per lab manual technical revisions.
02 April 2004	Clarification on the protocol: - Neonates eligible for the study are less than 30 days; - Eligibility of enrollment of any subject who may have potential therapeutic benefits from clopidogrel because of a related pathological condition requiring antiplatelet therapy (such as but not limited to Kawaski disease, vascular stent, Glenn shunt or Fontan physiology); - Stepwise approach for blood sampling extended, according to Investigator's judgment, to any subject without reliable vascular access (that is, difficult venipuncture, lack of central venous line or indwelling catheter) to limit the number of blood withdrawals while preserving the primary objective of the study (pharmacodynamic).

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/18195173