Clinical trial results:
Long-Term Safety Study in Patients Included in CLARINET Study With Cyanotic Congenital Heart Disease Palliated With A Systemic-To-Pulmonary Artery Shunt And For Whom The Shunt is Still in Place at One Year of Age

Summary

EudraCT number	2008-004999-53
Trial protocol	PT HU ES BE DE FR IT GB Outside EU/EEA
Global end of trial date	21 July 2010

Results information

Result version number	v1
This version publication date	02 May 2016
First version publication date	20 December 2014

Trial information

Trial identification

Sponsor protocol code	LTS10916

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00833703
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	21 July 2010
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	21 July 2010
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to assess the safety up to 18 months of age of the extended use of Clopidogrel (SR25990C, Iscover®,
Plavix®) 0.2 milligram/kilogram of body weight/day (mg/kg/day) in subjects for whom the shunt was still in place at one year of age.

Protection of trial subjects:

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

Background therapy:

All drugs usually required in subject with systemic-to-pulmonary artery shunts were authorized for concomitant use with the study drug. The most common concomitant medications were acetylcalicylic acid, diuretic, and antibiotics.

Evidence for comparator: -

Actual start date of recruitment	27 January 2009
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	Germany: 3
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	Portugal: 4
Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	Poland: 2
Country: Number of subjects enrolled	Hungary: 3
Country: Number of subjects enrolled	Brazil: 6
Country: Number of subjects enrolled	India: 1
Country: Number of subjects enrolled	Malaysia: 2
Country: Number of subjects enrolled	Mexico: 10
Country: Number of subjects enrolled	Russian Federation: 1

Country: Number of subjects enrolled	Taiwan: 9
Country: Number of subjects enrolled	United States: 1
Country: Number of subjects enrolled	France: 1
Worldwide total number of subjects	49
EEA total number of subjects	19

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	49
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:

49 subjects were enrolled between January 2009 and January 2010 in 25 sites in 15 countries (7 countries involved in CLARINET study were not selected as the delay in obtaining IRB/IEC and Health Authorities approvals would prevent recruitment and/or no subject would be recruited as the second surgery is always performed before 1 year of age).

Pre-assignment

Screening details:

Subjects from EFC5314/CLARINET study were included.

Period 1

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

Blinding implementation details:

Eligible subjects received 0.2 mg/kg/day of clopidogrel or placebo without the Investigator or the subject's parents/guardians knowing the treatment assigned. The clopidogrel and placebo were reconstituted in the same fashion and were identical in appearance.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

0.2 mL/kg/day matching placebo solution once daily.

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	Enteral use , Oral use

Dosage and administration details:

Placebo matching to clopidogrel 0.2 mg/kg/day.

Arm title	Clopidogrel 0.2 mg/kg/day

Arm description:

0.2 mL/kg/day clopidogrel reconstituted solution at 1 mg/mL once daily.

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

Dosage and administration details:

Clopidogrel powder 0.2 mg/kg/day.

Number of subjects in period 1	Placebo	Clopidogrel 0.2 mg/kg/day
Started	23	26
Treated	23	26
Completed Treatment	22 [1]	24 [2]
Completed	23	25
Not completed	0	1
Parent(s)/guardian(s)'s request	-	1

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Number of subjects who completed the treatment are the subjects who completed the placebo treatment as per scheduled duration; however, subjects who did not complete the treatment were followed up until end of the study period/early withdrawal.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Number of subjects who completed the treatment are the subjects who completed the clopidogrel treatment as per scheduled duration; however, subjects who did not complete the treatment were followed up until end of the study period/early withdrawal.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
0.2 mL/kg/day matching placebo solution once daily.	
Reporting group title	Clopidogrel 0.2 mg/kg/day
Reporting group description:	
0.2 mL/kg/day clopidogrel reconstituted solution at 1 mg/mL once daily.	

Reporting group values	Placebo	Clopidogrel 0.2 mg/kg/day	Total
Number of subjects	23	26	49
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: days			
arithmetic mean	368.1	368	
standard deviation	± 4.2	± 2.7	-
Gender categorical Units: Subjects			
Female	10	14	24
Male	13	12	25
Shunt on Cardiopulmonary Bypass Units: Subjects			
Yes	2	5	7
No	21	21	42
Type of Initial Shunt Palliation Units: Subjects			
Modified Blalock Taussig Shunt with Norwood	0	1	1
Modified Blalock Taussig Shunt without Norwood	18	20	38
Sano procedure with Norwood	0	0	0
Sano procedure without Norwood	1	1	2
Central Shunt	1	3	4
Stent of Ductus Arteriosus	3	1	4

Weight			
Units: kilograms (kg)			
arithmetic mean	7.9	8.1	
standard deviation	± 1.1	± 1.2	-
Height			
Units: centimetres (cm)			
arithmetic mean	71.8	70	
standard deviation	± 2.8	± 10.4	-
Age at Shunt Palliation			
Units: days			
arithmetic mean	25.7	13.7	
standard deviation	± 28.7	± 12.7	-

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
0.2 mL/kg/day matching placebo solution once daily.	
Reporting group title	Clopidogrel 0.2 mg/kg/day
Reporting group description:	
0.2 mL/kg/day clopidogrel reconstituted solution at 1 mg/mL once daily.	

Primary: Number of Subjects With Bleeding Events

End point title	Number of Subjects With Bleeding Events[1]

End point description:

All bleeding events experienced during the study period were collected as for any Adverse Event.

The 'on-treatment' period was defined as the period from inclusion in the extension study up to 28 days after treatment discontinuation, and subjects who experienced bleeding events during that period were counted. The analysis was performed on the Intent-to-treat (ITT) population that consisted of all included subjects. Subjects were analyzed in the treatment arm allocated at randomization into the CLARINET study.

End point type	Primary

End point timeframe:

Up to a maximum of 6 months

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Analysis for this end point were descriptive.

End point values	Placebo	Clopidogrel 0.2 mg/kg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	26		
Units: subjects				
Any bleeding event	0	2		
Serious	0	0		
Serious with an Outcome of Death	0	0		
Leading to Permanent Treatment Discontinuation	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects According to Bleeding Type/Etiology

End point title	Number of Subjects According to Bleeding Type/Etiology[2]

End point description:

For all reported bleeding events, the type and the etiology of the bleeding event were collected. Subjects who experienced bleeding events during the 'on-treatment period' were counted by bleeding type and etiology. Analysis was performed on ITT population.

End point type	Primary

End point timeframe:

Up to a maximum of 6 months

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Analysis for this end point were descriptive.

End point values	Placebo	Clopidogrel 0.2 mg/kg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	26		
Units: Subjects				
Spontaneous	0	1		
Puncture (vascular access site)	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Shunt Thrombosis Requiring Intervention or Deaths

End point title	Number of Subjects With Shunt Thrombosis Requiring Intervention or Deaths

End point description:

Outcome events, shunt thrombosis requiring intervention or death, experienced during the study period were recorded.

Subjects were counted excluding the events that occured after the subject's protocol study end (occurrence of shunt thrombosis, next surgical procedure for correction of the congenital heart disease, death, or 18 months of age, whichever came first). Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

Up to a maximum of 6 months

End point values	Placebo	Clopidogrel 0.2 mg/kg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	26		
Units: subjects				
Shunt Thrombosis Requiring Intervention	0	0		
Death	1	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All Adverse Events (AE) were collected from signature of the informed consent form up to the final visit (up to maximum of Month 6) regardless of seriousness or relationship to investigational product.

Adverse event reporting additional description:

Reported adverse events are treatment-emergent adverse events that is AEs that developed/worsened during the 'on treatment period' (on-treatment period is the time from the inclusion date in the study up to 28 days after the last dose of study medication).

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	13.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

0.2 mL/kg/day matching placebo solution once daily.

Reporting group title	Clopidogrel 0.2 mg/kg/day

Reporting group description:

0.2 mL/kg/day clopidogrel reconstituted solution at 1 mg/mL once daily.

Serious adverse events	Placebo	Clopidogrel 0.2 mg/kg/day	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 23 (13.04%)	6 / 26 (23.08%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
Low Cardiac Output Syndrome			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 23 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nodal Arrhythmia			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 23 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Ischaemic Stroke			

alternative assessment type: Systematic			
subjects affected / exposed	1 / 23 (4.35%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 23 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Diaphragmatic Paralysis			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 23 (4.35%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Artery Stenosis			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 23 (4.35%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchiolitis			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 23 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Croup Infectious			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 23 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			

alternative assessment type: Systematic			
subjects affected / exposed	0 / 23 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Tract Infection			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 23 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral Infection			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 23 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	Clopidogrel 0.2 mg/kg/day	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 23 (26.09%)	14 / 26 (53.85%)	
General disorders and administration site conditions			
Pyrexia			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 23 (0.00%)	3 / 26 (11.54%)	
occurrences (all)	0	3	
Gastrointestinal disorders			
Diarrhoea			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 23 (4.35%)	3 / 26 (11.54%)	
occurrences (all)	1	3	
Respiratory, thoracic and mediastinal disorders			
Cough			
alternative assessment type: Systematic			

subjects affected / exposed	0 / 23 (0.00%)	3 / 26 (11.54%)	
occurrences (all)	0	3	
Infections and infestations			
Ear Infection			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 23 (0.00%)	2 / 26 (7.69%)	
occurrences (all)	0	2	
Gastroenteritis			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 23 (8.70%)	2 / 26 (7.69%)	
occurrences (all)	2	2	
Lower Respiratory Tract Infection			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 23 (0.00%)	2 / 26 (7.69%)	
occurrences (all)	0	2	
Nasopharyngitis			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 23 (8.70%)	1 / 26 (3.85%)	
occurrences (all)	2	1	
Pharyngitis			
alternative assessment type: Systematic			
subjects affected / exposed	3 / 23 (13.04%)	1 / 26 (3.85%)	
occurrences (all)	3	1	
Upper Respiratory Tract Infection			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 23 (0.00%)	6 / 26 (23.08%)	
occurrences (all)	0	6	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported