# 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 | v2 (current) |
| This version publication date | 03 May 2016 |
| First version publication date | 20 December 2014 |
| Version creation reason | • New data added to full data set<br>Minor correction to non-serious adverse events data (number of occurrences) |

## 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<br>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<br>Units: days | | | |
| arithmetic mean | 368.1 | 368 | |
| standard deviation | ± 4.2 | ± 2.7 | - |
| Gender categorical<br>Units: Subjects | | | |
| Female | 10 | 14 | 24 |
| Male | 13 | 12 | 25 |
| Shunt on Cardiopulmonary Bypass<br>Units: Subjects | | | |
| Yes | 2 | 5 | 7 |
| No | 21 | 21 | 42 |
| Type of Initial Shunt Palliation<br>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 | Systematic |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 13.0 |

### Reporting groups

| | |
|---|---|
| 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 title | Placebo |

Reporting group description:

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

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

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

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 26 (3.85%) | 0 / 23 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Viral Infection | | | |
| subjects affected / exposed | 1 / 26 (3.85%) | 0 / 23 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 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 0.2 mg/kg/day | Placebo | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 14 / 26 (53.85%) | 6 / 23 (26.09%) | |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 3 / 26 (11.54%) | 0 / 23 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 3 / 26 (11.54%) | 1 / 23 (4.35%) | |
| occurrences (all) | 3 | 1 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 3 / 26 (11.54%) | 0 / 23 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Infections and infestations | | | |
| Ear Infection | | | |
| subjects affected / exposed | 2 / 26 (7.69%) | 0 / 23 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Gastroenteritis | | | |
| subjects affected / exposed | 2 / 26 (7.69%) | 2 / 23 (8.70%) | |
| occurrences (all) | 2 | 2 | |
| Lower Respiratory Tract Infection | | | |
| subjects affected / exposed | 2 / 26 (7.69%) | 0 / 23 (0.00%) | |
| occurrences (all) | 2 | 0 | |

| | | | |
|---|---|---|---|
| Nasopharyngitis | | | |
| subjects affected / exposed | 1 / 26 (3.85%) | 2 / 23 (8.70%) | |
| occurrences (all) | 1 | 2 | |
| Pharyngitis | | | |
| subjects affected / exposed | 1 / 26 (3.85%) | 3 / 23 (13.04%) | |
| occurrences (all) | 1 | 4 | |
| Upper Respiratory Tract Infection | | | |
| subjects affected / exposed | 6 / 26 (23.08%) | 0 / 23 (0.00%) | |
| occurrences (all) | 9 | 0 | |

## 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