International randomized double blind clinical study evaluating the efficacy and safety of clopidogrel 0.2mg/kg once daily versus placebo in neonates and infants with cyanotic congenital heart disease palliated with a systemic-to-pulmonary artery shunt (e.g. modified Blalock Taussig shunt)

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Primary:To evaluate the efficacy of 0.2 mg/kg/day of clopidogrel versus placebo for the reduction of all-cause mortality and shunt-related morbidity in neonates or infants with cyanotic congenital heart disease palliated with a systemic-to-pulmonary…

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Congenital cardiac disorders
Study type	Interventional

Summary

ID

NL-OMON30679

Source
ToetsingOnline

Brief title
CLARINET

Condition

- Congenital cardiac disorders
- Cardiac and vascular disorders congenital

Synonym
cyanotic congenital heart disease

Research involving
Human

Sponsors and support

Primary sponsor: Bristol-Myers Squibb
Source(s) of monetary or material Support: Pharmaceutical Industry

Intervention

Keyword: clopidogrel, infants, neonates, systemic-to-pulmonary artery shunt

Outcome measures

Primary outcome

PRIMARY ENDPOINT

The primary efficacy criterion is the first occurrence of any component of the

primary composite endpoint of:

- any death or

- shunt thrombosis requiring intervention or

- hospitalization for bi-directional Glenn procedure or any cardiac related

intervention prior to 120 days of age following an event or a shunt narrowing

considered of thrombotic nature

Secondary outcome

SAFETY

Evaluation for safety includes the incidence of adverse events and serious

adverse events including bleeding

Study description

Background summary

There is no consistent approach in preventing complications after systemic-to-pulmonary artery shunts. Initial treatment with unfractionated Heparin followed by ASA (1 to 10 mg/kg/d) is sometimes used. Children who develop shunt occlusion usually require further intervention, including thrombolytic therapy and/or stenting or surgical revision.

Although the therapeutic benefit of ASA as an antiplatelet drug has never been formally evaluated in children, it is common practice in some centers to use this drug in systemic-to-pulmonary artery shunt patients. The registry previously discussed, also showed that despite lack of evidence to support ASA efficacy, aspirin was used in 80% of the cases in this series of 1004 patients, at doses from less than 20 mg to more than 40 mg, and appeared to be associated with a lower risk of death after all of these palliative procedures, whatever the specific underlying cyanotic disease or the shunt type (1)

Nevertheless, chronic use of ASA cannot be mandated given the absence of formal demonstration of its efficacy and clinical benefit. Therefore, in the absence of any standardized anticoagulation or antiplatelet regimen for patients having systemic-to-pulmonary artery shunts, clinical trials with such drugs are warranted in this
high-risk patient population.

The potential that clopidogrel treatment could fulfill an unmet medical need in patients with a BTS or any systemic-to-pulmonary artery shunt led to a clinical development program that was established and initiated under the rules described in a formal Written Request from the United States Food and Drug Administration (FDA).

The current study (CLARINET) is a prospective, multinational, randomized, double-blind, placebo-controlled, two parallel group clinical study to determine efficacy and safety of 0.2mg/kg/day of clopidogrel in neonates or infants with cyanotic congenital heart disease palliated with a systemic-to-pulmonary artery shunt. Neonates (age less than or equal to 30 days at the time of randomization) or infants (age less than or equal to 92 days at the time of randomization) will be randomized to clopidogrel or placebo as early as possible after shunt placement and followed up to the earliest of shunt thrombosis or next surgical procedure for correction of the congenital heart disease, or death, or 1 year (365 days) of age, or common study end-date (CSED) defined as a date when it is projected that 174 primary events will have occurred.

(1) Li JS, Berezny KB, Yow E: Influence of aspirin use on mortality in infants

with cyanotic congenital heart disease palliated with a systemic-to-pulmonary artery shunt: a multicenter, international registry. Abstract AHA 2005.

Study objective

Primary:
To evaluate the efficacy of 0.2 mg/kg/day of clopidogrel versus placebo for the reduction of all-cause mortality and shunt-related morbidity in neonates or infants with cyanotic congenital heart disease palliated with a systemic-to-pulmonary artery shunt.

Secondary:
To assess the safety of clopidogrel in the study population.

Study design

Prospective, multinational, randomized, double-blind, placebo-controlled, two parallel group clinical study.
It is expected to enroll 490 patients in 130 sites worldwide to reach 174 events.

Intervention

Patients will be randomized to either clopidogrel 0.2 mg/kg or placebo.
Patients may receive concomitant background therapy, with or without acetyl salicylic acid (ASA), as per usual practice at each site.

Study burden and risks

Medical office visits for efficacy and safety assessment are scheduled at baseline and at 4 weeks, 12 weeks, 24 weeks, 36 weeks and at final visit.

Final visit is defined as the earliest of shunt thrombosis or next surgical procedure for correction of the congenital heart disease, or death, or 1 year (365 days) of age, or common study end-date (CSED) defined as a date when it is projected that 174 primary events will have occurred.

Contacts (at minimum by telephone) are scheduled every 2 weeks until 12 weeks visit and every 4 weeks thereafter for adjustment of the study drug dose to be administered with respect to patient's weight.

Contacts

Public

Bristol-Myers Squibb

Vijzelmolenlaan 9
3447 GX Woerden
NL
Scientific
Bristol-Myers Squibb

Vijzelmolenlaan 9
3447 GX Woerden
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Children (2-11 years)

Inclusion criteria

1. Neonate or infant (age less than or equal to 92 days at the time of randomization) with cyanotic congenital heart disease;2. Treated by any palliative systemic-to-pulmonary artery shunt (closed shunt or open shunt, Norwood, Sano, stent of ductus arteriosus).;3. Signed informed consent obtained from patient's legally acceptable representative (parents for guardians) according to local regulations.

Exclusion criteria

1. Active bleeding, increased risk of bleeding (bleeding disorders [e.g., hemophilia, von Willebrand disease], arterio-venous malformations, aneurysms) or previous intracranial (Grades II-IV) or life-threatening hemorrhage;2. Allergy to 2 or more classes of drug;3. Current treatment with thienopyridine (open label clopidogrel or ticlopidine), dipyridamole or oral anticoagulant;4. Adjusted gestational age less than 34 weeks;5. Unable to receive study drug orally or enterically;6. Concurrent use of another experimental drug/device or participation in another investigational drug or device trial within the last 30 days, except if the study involves an FDA approved drug/device;7. Current clinically significant or persistent

thrombocytopenia, neutropenia, severe hepatic or renal failure (i.e. more than 2.5 times the upper limit for age of hepatic enzymes or creatinine);8. Inability to follow the study procedure.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	16-08-2007
Enrollment:	6
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Plavix
Generic name:	Clopidogrel
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	28-12-2006
Application type:	First submission

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-04-2007
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	06-08-2007
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	27-08-2007
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	05-10-2007
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-10-2008
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	25-08-2009
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-09-2009
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2006-000946-38-NL
CCMO	NL14751.078.06