Multicenter, double-blind, placebo-controlled, randomized, prospective study of bosentan as adjunctive therapy to inhaled nitric oxide in the management of persistent pulmonary hypertension of the newborn (PPHN)

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To assess the efficacy of bosentan in neonates with persistent pulmonary hypertension of the newborn (PPHN) who are in need of continued inhaled nitric oxide (iNO) after at least 4 hours of continuous iNO treatment and to evaluate the...

Ethical review	Not approved
Status	Will not start
Health condition type	Cardiac and vascular disorders congenital
Study type	Interventional

Summary

ID

NL-OMON35761

Source
ToetsingOnline

Brief title
FUTURE 4

Condition

- Cardiac and vascular disorders congenital
- Pulmonary vascular disorders

Synonym
high blood pressure in the lungs in neonates, PPHN

Research involving
Human

Sponsors and support

Primary sponsor: Actelion Pharmaceuticals
Source(s) of monetary or material Support: Actelion Pharmaceuticals Ltd.

Intervention

Keyword: Bosentan, Efficacy, Neonates, PPHN

Outcome measures

Primary outcome

Exploratory efficacy endpoints:

* Proportion of patients with treatment failure:

- Need for extra corporeal membrane oxygenation (ECMO) or

- Initiation of alternative pulmonary vasodilator

* Time to complete weaning from iNO

* Time to weaning from mechanical ventilation

* Proportion of patients requiring re-initiation of iNO therapy

* Change from baseline to 3, 5, 12, and 24 hours following the first drug

administration and thereafter daily until end of study treatment for:

- Oxygenation index

- Arterial blood gas values (pH, SaO2, PaO2, PaCO2)

- Pulse oximetry (SpO2)

* Pulmonary hypertension (assessed by echocardiography)

Change from baseline to 24 hours and end of study treatment in:

* Extra-pulmonary shunting of blood at the PFO or PDA (if present)

* Estimated RVSP/systemic arterial pressure ratio by TRJV or by gradient across PDA or across septal defects (if present)

* RV dilation and interventricular septal movement pattern

In order to interpret the exploratory efficacy data, the following information at 3, 5, 12, and 24 hours following the first drug administration, then daily until EOS will be collected:

- If on mechanical ventilation: mean airway pressure, PEEP (positive end-expiratory pressure), PIP (peak inspiratory pressure), rate, and tidal volume or,

- If on high frequency oscillatory ventilation: mean airway pressure, frequency, and amplitude

Secondary outcome

TOLERABILITY / SAFETY ENDPOINTS:

Treatment-emergent adverse events (AEs) and SAEs

* AEs leading to premature discontinuation of study drug

* Change from baseline in vital signs during the treatment period

* Treatment-emergent electrocardiogram (ECG) abnormalities reported as AE

* Treatment-emergent laboratory abnormalities

* Incidence of treatment-emergent ALT or AST > 3 × ULN

* Incidence of treatment-emergent severe intracranial hemorrhage (grade III or IV), periventricular leukomalacia, and ventriculomegaly

Treatment emergent AEs and SAEs are those for which onset occurs from 1st dosing with double-blind treatment and up to 7 days after last double-blind treatment administration.

PHARMACOKINETIC ENDPOINTS:

All PK endpoints will be evaluated based on concentrations measured in dried blood spot samples.

The following endpoints will be derived by non-compartmental analysis of concentration-time profiles obtained on Day 1 and on Day 5 of bosentan treatment, if applicable.

o Cmax and tmax (Days 1 and 5), AUC0-12h (Day 1), AUC0-* (Day 5), and AUC0-24h (Days 1 and 5) for bosentan and its metabolites (Ro 48-5033, Ro 47-8634, Ro 64-1056) following administration of bosentan.

o For those subjects whose PK assessments will be performed on Days 1 and 5, the accumulation index, defined as the ratio between AUC0-* (Day 5) and AUC0-12h (Day 1) will be calculated.

Study description

Background summary

Persistent pulmonary hypertension of the newborn (PPHN) is an uncommon and life-threatening disease that occurs in 2 out of 1,000 live births and that causes severe breathing difficulties. Before birth, infants get his/her oxygen from the mother. After birth, changes occur that will allow blood to reach the

baby's lungs where it gets a fresh supply of oxygen. Because these changes fail in babies with PPHN, the blood carries less oxygen and the baby suffers from breathing difficulties that can lead to suffocation and death.
The standard treatment for PPHN is to improve oxygenation using breathing assistance (mechanical ventilation) and increasing the proportion of oxygen in the inhaled air. A gas called nitric oxide (NO) is also added to the air inhaled by the baby. This gas is the only treatment currently approved by health authorities to treat babies suffering from PPHN. It helps by dilating the small blood vessels in the lungs which results in better oxygenation of blood within a few hours of treatment. However, a significant number of babies do not respond well to this treatment or remain dependent on it and this appears to be the case for the baby.
Tracleer (bosentan) is a drug that reduces the unwanted effects of a hormone (a chemical messenger in the body) called endothelin. There is an increased amount of endothelin in the blood of patients with pulmonary arterial hypertension (PAH) which contributes to the narrowing of the small blood vessels in the lungs. Taking bosentan blocks the effect of endothelin and improves the flow of blood in the lungs and the rest of the body. This helps to make patients breathing easier.
Tracleer (bosentan) is approved in over 30 countries for the treatment of moderate to severe PAH.
To date, the potential effects of bosentan in babies with PPHN have not been studied. As in PAH patients, there is an increased amount of endothelin in the blood of babies with PPHN which contributes to the narrowing of small blood vessels in the lungs. Some of the mechanisms involved in PPHN are the same as in PAH. Bosentan could help to make breathing easier in babies with PPHN. Few cases of babies with PPHN have been reported to be successfully treated with bosentan; nevertheless this still needs to be confirmed in a controlled clinical trial.
The main purpose of this study is to evaluate the efficacy and safety of bosentan in babies with PPHN and for whom standard treatment with inhaled NO (iNO) is not satisfactory.

Study objective

To assess the efficacy of bosentan in neonates with persistent pulmonary hypertension of the newborn (PPHN) who are in need of continued inhaled nitric oxide (iNO) after at least 4 hours of continuous iNO treatment and to evaluate the pharmacokinetics (PK), tolerability, and safety of bosentan in this patient population.

Study design

Exploratory, multicenter, double-blind, randomized, placebo-controlled, parallel-group, phase 3 study.
An interim pharmacokinetic (PK) and safety analysis will be performed on the

first six PK evaluable patients in order to amend the dose if necessary.

Intervention

Formulation: dispersible and quadrisectible 32 mg tablet of bosentan or matching placebo.
Route: nasogastric or orogastric tube, according to site standard practice.
Dose 2 mg/kg of weight at birth twice daily (b.i.d.) Dose could be changed depending on the results of the interim PK and safety analysis.
Randomization 2:1. 20 patients receive bosentan, 10 placebo

Study burden and risks

RISKS
The study medication and procedures have risks and discomforts: as in any clinical research study there is a possibility of experiencing side effects to the study medication or procedures. Bosentan can have side effects even when used as directed.
Bosentan has never been used in newborns in a controlled trial and therefore very limited information is available regarding safety of bosentan in newborns.
In animals, a preclinical study in rat newborns has recently evaluated bosentan effects on development (growth and organ maturation), behavior (hearing, movement capacity, learning, and memory), fertility, and histology (microscopic analysis of organs). This study established that bosentan had no observable side effects at daily doses that are close to 4 times higher than the dose used in this study.
In humans, few cases of bosentan use in newborns with PPHN have been published, three of them reported no side effect, and one had mild systemic hypotension (slightly low blood pressure) shortly after bosentan administration which has been quickly corrected without treatment interruption. Over 9 years of post-marketing experience, Actelion's safety department has been informed of 1 case of side effect reported to be related to bosentan use in newborns. The newborn was reported to have mild abnormal liver function which resolved 2 days after bosentan discontinuation.
The side effects collected from 20 placebo-controlled studies in teenagers and adults treated with bosentan are described in the table below. They are ranked according to their frequency using the following convention: very common (affects more than 1 patient in 10); common (affects 1-10 patients in 100); uncommon (affects 1-10 patients in 1,000); rare (affects 1-10 patients in 10,000).
Very common Headache
Very common Abnormal liver function blood test
Very common Oedema, fluid retention (swelling of the legs and ankles)
Common Anemia*, hemoglobin decrease
Common Allergic reactions (including skin inflammation, itching and rash)
Common Syncope (fainting)

Common Palpitations
Common Flushing
Common Low blood pressure
Common Diarrhea
Common Skin redness
Uncommon Thrombocytopenia (low number of blood platelets)
Uncommon Neutropenia, leukopenia (low number of white blood cells)
Uncommon Aminotransferase elevations associated with hepatitis and/or jaundice (yellowing of the skin or the whites of the eyes)
Rare Anaphylaxis (generally allergic reaction) and/or angioedema (swelling, most commonly around the eyes, lips, tongue or throat)
Rare Liver cirrhosis (scarring of the liver), liver failure (serious disturbance of liver function)
* Sometimes requiring transfusion
The study will be conducted during the baby's stay in the hospital intensive care unit where the investigators and other medical staff will pay the greatest attention to any unusual effects throughout the treatment period.
It is possible that complications and side effects of study drug, which are still unknown at this time, may occur. The ethics committees and health authorities will be informed about any new findings on bosentan.

FERTILITY IN MALES
Compounds of the same class as bosentan have been linked to the development of testicular injury and sterility in rats when used at very high doses for a long period of time. A recent study with bosentan administered for 70 days to rat newborns did not show any testicular injury at daily doses close to 4 times the dose that is used in this study. In this study, very high doses of bosentan (> 10 times and > 33 times the study dose) have been associated with a decrease in testis weight and sperm number but without microscopic alterations of testis and sperm quality.
It is not known whether testicular injury can occur with bosentan in humans when the dose and length of exposure is much less than the test doses used in rats. To date, there was no confirmed report of fertility impairment in men who received bosentan, but this does not rule out the possibility of a risk of a testicular injury.

BENEFITS
There is no guarantee that the patient population will benefit directly from this research. Information obtained during the course of this clinical research study may contribute to a better understanding of the disease and may be useful in selecting medicines for future treatment for PPHN. Regardless of any individual benefit, the knowledge gained from this study may contribute to information that would allow the use of this drug or similar drugs in other newborns with PPHN.

Contacts

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Actelion Pharmaceuticals

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Children (2-11 years)

Inclusion criteria

1. Signed informed consent by the parent(s) or the legal representative(s).
2. Term and near-term newborns (gestational age > 34 weeks).
3. Post natal age * 12 hours and < 7 days.
4. Weight at birth * 2,500 g.
5. Idiopathic PPHN or PPHN due to parenchymal lung disease (e.g., respiratory distress syndrome, meconium aspiration syndrome, pneumonia, sepsis without multi-organ failure).
6. Pulmonary hypertension (PH) confirmed by echocardiography:
a) Predominant extrapulmonary right-to-left or bidirectional shunting of blood at a patent foramen ovale (PFO) or patent ductus arteriosus (PDA) or
b) Estimated right ventricular systolic pressure (RVSP) > 2/3 of systemic arterial pressure by tricuspid regurgitant jet velocity (TRJV) or by gradient across septal defect (if present) or
c) Marked right ventricular (RV) dilation and paradoxical shift of interventricular septum.
7. Need for continued iNO at a dose > 10 ppm after at least 4h of continuous iNO treatment.

8. Last two consecutive oxygenation index (OI) values prior to randomization * 15.
9. Mechanical ventilation with fraction of inspired oxygen (FiO2) * 50%.

Exclusion criteria

1. Pulmonary Hypertension associated with conditions other than PPHN.
2. Immediate need for cardiac resuscitation or extracorporeal membrane oxygenation (ECMO) (profound hypoxemia [PaO2] < 30 mm Hg; OI > 40).
3. Lethal congenital anomalies.
4. Congenital diaphragmatic hernia.
5. Significant congenital heart disease or significant left to right shunt.
6. Pneumothorax.
7. Active seizures.
8. Expected duration of mechanical ventilation of less than 48 hours.
9. Mean systemic blood pressure < 35 mmHg despite therapy with volume infusions and cardiotonic support.
10. Hepatic failure or all conditions with aspartate aminotransferase (AST) or alanine aminotransferase (ALT) values > 2 × upper limit of normal (ULN).
11. Renal function impairment such as serum creatinine > 3 × ULN or anuria.
12. Known intracranial hemorrhage grade III or IV.
13. Hemoglobin or hematocrit level < 75% of the lower limit of normal (LLN).
14. Thrombocytopenia (platelet count < 50,000 cells /*L).
15. Leukopenia (white blood cells [WBC] < 2,500 cells/ *L).
16. Any condition precluding the use of a nasogastric/orogastric tube.
17. Administration of prohibited medication prior to randomization.

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:	Will not start
Enrollment:	10
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	placebo
Generic name:	placebo
Product type:	Medicine
Brand name:	Tracleer
Generic name:	Bosentan
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	04-08-2011
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Not approved

Date:	17-01-2012
Application type:	First submission
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	EUCTR2011-000203-41-NL
CCMO	NL37236.078.11