Pediatric Formulation of bosentan in pulmonary arterial hypertension.

No registrations found.

Ethical review	Not applicable
Status	Pending
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON20918

Source
NTR

Brief title
FUTURE 4

Health condition

Persistent pulmonary arterial hypertension
PPHN
bosentan
pediatrics
persisterende pulmonale arteriële hypertensie
pasgeborene

Sponsors and support

Primary sponsor: ACTELION Pharmaceuticals Ltd
Gewerbestrasse 16
CH-4123 Allschwil
Switzerland
Source(s) of monetary or material Support: fund = initiator = sponsor

Intervention

Outcome measures

Primary outcome

To assess the efficacy of bosentan in neonates with PPHN who are in need of continued inhaled iNO after at least 4 hours of continuous iNO treatment and to evaluate the PK, tolerability, and safety of bosentan in this patient population.

Secondary outcome

Exploratory efficacy endpoints:

1. Proportion of patients with treatment failure:

A. Need for extra corporeal membrane oxygenation (ECMO) or;

B. Initiation of alternative pulmonary vasodilator.

2. Time to complete weaning from iNO;

3. Time to weaning from mechanical ventilation;

4. Proportion of patients requiring re-initiation of iNO therapy;

5. Change from baseline to 3, 5, 12, and 24 hours following the first drug administration and thereafter daily until end of study treatment for:

A. Oxygenation index;

B. Arterial blood gas values (pH, SaO_2, PaO_2, $PaCO_2$);

C. Pulse oximetry (SpO_2).

6. Pulmonary hypertension (assessed by echocardiography).

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

1. Extra-pulmonary shunting of blood at the PFO or PDA (if present);

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

3. 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:

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

2. If on high frequency oscillatory ventilation: Mean airway pressure, frequency, and amplitude.

Tolerability/safety endpoints:

Treatment-emergent adverse events (AEs) and SAEs:

1. AEs leading to premature discontinuation of study drug;

2. Change from baseline in vital signs during the treatment period;

3. Treatment-emergent electrocardiogram (ECG) abnormalities reported as AE;

4. Treatment-emergent laboratory abnormalities;

5. Incidence of treatment-emergent ALT or AST > 3 × ULN;

6. 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:

1. Cmax and tmax (Days 1 and 5), AUC0-12h (Day 1), AUC0-τ (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;

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

Study description

Background summary

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 objective

No formal hypothesis is set in this study. The sample size is based on feasibility considerations.

Study design

The maximum duration of the study for an individual patient is up to 28 days from screening to end of study (EOS).

Screening period:

1. From PPHN diagnosis to randomization (maximum 7 days).

Double-blind treatment period:

1. Up to treatment failure, or;

2. Up to successful weaning from iNO, or;

3. Up to a maximum of 14 days of study drug treatment.

End of Study (EOS):

1. End of Treatment + 7 days.

Follow-up period:

1. From EOS to 60 days after last double-blind treatment administration (phone call to document any serious adverse events [SAEs]).

Intervention

Bosentan (2 mg/kg body weight b.i.d.) or placebo. Treatment allocation is designed to occur in a 2:1 ratio (active treatment to placebo, respectively).

Route: Nasogastric or orogastric tube.

Contacts

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Eligibility criteria

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 more or equal to 12 hours and < 7 days;

4. Weight at birth more or equal to 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 more or equal to 15;

9. Mechanical ventilation with fraction of inspired oxygen (FiO2) more or equal to 50%.

Exclusion criteria

1. PH 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 times upper limit of normal (ULN);

11. Renal function impairment such as serum creatinine > 3 times 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 /microL);

15. Leukopenia (white blood cells [WBC] < 2,500 cells/ microL);

16. Any condition precluding the use of a nasogastric/orogastric tube;

17. Administration of prohibited medication prior to randomization.

Study design

Design

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-09-2011
Enrollment:	30
Type:	Anticipated

Ethics review

Not applicable

Application type:	Not applicable

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
NTR-new	NL2792
NTR-old	NTR2932
Other	Actelion Pharmaceuticals Ltd / EudraCT : AC-052-391 / 2011-000203-41;
ISRCTN	ISRCTN wordt niet meer aangevraagd.

Study results

Summary results
N/A