A prospective, multicenter, open-label extension of FUTURE 3 to assess the safety, tolerability and efficacy of the pediatric formulation of bosentan two versus three times a day in children with pulmonary arterial hypertension

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To evaluate the long-term safety, tolerability and efficacy of the pediatric formulation of bosentan two versus three times a day in children with pulmonary arterial hypertension (PAH).

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Cardiac and vascular disorders congenital
Study type	Interventional

Summary

ID

NL-OMON36321

Source
ToetsingOnline

Brief title
FUTURE 3 study extension

Condition

- Cardiac and vascular disorders congenital
- Pulmonary vascular disorders

Synonym
high bloodpressure in the lungs, PH

Research involving
Human

Sponsors and support

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

Intervention

Keyword: b.i.d. versus t.i.d., PAH, Pediatric, Study extension

Outcome measures

Primary outcome

No primary endpoint was defined in this study

Secondary outcome

Exploratory efficacy endpoints

- Change from baseline to end of study in WHO functional class

- Time to death, lung transplantation or hospitalization for PAH-Progression

- Time to death, lung transplantation, hospitalization for PAH-progression or initiation of new therapy for PAH or new/worsening right heart failure.

- Changes from baseline to 3, 6, 9, 12, 15 and 18 months of treatment over AC 052 373 and AC-052-374 in Global Clinical Impression scale assessed by the physician and parents.

Safety and tolerability endpoints

- Treatment-emergent AEs and serious adverse events (SAEs) up to 7 days after permanent discontinuation of study drug

- Adverse events leading to premature discontinuation of study drug

- Serious adverse events from 7 up to 60 days after permanent discontinuation

of study drug

- Changes from baseline to end of study in vital signs, body weight, and

height/length

- Treatment-emergent marked laboratory abnormalities up to end of study

Study description

Background summary

Pulmonary arterial hypertension (PAH) is a rare and progressive disease associated with high morbidity and mortality.
PAH is a disease of the pulmonary arteries characterized by vasoconstriction, vascular proliferation and remodelling,
and thrombosis in situ. It results in a progressive increase of pulmonary artery pressure, pulmonary vascular
resistance, and ultimately right ventricular failure and death. The definition of PAH in adults and children is the same: a
mean pulmonary artery pressure > 25 mmHg at rest or > 30 mmHg during exercise, with normal pulmonary artery
wedge pressure smaller or equal to 15 mmHg and pulmonary vascular resistance >3 Wood units.m2. Despite recent
major improvements in symptomatic treatments, no current pharmacological treatment cures PAH. However, during the
past 20 years, several drugs with potent vasodilatory effects on the pulmonary vasculature have been approved for the
treatment of PAH in adults. In adults and adolescents, epoprostenol, sildenafil and bosentan have been shown to
improve quality of life, exercise capacity, hemodynamics, and clinical outcomes in
patients with PAH.

In patients younger than 12 years, the efficacy, tolerability, and safety of these drugs are less well documented.
Although the approved drugs in adults are being used in younger patients, only bosentan has been formally approved
for the treatment of PAH in children: the European Commission has approved dispersible 32 mg tablets for use in children above 2 years of age.

Study objective

To evaluate the long-term safety, tolerability and efficacy of the pediatric

formulation of bosentan two versus three times a day in children with pulmonary arterial hypertension (PAH).

Study design

This is a prospective, multicenter, multinational, open-label, double-arm exploratory Phase 3 extension study enrolling those patients who completed the FUTURE 3 core study (AC 052-373). It is designed to evaluate the long-term tolerability and safety of bosentan using the pediatric formulation in children with idiopathic or heritable PAH or PAH persisting after complete repair of a congenital heart defect.

Patients will receive the bosentan pediatric formulation. The bosentan dosage will be adjusted to the patient*s body weight during the study to achieve a maintenance dose of 2 mg/kg either b.i.d. or t.i.d. Patients will receive the maintenance dose (2 mg/kg either b.i.d. or t.i.d.) of bosentan using the pediatric formulation for the entire duration of the study.

The maximum number of participants corresponds to the number of patients treated in the FUTURE 3 core study (AC-052-373).
The study will be conducted at expert pediatric PAH centers in Europe, US, Latin America, Australia and Asia.

The study will consist of a treatment period and a post-treatment follow-up period of 60 days.
The treatment period in FUTURE 3 Study Extension will last for 12 months or until:
• The investigator or the patient decides to discontinue the study treatment permanently
• the sponsor decides not to pursue the development of the pediatric formulation of bosentan.

No interim analysis is planned.

Intervention

Bosentan dispersible tablet (32 mg) in the dosage of 2 mg/kg b.i.d. or 2 mg/kg t.i.d.

Study burden and risks

At screening standard physical examination (including vital parameters, length and weight) and laboratory assessments. Physical examinations are repeated at each visit; laboratory assessements will be done monthly.

Adverse events of bosentan are listed in the Investigator Brochure version 13

(30Aug2010; see also E9).

The conduction of this trial can be justified because PAH is a serious disease which cannot be cured and might lead to
death. A good insight in the long-term safety, tolerability and safety of bosentan in children is very important to come to optimal treatment options for children affected with this disease.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Children (2-11 years)

Inclusion criteria

1. Patients who completed the FUTURE 3 core study (AC 052-373) or prematurely discontinued due to PAH-progression, if bosentan was not permanently discontinued
2. Patients who tolerated bosentan pediatric formulation and for whom bosentan is considered beneficial at the end of the FUTURE 3 core study (AC-052-373)

3. Signed informed consent by the parents or the legal representatives prior to any study-mandated procedure.

Exclusion criteria

1. Known intolerance or hypersensitivity to bosentan or any of the excipients of the dispersible bosentan tablet
2. Any clinically significant laboratory abnormality that precludes continuation of bosentan therapy
3. Pregnancy
4. AST and/or ALT values > 3 times the upper limit of normal range (ULN)
5. Moderate to severe hepatic impairment, i.e., Child-Pugh Class B or C
6. Premature and permanent study drug discontinuation during the FUTURE 3 core study (AC-052-373)
7. Any major violation of the FUTURE 3 core study (AC-052-373) protocol.

Study design

Design

Study phase:	3
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	09-11-2011
Enrollment:	4
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Tracleer

Generic name:	Bosentan
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	24-02-2011
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	09-11-2011
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	15-12-2011
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	21-06-2012
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	03-08-2012
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	21-12-2012
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	EUCTR2010-021793-12-NL
CCMO	NL35152.042.11