Proof of Concept Study to Investigate the Efficacy, Haemodynamics and Tolerability of Terguride vs. Placebo in Patients with Pulmonary Arterial Hypertension. Double-blind, randomized, prospective Phase II proof of concept study for 12 weeks of constant treatment with Terguride or placebo. Having finished this proof-of-concept
study it is intended that patients will continuously be treated in an open label extension on a voluntary basis.

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Heart failures
Study type	Interventional

Summary

ID

NL-OMON35522

Source
ToetsingOnline

Brief title
TERPAH

Condition

- Heart failures

Synonym
high pulmonary blood pressure, pulmonary arterial hypertension

Research involving
Human

Sponsors and support

Primary sponsor: ErgoNex Pharma GmbH
Source(s) of monetary or material Support: ErgoNex Pharma GmbH

Intervention

Keyword: Ergonex, Pulmonary Arterial Hypertension, Serotonin-Receptor Antagonist, Terguride

Outcome measures

Primary outcome

Primary endpoint is the investigation into:

Pulmonary vascular resistance at final right heart catheterisation (15 weeks

from initial right heart catheterisation) as objective measure

Benchmark: significant reduction (20% vs. baseline) of pulmonary vascular

resistance

In the open-label extension procedure safety parameters and time to clinical

worsening will be addressed.

Secondary outcome

Secondary endpoints are to evaluate the effects of the treatment regimen on:

1. Time from randomisation to clinical worsening (defined as the combined end point of death, lung transplantation, hospitalisation for pulmonary hypertension, leading to discontinuation or need for additional specific PAH therapy)

2. Change in six minutes walk distance (baseline/ 15. week)

3. Change in Borg Dyspnea Index (baseline/ 15.week)

4. Change in WHO functional class (a modification of the New York Heart Association class; baseline/15. week)

5. Change in cardiac output-index

6. Change in PA pressure

7. Circulating levels of NT-pro-BNP (baseline/ 15. week)

8. Quality of life questionnaire (SF 36, baseline/ 15. week)

9. Adverse events

10. Concomitant medication

Study description

Background summary

Terguride is a high affinity antagonist at the 5-HT2B receptor and non-competitively inhibits the 5-HT2A receptor under physiological conditions. In a rodent model of monocrotaline induced PAH Terguride dose-dependently ameliorated the rise in pulmonary pressure, right heart hypertrophy and the extent of lesion-induced muscularisation of pulmonary arterioles. In the bleomycin mouse model of lung fibrosis Terguride attenuated the increase in collagen deposition as assessed by hydroxyproline determination.

Study objective

The aim of this Phase II proof of concept study is to assess efficacy, haemodynamics and safety of Terguride vs. placebo in patients with pulmonary

arterial hypertension (PAH). Having finished this proof-of-concept study it is intended that patients will continuously be traeted in an open label extension procedure with Terguride (05mg) on a voluntary basis.

Study design

The study is a prospective, randomised, double-blind trial with 3 different treatment phases
- Up-titration over 3 weeks
- 12 weeks treatment on constant dosage (minimal dosage 1,5 mg, max 3 mg per day)
- Down titration over 5 days to 1 week

Having finished this proof-of-concept study it is intended that patients will continuously be traeted in an open label extension procedure with Terguride (05mg) on a voluntary basis. Patients having finished the proof-of-concept study *after Visit 6- will continuously be treated in an open label extension procedure on a voluntary basis. On investigator*s responsibility and on patient*s agreement treatment with the active drug substance Terguride will be continued on sponsor*s expenses starting again with up-titration schedule. The Study Extension will be covered by an insurance. The foreseen duration of the treatment is *up to know- until 31 March 2011 (proof-of-concept study plus open label extension procedure). A seperate informed consent has to be signed by the patients.

Intervention

The patient will undergo several special investigations (Pulmonary Function Test, Diffusion-Limited Carbon Monoxide, ECG, Echocardiogram, Oxygen Saturation, Right Heart Catheterisation (under local anaesthesia), Laboratory Assessments (approx 16 x 14 ml during the full duration of participation) which are part of the clinical routine.

Study burden and risks

Patients may benefit directly from the inhibition of trophic effects of Terguride by ameliorating, stopping or possibly reversing remodelling processes. Possible risks may be the side-effects of Terguride which are already known (nausea, vomiting, dizziness, vertigo, headache, reduction in blood pressure), reactions to the heart catherisation (problems at the puncture site, cardiac dysrhythmias, allergic reactions to the contrast agent), reactions to the skin puncture for blood sampling (bruise, local irritation, local pain or in rare cases, an infection, nerve damage or venous inflammation in the area of the puncture site) and self-sticking ECG electrodes on patients with sensitive skin can lead to itching and redness under the electrodes.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Female and male patients of any racial origin with PAH (WHO classification II-IV)
2. On stable treatment with best supportive care with anticoagulant drugs, diuretics, cardiac glycosides, supplemental oxygen and calcium channels blockers, adjusted to the individual need of the respective patient. Specific PAH mono-therapy (or combination-therapy not exceeding two PAH specific drugs) with either endothelin receptor antagonists or phosphodiesterase type 5 inhibitors or non-parenteral prostanoids (i.e. inhaled, oral, s.c.) is allowed (pre-treated patients) but not mandatory (treatment naive patients). Patients already on PAH specific drugs must be receiving a stable dose of the medication for at least 3 months
3. Having fulfilled his/her 18th birthday on Day 1 of the study but not older than 80 years (up to the patient*s 81st birthday).
4. PAH due to idiopathic pulmonary arterial hypertension or connective tissue disease associated PAH

5. Right heart catheterisation 4 weeks prior to screening or at screening with PAH, specifically PAPm *25 mmHg (at rest), Pulmonary capillary wedge pressure (PCWP) *16 mmHg, pulmonary vascular resistance *500 dyn x sec x cm-5. Echocardiogram at screening consistent with PAH, specifically evidence of right ventricular hypertrophy or dilation, evidence of normal left ventricular function, and absence of mitral valve stenosis
6. Six minutes walk distance above 150 m
7. Receiving conventional PAH therapy, stable for one month.
8. Presentation of negative test results in regard to HIV, Hepatitis C/B, not older than 4 weeks.
9. Able to understand and willing to sign the Informed Consent Form.

Exclusion criteria

1. PAH of any cause other than permitted in the entry criteria
2. Contraindication for heart catheterisation
3. Any change in disease-targeted therapy within the last month before screening
4. Patients requiring intravenous prostanoid therapy within 3 months prior to study start
5. Any subject who had received any investigational medication within 1 month prior to the start of this study or who is scheduled to receive another investigational drug during the course of this study
6. Known intolerance to Terguride
7. Active liver disease, porphyria or elevations of serums transaminases >3 x ULN (upper limit of normal) or bilirubin > 1.5 x ULN
8. History or suspicion of inability to cooperate adequately.
9. Cancer or other malign haematological disease
10. Pulmonary Hypertension caused by left heart disease
11. Pulmonary Arterial Hypertension associated with congenital heart disease (PAH-CHD)
12. Pulmonary Arterial Hypertension associated with human immunodeficiency virus infection (PAH-HIV)
13. Portopulmonary Hypertension (PPHT)
14. CTEPH Chronic Thromboembolic Pulmonary Hypertension
15. Pulmonary Hypertension associated with other diseases excluding aforementioned: PAH due to idiopathic pulmonary arterial hypertension or tissue disease associated PAH, PAH associated with connective tissue disease including systemic sclerosis (sclerodermia) and systemic lupus erythematosus (SLE).
16. Pulmonary Hypertension associated with other chronic lung diseases
17. Additionally, women with child bearing potential must be excluded if:
* They have not used reliable contraception in the cycle before the study. According to CPMP/ICH/286/95 (modification) highly effective methods of birth control (defined by a failure rate < 1% per year) include the consistent and correct use of implants, injectables combined oral contraceptives, selected intrauterine devices (IUD), sexual abstinence or vasectomised partner. The subject has to agree to continue using such highly reliable contraception during the entire study period and the

cycle after the study
* They are pregnant or lactating. (A negative pregnancy test must be provided for all patients)

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	14-04-2008
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	not applicable
Generic name:	Terguride

Ethics review

Approved WMO

Date:	18-10-2007
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO Date:	18-02-2008
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-03-2008
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-12-2008
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-01-2009
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-04-2009
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-09-2009
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-02-2010
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-03-2010
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-04-2010
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	13-04-2010
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-05-2010
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-09-2010
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-10-2010
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-10-2010
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2007-003975-38-NL
CCMO	NL19715.029.07