A Multicenter, Single-arm, Open-label, Phase 3b Study to Assess the Effects of Switching From FlolanÂ® to ACT-385781A in Patients with Pulmonary Arterial Hypertension

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- To evaluate the change in cardiac hemodynamics from baseline to 3-month following switch from Flolan to EFI in patients with PAH.- To evaluate the safety and tolerability of switching from Flolan to EFI in patients with PAH.- To evaluate the...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Pulmonary vascular disorders
Study type	Interventional

Summary

ID

NL-OMON36699

Source
ToetsingOnline

Brief title
EPITOME-2

Condition

- Pulmonary vascular disorders

Synonym
Pulmonary arterial hypertension

Research involving
Human

Sponsors and support

Primary sponsor: Actelion Pharmaceuticals
Source(s) of monetary or material Support: Actelion (zie B7)

Intervention

Keyword: Open label, Pulmonary Arterial Hypertension, Switching From Flolan® to ACT-385781A

Outcome measures

Primary outcome

TOLERABILITY / SAFETY ENDPOINTS

**Treatment-emergent adverse events (AEs) up to 24 hours post-EOT

**Change from baseline to EOT in vital signs [heart rate (HR) and blood

pressure (BP)] and body weight

**AEs leading to premature discontinuation of study drug

**Treatment-emergent serious AEs (SAEs) up to 30 days

post-EOT QUALITY OF LIFE ENDPOINTS

**Change from baseline to EOT in each TSQM-9 domain score

EFFICACY ENDPOINTS

**Change from baseline to EOT in cardiac hemodynamics including:

o Pulmonary vascular resistance (PVR)

o Mean pulmonary arterial pressure (mPAP)

o Right atrial pressure (RAP)

o Pulmonary artery occlusion pressure (PAOP)

o Cardiac index (CI)

**Change from baseline to EOT in:

o 6-minute walk distance (6MWD)

o Borg dyspnea score

o NYHA PAH functional class

o NT-proBNP level

Secondary outcome

Not applicable

Study description

Background summary

1.1 Pulmonary arterial hypertension
Pulmonary arterial hypertension (PAH) is characterized by pulmonary arterial vasoconstriction and vascular remodeling resulting in a progressive increase in pulmonary arterial pressure and pulmonary vascular resistance, ultimately leading to right ventricular failure and death. PAH is defined as a resting mean pulmonary arterial pressure (mPAP) > 25 mm Hg and pulmonary capillary wedge pressure (PCWP) * 15
mm Hg [Badesch 2009]. If left untreated, the prognosis for PAH patients is poor; untreated patients have a median life expectancy of 2.8 years from diagnosis [D*Alonzo 1991]. Currently approved treatments include prostanoids, endothelin receptor antagonists (ERAs), and phosphodiesterase-5 inhibitors (PDE-5). The pathophysiology of PAH involves multiple pathways, which are influenced by many
overlapping secondary messenger systems. Vasoconstriction, obstructive remodeling of the pulmonary vessel wall, inflammation, and thrombosis within the pulmonary arteries are promoted by activation of these pathways, and lead to elevated PAP and PVR, and
eventually right ventricular failure.

1.2 Prostacyclin pathway
Patients with PAH have been shown to have a deficiency of prostacyclin (PGI2; IP) and PGI2 synthase, which led to the hypothesis that targeting the PGI2 pathway with IP receptor agonists could be beneficial. PGI2, a metabolite of arachidonic acid, is produced by both endothelial and smooth muscle cells in the vasculature and is a potent endogenous vasodilator and inhibitor of platelet aggregation and smooth muscle cell

proliferation through its activity at the IP receptor [O*Grady 1980]. Several drugs acting on the IP receptor have already been approved for the treatment of PAH. The first was epoprostenol, approved in 1995 for modified New York Heart Association (NYHA) Functional Class III -IV idiopathic PAH (IPAH) and PAH associated with scleroderma, and shown to improve exercise tolerance and survival in IPAH [Barst 1996]. Approved prostacyclin analogs include: intravenous prostacyclin (epoprostenol sodium or Flolan), subcutaneous, intravenous or inhaled treprostinil sodium (Remodulin®), and inhaled iloprost (Ventavis®).

1.3 ACT-385781A (Epoprostenol for injection, EFI)
ACT-385781A (Epoprostenol for injection, EFI) is a new formulation containing the same active ingredient as Flolan. The new formulation includes the omission of sodium chloride, the substitution of mannitol by sucrose, the substitution of L-glycine by L-arginine, and a higher pH.

Study objective

- To evaluate the change in cardiac hemodynamics from baseline to 3-month following switch from Flolan to EFI in patients with PAH.
- To evaluate the safety and tolerability of switching from Flolan to EFI in patients with PAH.
- To evaluate the change from baseline to 3-month following switch from Flolan to EFI on exercise capacity, NT-proBNP level, Borg dyspnea score and NYHA functional class.
- To evaluate treatment satisfaction and quality of life before and after switch from Flolan to EFI.

Study design

Multicenter, single-arm, open-label, phase 3b study

Intervention

This is a prospective, multicenter, single-arm, open-label, phase 3b study to assess the effects of switching from Flolan to EFI in patients with pulmonary arterial hypertension. Between 25 and 35 patients will be evaluated for 90 days treatment.
The study includes the following consecutive periods which total up to approximately 104 days of study participation:
- Screening period: up to 14 days prior to this study.
- Treatment period: from the switching from Flolan to EFI (Day 1) to the end of study treatment (Day 90 or premature discontinuation).

Study burden and risks

Study drug risks: There is the chance of experiencing side effectsadverse events to the study drug. The adverse events side effects are unknown and have not been studied. However, Epoprostenol for injection (EFI) is expected to have similar risks as Flolan®. For Flolan® the most common adverse events side effects reported to date are flushing, headache, nausea, vomiting, hypotension (low blood pressure), anxiety (nervousness), chest pain, dizziness, bradycardia (slow heartbeat), abdominal pain, musculoskeletal pain, jaw pain, diarrhea, nausea, vomiting, and flu-like symptoms. These adverse events side effects may occur at the medically recommended dose, which is used in this study. It is possible that complications and adverse events side effects of EFI, which are still unknown at this time, may occur.
The transition to EFI will occur simultaneously with the termination of Flolan®. EFI will directly replace Flolan® in the infusion pump and cathetersyringe or cassette in the infusion pump at a time designated by the investigator. The dose of EFI will be the same dose (+-10%) as the most recent one of Flolan®. Patients will be carefully monitored during the transition for signs and symptoms of PAH and vital signs. The patient will remain hospitalized for approximately 48 hours. The patient is discharged after the investigator determines that she/he is clinically stable and appropriately trained on the preparation and administration of EFI.

The dose and infusion rate of EFI may be adjusted throughout the study in order to balance tolerability and maximum clinical benefit. Dose adjustment is dependent on the investigator*s judgment. Patients are evaluated during phone and clinic visits, according to schedule, at which time it assessed whether a dose adjustment is appropriate. The investigator will provide instruction to the patient on when to up- or down-titrate the study medication.

Blood Draw Risks: During the study, patient blood will be drawn twice to perform a variety of tests. The risks of drawing blood include temporary discomfort from the I.V. in patient arm, bruising, swelling at the I.V. site, and in rare instances, infection. Standard care will be taken to avoid these complications.

Right heart catheterization involves placing a thin, flexible tube into the patient vein in their arm, neck or groin which then follows the blood stream inside the heart into their main lung artery, where it can be used to measure their lung artery pressures. X-ray may be used to follow the tube. The procedure is typically more uncomfortable than painful and will usually be done while they are awake, because their doctor needs their cooperation. Right heart catheterization may be associated with side effectsadverse events. Minor local adverse events side effects include bruising or hematoma, swelling and infection. Sometimes patients may have an irritating sensation in the chest, less frequently this is felt as pain and is usually not harmful. Side effects that are seen rarely include heart rhythm abnormalities, low blood pressure, bleeding, general infection, collapsed lung, or clotting of the blood, sometimes followed by an obstruction of an artery. As with any procedure

involving the heart, complications can sometimes, although rarely, be fatal.

Other medicines and EFI: patients are asked to tell their study doctor before starting treatment about any medicines they are taking or have recently taken. This includes medicines they have bought without prescription as some of these could interact with EFI. Patients are reminded that it is especially important to tell their study doctor if they are taking: diuretics, antihypertensives or other vasodilators such as calcium channel blockers or converting enzyme inhibitors (to treat high blood pressure), platelet aggregation inhibitors, anticoagulants, or non steroidal anti-inflammatory drugs.

Contacts

Public
Actelion Pharmaceuticals Ltd

Gewerbestrasse 16
CH-4123 Allschwil
CH
Scientific
Actelion Pharmaceuticals Ltd

Gewerbestrasse 16
CH-4123 Allschwil
CH

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Male or female aged 18 years and above
2. Patients with the following types of pulmonary arterial hypertension (PAH) belonging to WHO Group I:
* Idiopathic (IPAH)
* Heritable (HPAH)
* Associated (APAH) with
o Connective tissue diseases
o Drugs and toxins
3. Patients treated with Flolan for at least 12 months and on a stable dose for at least 3 months prior to enrollment
4. Patients who are currently treated with concomitant PAH therapy listed below must have been treated for at least 90 days and on a stable dose for 30 days prior to enrollment:
* Bosentan
* Ambrisentan
* Sitaxsentan
* Sildenafil
* Tadalafil
5. Women of childbearing potential must use a reliable method of contraception
6. Signed informed consent prior to initiation of any study mandated procedure

Exclusion criteria

1. Patients with respiratory and/or cardiovascular distress in need of emergency care
2. Known or suspicion of pulmonary veno-occlusive disease (PVOD)
3. Current use of IV inotropic agents
4. Current use of any prostacyclin or prostacyclin analog other than Flolan
5. Tachycardia with heart rate > 120 beats/min at rest
6. PAH related to any condition other than those specified in the inclusion criteria
7. Known hypersensitivity to the formulations Epoprostenol for injection or any of its excipients, and Flolan or any of its excipients
8. Cerebrovascular events (e.g., transient ischemic attack or stroke) within 6 months of screening
9. History of myocardial infarction
10. History of left-sided heart disease, including any of the following:
* hemodynamically significant aortic or mitral valve disease
* restrictive or congestive cardiomyopathy
* left ventricular ejection fraction < 40% by multigated radionucleotide angiogram (MUGA), angiography, or echocardiography
* unstable angina pectoris
* life-threatening cardiac arrhythmias
11. Chronic bleeding disorders
12. Central venous line infection within 90 days prior to screening and/or a history of

recurring line infections
13. Women who are pregnant or breast-feeding
14. Participation in another clinical trial, except observational, or receipt of an investigational product within 30 days prior to enrollment
15. Any known factor or disease that might interfere with treatment compliance, study conduct or interpretation of the results such as drug or alcohol dependence or psychiatric disease
16. Known concomitant life-threatening disease other than PAH with a life expectancy < 12 months

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):	05-12-2011
Enrollment:	5
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	n.v.t.
Generic name:	Epoprostenol for injection

Ethics review

Approved WMO

Date:	07-03-2011

Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-07-2011
Application type:	First submission
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	EUCTR2010-018322-40-NL
CCMO	NL34263.029.11