A MULTI-CENTRE, RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE-BLIND, TWO-ARMED, PARALLEL GROUP STUDY TO EVALUATE EFFICACY AND SAFETY OF IV SILDENAFIL IN THE TREATMENT OF NEONATES WITH PERSISTENT PULMONARY HYPERTENSION OF THE NEWBORN (PPHN) OR HYPOXIC RESPIRATORY FAILURE AND AT RISK FOR PPHN, WITH A LONG TERM FOLLOW-UP INVESTIGATION OF DEVELOPMENTAL PROGRESS 12 AND 24 MONTHS AFTER COMPLETION OF STUDY TREATMENT

Published: 28-02-2013
Last updated: 24-04-2024

Primary Objectives: The primary objectives of this study are to evaluate the efficacy and safety of IV sildenafil when added to iNO for the treatment of neonates with PPHN or hypoxic respiratory failure and at risk for PPHN. Secondary Objectives: *...

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

Summary

ID

NL-OMON37174

Source
ToetsingOnline

Brief title
A1481316 (207824)

Condition

- Other condition
- Neonatal respiratory disorders

Synonym
PPHN

Health condition

Aanhoudende pulmonale hypertensie van de pasgeborene (PPHN)

Research involving
Human

Sponsors and support

Primary sponsor: Pfizer
Source(s) of monetary or material Support: Pfizer

Intervention

Keyword: pasgeborene, PPHN, pulmonale hypertensie, sildenafil

Outcome measures

Primary outcome

Co-Primary Endpoints: Assessed at Day 14 or hospital discharge, whichever

occurs first:

- Time on iNO treatment after initiation of IV study drug for subjects without

treatment failure;

- Treatment failure rate, defined as need for additional treatment targeting

PPHN, need for ECMO, or death during the study.

Secondary outcome

Secondary Endpoints: Assessed at Day 14 or hospital discharge, whichever occurs first:

- Time to final weaning of mechanical ventilation for PPHN;

- Time from initiation of study drug to treatment failure; each component will also be evaluated separately;

- Proportion of subjects with individual components of treatment failure (needing additional treatment targeting PPHN, needing ECMO, or who die);

- Change in OI at 6, 12, and 24 hours from baseline;

- Change in differential saturation (pre- and post-ductal) at 6, 12, and 24 hours from baseline;

- Change in P/F ratio at 6, 12, and 24 hours from baseline;

- Sildenafil and UK-103,320 plasma concentrations and the corresponding PK parameters obtained from a population PK analysis; and

- Safety parameters: Incidence and severity of adverse events and abnormal laboratory parameters.

Study description

Background summary

Neonates with persistent pulmonary hypertension of the newborn (PPHN) or hypoxic respiratory failure (HRF) who do not respond to comprehensive supportive intensive care measures are typically treated with inhaled nitric oxide (iNO), which is considered standard therapy. Inhaled nitric oxide treatment increases the partial pressure of arterial oxygen (PaO2) by dilating pulmonary vessels in better ventilated areas of the lung, redistributing pulmonary blood flow away from regions with low ventilation. Inhaled nitric oxide appears to reduce the need for extracorporeal membrane oxygenation (ECMO)

in HRF, while mortality is not affected.1 However, treatment with iNO is not effective for all patients and requires continued intubation and artificial ventilation.

Sildenafil citrate is a selective inhibitor of phosphodiesterase type 5 (PDE5), which is found in high concentrations in the lungs. Inhibition of PDE5 should enhance the vasodilatory effects of naturally occurring and inhaled nitric oxide, promoting relaxation of vascular smooth muscle, and increasing blood flow. Therefore, sildenafil may have utility in the treatment of neonates with PPHN and HRF at risk for PPHN. Case reports of off-label use of sildenafil in conjunction with iNO indicate that sildenafil could enhance the efficacy of iNO and reduce the time on iNO therapy. The effects of the addition of IV sildenafil to standard iNO therapy in the acute stage of this disease will be studied in this clinical study.

Study objective

Primary Objectives:
The primary objectives of this study are to evaluate the efficacy and safety of IV sildenafil when added to iNO for the treatment of neonates with PPHN or hypoxic respiratory failure and at risk for PPHN.

Secondary Objectives:
*To monitor the developmental progress of patients with PPHN treated with IV sildenafil or placebo, at 12 and 24 months after the end of study treatment.
* Pharmacokinetics (PK): To further characterize the PK of sildenafil and UK-103,320 in neonates with PPHN or HRF and at risk of developing PPHN.

Study design

This study will be conducted in two parts. Part A is the double-blind phase to assess the efficacy and safety of IV sildenafil versus placebo when added to iNO for no more than 14 days, during the acute phase of the disease, with follow-up at 7 and 28 days after the end of study drug infusion. Part B is the long-term, non-interventional phase, during which all subjects will be encouraged to return at 12 and 24 months after the end of study drug infusion, to take part in developmental assessments, hearing and ophthalmology tests.

Analysis of the double-blind phase of the study (Part A) will be performed when all subjects have completed or discontinued from the double-blind phase, and a study report will be written. Analysis of the non-interventional phase of the study (Part B) will be performed when all subjects have completed or discontinued from the 2-year follow-up visit, and a final study report will be written.

Intervention

Intravenuous application of sildenafil or placebo, drawing of blood samples.

Study burden and risks

- Blood samples will be taken for safety, oxygenation assessments, and PK analysis. Whenever possible, the actual times of blood sampling may coincide with the collection of clinical samples. Additional study blood samples may be taken provided the total volume taken for the study does not exceed 10 mL.
- The study doctor will be visited for screening, infusion (up to 14 days), and 4 follow-up visits in two years time.
- Assessments will be performed as mentioned in question E4 (physical examination, weight, head circumference, ECG, cranial ultrasound, ECG, blood samples, infusion study medication, hear test, ophthalmology examination, neurological examination, developmental examination). See also page 9 and 10 of the protocol dated 23 August 2012.
- The patient is being asked to complete a diary with adverse events and a questionnaire for the neurological assessment and developmental assessment.
- The most common adverse events occurring more often in children taking sildenafil than those taking inactive drug (placebo) were: headache, chest infections, fever, vomiting and Diarrhoea

SPACE FOR DR VAN HEIJST TO INDICATE WHY HE THINKS THAT THE RISKS AND BURDEN OUTWEIGH THE BENEFIT OF THE STUDY. OTHERWISE THE FOLLOWING TEXT WILL BE USED

Casusbeschrijvingen van off-label gebruik van sildenafil in combinatie met stikstof laten een verhoogde effectiviteit, en een kortere behandeling met stikstof zien. Als dit in een georganiseerd onderzoek bevestigd zou worden levert dit een voordeel op voor de patienten in het onderzoek, en toekomstige patienten.

Contacts

Public
Pfizer

Eastern Point Road MS 8260-2561
Groton CT 06340
US
Scientific
Pfizer

Eastern Point Road MS 8260-2561
Groton CT 06340
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Children (2-11 years)

Inclusion criteria

Subject eligibility should be reviewed and documented by an appropriately qualified member of the investigator*s study team before subjects are included in the study.
Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:
1. PPHN or hypoxic respiratory failure (HRF) at risk for PPHN associated with:
* Idiopathic PPHN;
* Meconium aspiration syndrome;
* Sepsis; or
* Pneumonia.
2. *72 hours of age and *34 weeks of gestation at screening.
3. OI >15 and <60, calculated using two blood gases taken at least 30 minutes apart prior to randomization and start of study drug infusion.
4. Concurrent treatment with iNO at 10-20 ppm on *50% oxygen.
5. Screening echocardiogram, within 24 hours of study start, to confirm presence of pulmonary hypertension for continued participation in the trial.
6. Screening cranial ultrasound, within 24 hours of study start, to eliminate patients with clinically significant intracranial bleeds per investigator judgment.
7. Evidence of a personally signed and dated informed consent document indicating that the subject*s legal representative has been informed of all pertinent aspects of the study; and
8. Subjects whose legal representative is willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

Exclusion criteria

Subjects presenting with any of the following will not be included in the study:
1. Prior or immediate need for ECMO or CPR.
2. Expected duration of mechanical ventilation of less than 48 hours.
3. Life-threatening or lethal congenital anomaly.

4. Profound hypoxemia: PaO2 <30 mm Hg on any arterial blood gas drawn within 30 minutes of starting study drug infusion.
5. Severe hypotension at baseline (mean arterial pressure (MAP) <30 mmHg) not responsive to medical management, or shock any time during screening.
6. Significant congenital heart disease or defect exclusive of inter-atrial communication or patent ductus arteriosus.
7. Large left to right intracardiac or ductal shunting (diagnosed from echocardiogram within 24 hours of admission).
8. Large clinically significant intracranial bleed (diagnosed from cranial ultrasound within 24 hours of admission).
9. Lung hypoplasia syndromes diagnosed on the basis of prolonged oligohydramnios or hydrops faetalis.
10. Congenital diaphragmatic hernia.
11. Clinically significant active seizures, as per clinical judgment of the investigator.
12. Apgar score of <3 at 5 minutes after birth.
13. Bleeding diathesis, as per clinical judgment of the investigator.
14. Receipt of any prohibited concurrent medication/therapy at any time prior to screening:
* Potent cytochrome P450 3A4 inhibitors (eg, erythromycin, ketoconazole, itraconazole, and protease inhibitors), erythromycin ophthalmic ointment is allowed;
* Ritonavir or nicorandil;
* Endothelin antagonists (eg, Tracleer (RTM)/bosentan, Letairis(RTM)/ambristan, etc);
* PDE5 inhibitors (eg, sildenafil, tadalafil, vardenafil), IV or per orogastric tube;
* Nitrates or nitric oxide donors, except iNO (A subject is eligible if nitroprusside was used only if it was discontinued at least 2 hours prior to study drug infusion; iNO may be used per protocol);
* Vasodilators (eg, alpha blockers, magnesium sulfate as infusion, calcium channel blockers, other PDE inhibitors, prostacyclins, etc) at study entry (Excludes milrinone, which is allowed during the study as concurrent therapy) at study entry; or
* Supplemental arginine administered for the purpose of improving NO-dependent vasodilation (Maintenance quantities in total parental nutrition (TPN) are allowed).
15. Known hereditary degenerative retinal disorders, such as retinitis pigmentosa.
16. Symptoms of drug- or alcohol-related withdrawal.
17. In the opinion of the investigator, a subject inappropriate for the study for any reason.
18. Other acute or severe medical conditions, or marked laboratory abnormalities that may increase the risk associated with study participation or investigational product administration, or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.
19. Participation in any other experimental studies involving other drug or non-interventional therapies before the current study begins and/or during study participation.
Subjects who are relatives of investigational site staff members or Pfizer employees directly involved in the conduct of the trial.

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:	Recruitment stopped
Start date (anticipated):	19-09-2013
Enrollment:	17
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Revatio
Generic name:	Sildenafil citrate
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	28-02-2013
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	16-07-2013
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	18-12-2013

Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	27-12-2013
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	24-03-2014
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	09-04-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	26-05-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	30-06-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	02-10-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	06-10-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	25-07-2018
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	01-08-2018

Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	20-08-2018
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	11-03-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	27-05-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	06-07-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	EUCTR2012-002619-24-NL
CCMO	NL42637.091.12

Study results

Date completed: 21-01-2020

Actual enrolment: 5

Summary results
Trial is onging in other countries