A phase 3, placebo controlled, double-blind, randomized, clinical study to determine efficacy, safety and tolerability of pulsed, inhaled nitric oxide (iNO) versus placebo in symptomatic subjects with pulmonary arterial hypertension (PAH): INOvation-1 (Part 1 and Part 2)

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Part 1 -Blinded Treatment Period: Primary Objective:To evaluate the efficacy of inhaled nitric oxide (iNO) on exercise using 6-minute walk distance (6MWD) in subjects with pulmonary arterial hypertension (PAH) currently receiving background PAH...

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

Summary

ID

NL-OMON46327

Source
ToetsingOnline

Brief title
PULSE-PAH-004

Condition

- Pulmonary vascular disorders

Synonym
Pulmonary Arterial Hypertension (PAH)

Research involving
Human

Sponsors and support

Primary sponsor: Bellerophon Pulse Technologies LLC
Source(s) of monetary or material Support: Bellerophon Pulse Technologies LLC

Intervention

Keyword: arterial, hypertension, pulmonary

Outcome measures

Primary outcome

Part 1 Blinded Treatment Period:

Primary Endpoint: The efficacy of iNO as measured by the placebo-adjusted

change in 6MWD from baseline to 18 weeks.

Open Label Period: Primary Endpoint:

The incidence of AEs and SAEs with long term therapy

Secondary outcome

Secondary Endpoints:

1. TTCW: The time (in days) from start of treatment to first event (first day

the event is noted), with iNO as compared to placebo, measured from baseline

to 18 weeks. TTCW event is defined as any of the following:

a. Death (all-cause mortality)

b. Atrial septostomy

c. Hospitalization due to worsening of PAH (adjudicated)

d. Start of new specific PAH treatment (endothelin receptor antagonists [ERAs], phosphodiesterase type-5 [PDE-5] inhibitors or prostanoids), an increase in the dose of an ERA or PDE-5, increase in the dose or frequency of an inhaled prostanoids, or an increase in the dose of an intravenous or subcutaneous prostanoids by >10%.

e. Decrease of >15% from baseline or > 30% compared with the last study related measurement in 6MWD and should be confirmed by a repeat measurement performed at least 14 days later

f. Worsening of WHO Functional Class (e.g., from Class II to Class III or IV, OR Class III to Class IV); and should be confirmed by a repeat assessment at least 14 days later

2. Change in WHO Functional Class, with iNO as compared to placebo, from baseline to 18 weeks.

Tertiary Endpoints:

1. Change in health-related quality of life (using SF-36 version 2 health survey), with iNO as compared to placebo, from baseline to 18 weeks

2. Change in pulmonary hemodynamics (i.e., cardiac output [CO], cardiac index [CI], mean pulmonary artery pressure [mPAP], mean pulmonary capillary wedge pressure [mPCWP], systolic pulmonary artery pressure [sPAP], diastolic pulmonary artery pressure [dPAP], pulmonary vascular resistance [PVR], and oxygen saturation by pulse oximeter [SpO2], mixed venous O2, and right atrial pressure [RAP]), measured by right heart catheterization (RHC), with iNO as compared to placebo, from baseline to 18 weeks, in a subset of subjects (approximately 50), at selected sites

3. Change in echocardiogram measurements right ventricular function (including right ventricular fractional area change, systolic pulmonary artery pressure [sPAP], tricuspid annular motion/tricuspid annular plane systolic excursion, tricuspid annular systolic velocity, and Tei index) and left ventricular function (including left ventricular ejection fraction [LVEF], LV size, and improvement in LV early diastolic relaxation velocity), with iNO as compared to placebo, from baseline to 18 weeks, in a subset of subjects (approximately 50), at selected sites

4. Change in NT-proBNP, with iNO as compared to placebo, from screening to 18 weeks

5. Change in Borg dyspnea score immediately following 6MWT, with iNO as compared to placebo, from baseline to 18 weeks

6. Change in 6MWD as related to degree of drug adherence, with iNO as compared to placebo, from baseline to 18 weeks

7. The number of subjects with unsatisfactory clinical response, with iNO compared to placebo, from baseline to 18 weeks. Defined as: WHO Functional Class III or IV symptoms with no improvement in 6MWD

8. Number of subjects undergoing heart-lung or lung transplantation, number of subjects listed for transplantation, and deaths while awaiting transplantation, from baseline to 18 weeks

9. Medical resource utilization, with iNO as compared to placebo, from baseline to 18 weeks

Safety Endpoints:

1. Incidence and severity of adverse events (AEs)

2. Incidence of device malfunction and/or device failure leading to an AE

3. Incidence of rebound pulmonary hypertension (PH)

4. Clinically significant changes in the following:

a. Clinical laboratory tests

b. Pulmonary function tests

c. Vital signs

Part 2 Open Label Period: Secondary Endpoint: To evaluate the change in 6MWD in subjects who switch from placebo to active therapy at 4 months, 8 months and 12 months of therapy.

Study description

Background summary

PAH is associated with an imbalance of NO production, partly due to the decreased activity of nitric oxide synthase in the endothelium of pulmonary arteries. Consequently, the chronic administration of iNO can be considered as a replacement therapy in some patients and it represents a logical choice for clinical research.

Study objective

Part 1 -Blinded Treatment Period: Primary Objective:
To evaluate the efficacy of inhaled nitric oxide (iNO) on exercise using 6-minute walk distance (6MWD) in subjects with pulmonary arterial hypertension (PAH) currently receiving background PAH medication and LTOT.
Secondary Objectives:
1. To evaluate the time to clinical worsening (TTCW)
2. To evaluate change in World Health Organization (WHO) Functional Class
Safety Objectives:
1. To evaluate the safety and tolerability of iNO
Tertiary Objectives:
1. To evaluate changes in health-related quality of life using the Short Form-36 (SF-36) version 2 health survey

2. To evaluate the impact of iNO on pulmonary hemodynamics in a subset of subjects
3. To evaluate changes in right ventricular (RV) and left ventricular (LV) function as measured by echocardiography, in a subset of subjects
4. To evaluate changes in N-terminal of the prohormone brain natriuretic peptide (NT-proBNP)
5. To evaluate change in Borg dyspnea score immediately following 6-minute walk test (6MWT)
6. To evaluate change in 6MWD as related to degree of correlation between drug adherence and clinical efficacy measurement
7. To evaluate subjects with unsatisfactory clinical response
8. To evaluate the impact of iNO on frequency of heart-lung or lung transplantation, and deaths while awaiting transplantation
9. To evaluate the impact of iNO on medical resource utilization

Part 2 Open Label Period: Primary Objective:
1. To Evaluate the long term safety and tolerability of iNO
Secondary Objective:
To Evaluate the change in exercise tolerance in subjects who switch from placebo to active therapy

Study design

This is a multi-center, randomized, double-blind, placebo-controlled, parallel-group design to determine the efficacy, safety and tolerability of pulsed iNO versus placebo in symptomatic subjects with PAH currently receiving background PAH.
The study consists of two parts Part 1, the Blinded Treatment Period, and Part 2, the Open Label Extension Period. After the Screening period, the subjects will be randomized at Week 0 then enter a double-blind, Run-in period (Week 0 to Week 2) to assess their eligibility to continue in the study by their usage of the INOpulse device for an average >= 12 hours (rounded to the nearest hour) per day with no more than 2 days of usage < 8 hours per day. All subjects will be analyzed for safety during this Run-in period. Those subjects not meeting the 12 hour INOpulse device usage requirement (by Week 2) will be discontinued and ineligible to proceed to the next phase of treatment. Subjects meeting the device usage requirement, and all Inclusion/Exclusion criterion (by Week 2), will qualify to enter into the next phase of treatment.
Subjects who are unable to meet enrollment criteria during the Run-in period may be rescreened at the discretion of the Sponsor.
Subjects will be randomized to a treatment assignment as described in Table 1 below. Subjects randomized to active iNO will receive a reduced dose of iNO during run in and subjects randomized to placebo will receive placebo during run in.
At Baseline, all subjects will be stratified for prostanoids usage.
LTOT flow rates should be kept constant throughout the study unless the subject has persistent desaturations to less than 88% of SpO2, or otherwise clinically

indicated. LTOT flow rate with the estimated length of use per day must be documented in the eCRF at all visits. Subjects will be encouraged to use their oxygen during the day and night as prescribed by their treating physician. All 6MWTs will be performed while subjects are receiving oxygen and carrying the iNOpulse device (including baseline assessments).
Additional specific PAH therapies may be added only for evidence of clinical worsening due to PAH as defined in the protocol throughout the trial.
Subjects will remain in the study and continue to receive blinded treatment according to their randomization for an additional 16 weeks for a total of 18 weeks.
Part 2-Open Label Period -Subjects will be offered open label therapy when a subject completes 18 weeks of blinded drug therapy.
Subjects will be given the opportunity continue in Part 2 Open Label Treatment and will receive iNO at 75 mcg/kg IBW/hr with the INOpulse delivery device until the drug-device investigational product is approved and available as a marketed product or the Sponsor decides to discontinue development of iNO for PAH.

Intervention

- Right heart catheterization
- Venipuncture
- Echocardiogram

Study burden and risks

The known potential risks associated with breathing the study drug are:
- Rebound Pulmonary Hypertension
In critically ill patients, such as in an ICU, who are on a machine that helps someone breathe, if inhaled nitric oxide is stopped too quickly, the blood pressure in the lungs may suddenly increase and this can result in a decrease in the blood oxygen level (oxygen desaturation or hypoxemia), low blood pressure in the body (hypotension) or, in very severe cases, stopping of the heart (cardiac arrest) or death. This is called *rebound pulmonary hypertension syndrome.* The treatment is to restart the study drug, give oxygen, and treat any symptoms.
In PAH patients who are not critically ill in the ICU and not on a machine that helps someone breathe, rebound pulmonary hypertension syndrome has not been reported. Additionally, when patients with PAH have a right heart catheterization and undergo a test to determine if the pressures in their pulmonary arteries can decrease with the study drug or another drug for 5 10 minutes, rebound pulmonary hypertension has also not been observed.
If symptoms of rebound pulmonary hypertension occur when the study drug is suddenly stopped (such as if the study device fails to work properly or when you remove it) or occurs at any time when the patient stops the study drug, he/she should restart the study drug and call the study doctor immediately.

These symptoms include: low blood pressure, slow or fast heart rate, fainting, or low oxygen levels in your blood.
- Methemoglobinemia
Breathing in high amounts of study drug for long periods of time may cause the production of methemoglobin (an abnormal form of hemoglobin in the blood; hemoglobin is the chemical in blood which carries oxygen), which could worsen the blood oxygen level. The study drug doses used in this study are lower than those that have shown to cause increases in methemoglobin levels in healthy individuals. In this study, the patient will be periodically tested for methemoglobin levels. If the patient should develop methemoglobinemia, the increase in methemoglobin does not require any treatment and will go away by itself, once the patient is discontinued from the study drug.
- Lung Irritation or Inflammation: Inhaled nitric oxide can react with oxygen to form nitrogen dioxide (NO_2). NO_2 can cause lung irritation or inflammation. The study device contains safety features to prevent NO_2 from forming.
- For the Study Device (INOpulse): The main risk of the study device is if the device fails to work properly, due to malfunction or damage. If this occurs, the study drug will not be delivered appropriately. In these instances, the patient should use the backup device provided and call the study doctor.
- Right-heart Catheterisation: Possible risks associated with a right heart catheterisation include:
• Bruising of the skin at the site where the catheter is inserted
• Excessive bleeding because of puncture of the vein during catheter insertion
• Pneumothorax (partial collapse of the lung) if neck or chest veins are used to insert the catheter
Other, rare complications may include:
• Abnormal heart rhythms, such as ventricular tachycardia (fast heart rate in the lower heart chambers)
• Cardiac tamponade (fluid buildup around your heart that affects its ability to pump blood effectively)
• Low blood pressure
• Infection
• Air embolism (air leaking into the heart or chest area)
• Blood clots at the tip of the catheter that can block blood flow
• Pulmonary artery rupture. This is damage to the main artery in the lung. This can result in serious bleeding, making it difficult to breathe.
For some patients, having to lie still on the cardiac catheterisation table for the length of the procedure may cause some discomfort or back pain.
- Acute Pulmonary Vasoreactivity Testing: Potential risks of acute vasoreactivity testing will include bronchospasm, thoracic pain and bradycardia
- For the Nasal Cannula: The patient may have redness, bleeding or, in severe cases, ulceration (sores) within the nose from irritation, due to the tubing or the constant flow of gas into the nose.
- For the Blood Draw (Venepuncture): The blood will be drawn from the arm. The patient may feel some pain when the blood is drawn. There is a small chance the needle will cause bleeding, a bruise, or an infection.
- For Pregnancy/Risk to Fetus (For Women): If the patient is nursing an infant

or she is pregnant, she cannot take part in the study, because we do not know how the study drug could affect a fetus or a nursing infant. If the patients are sexually active and are at risk of getting pregnant, the patient must use 2 methods of birth control that work well, like birth control pills, Depo Provera, Norplant, an IUD, a diaphragm or condom with spermicide, or abstinence. The patient must agree to use 2 methods of birth control for the entire time she is in this study. If she becomes pregnant during the study, she should warn the study doctor and her health care provider immediately. The patient will be withdrawn from the study. The long-term inhalation of nitric oxide on reproductive and developmental toxicology studies are unknown, and exposure to nitric oxide during pregnancy and lactation should be avoided. Because there is no information on the effect of the study drug on pregnancy or the unborn child, the study doctor or research team will contact the patient during the course of the pregnancy and will ask to follow the outcome of the pregnancy and condition of the newborn.
- For Pregnancy/Risk to Fetus (For Men): If the patient is a sexually active male and at risk of causing a pregnancy, he must be sure that his female partner(s) are using a method of birth control that works well, like birth control pills, Depo-Provera, Norplant, an IUD, or a diaphragm with spermicide, and he must use a condom with spermicide during sexual intercourse, or abstinence. The patient must use 2 methods of birth control the entire time you are in this study. A vasectomy is an acceptable method of birth control for this study. If a sexual partner becomes pregnant during the research study, the patient should tell the study doctor and ask his partner to tell her health care provider immediately. Because
there is no information on the effect of the study drug on pregnancy or the unborn child, the study doctor or study team member will contact the patient during the course of the pregnancy and will ask to follow the outcome of the pregnancy and condition of the your newborn.
- For Potential Drug Interactions: There are several drugs (prescription and non-prescription) that may cause problems when taken with the study drug. The study doctor will carefully review all of the drugs the patient is taking before giving him/her the study drug. If any other health care provider prescribes any new drug(s) for the patient while he/she is in this study, the patient should tell the study doctor before taking the new drug. The patient could also have that provider talk to the study doctor before prescribing the new drug. The patient should not take any new over-the-counter drugs while he/she is in this study unless he/she first checks with the study doctor.
- Unknown Risks: There may be risks that are currently not known or cannot be predicted. The patient's condition may worsen, remain the same, or improve as a result of taking part in this research study. The patient should tell the study doctor or staff about all problems, illnesses, or injuries that happen during the study, even if they think they are not related to your taking part in this study. The patient might have side effects or discomforts that are not listed in this form. Some side effects may not be known yet. New ones could happen. The patient should tell the study doctor or study staff right away if he/she

has any problems.

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

Part 1 Blinded Treatment Period:
1. Signed Informed Consent Form (and assent as appropriate) prior to the initiation of any study mandated procedures or assessments
2. A confirmed diagnosis of PAH Group 1 who have either idiopathic PAH (IPAH), heritable PAH, drug and toxin-induced PAH, associated PAH (APAH) with connective tissue disease (CTD), APAH with congenital heart disease (unrepaired or repaired at least 1 year prior to Screening), APAH with human immunodeficiency virus (HIV), or APAH with portal hypertension
3. Subjects receiving at least one PAH specific therapy (ERA or PDE-5 inhibitor, or inhaled,

subcutaneous, or intravenous prostacyclin or a prostacyclin analog) with the same type of therapy for at least 3 months with stable dosing 4 weeks prior to Screening. (Subjects should be receiving optimal therapy according to the disease severity);4. Subjects using oxygen therapy by nasal cannula for at least 4 weeks prior to Screening;5. PAH diagnosis confirmed by RHC within the previous 5 years, according to the following definitions:
• PVR >= 400 dynes.sec.cm-5 (5 Wood units)
• mPAP >= 25 mmHg
• PCWP or LVEDP <= 15 mmHg
• Subjects who otherwise meet all the inclusion criteria and none of the exclusion criteria but have not undergone a RHC within the previous 5 years may be considered eligible for the study if they undergo a RHC and then meet the pulmonary hemodynamics criterion
6. 6MWD >= 100 meters and <= 450 meters prior to randomization
7. WHO Functional Class II-IV. Subjects with WHO Functional Class IV should be treated with prostacyclin or a prostacyclin analog (subcutaneous or intravenous), plus at least one additional PAH specific therapy (ERA or PDE-5), if available to the subject and reimbursed by health insurance
8. Age between 18 and 85 years (inclusive)
9. Willingness to use INOpulse delivery device for at least 12 hours per day
10. Willingness to continue on study drug until subject completes Week 18 assessments
11. Female subjects of childbearing potential must have a negative pre-treatment pregnancy test (serum or urine). All female subjects should take adequate precaution to avoid pregnancy.;Part 2 Open Label Period:
Inclusion Criteria Part 2:
1. Informed Consent Form prior to the initiation of any study mandated procedures or assessments
2. Subject must have completed 18 weeks of blinded therapy and all assessments at week 18
3. In the opinion of the Investigator, open label treatment is in the best interest of the subject after 18 weeks of blinded treatment is completed

Exclusion criteria

Part 1 Blinded Treatment Period:
1. Subjects with known HIV infection who have a history within the past 3 months of any opportunistic pulmonary disease (e.g., tuberculosis, Pneumocystis carinii pneumonia, or other pneumonias) at the time of Screening
2. PAH associated with untreated thyroid disorders, glycogen storage disease, Gaucher*s disease, hereditary hemorrhagic telangiectasia, hemoglobinopathies, myeloproliferative disorders or splenectomy
3. Subjects with pulmonary conditions that may contribute to PAH including, but not limited to, chronic bronchiectasis, cystic fibrosis, or other pulmonary condition that the Investigator may deem to contribute to the severity of the disease or impair the delivery of iNO due to airway disease
4. Subjects receiving riociguat
5. Subjects receiving oral prostanoids as monotherapy
6. PAH associated with significant venous or capillary involvement, known or suspected

pulmonary veno-occlusive disease, or pulmonary capillary hemangiomatosis
7. Any subject with WHO PH Groups 2, 3, 4 or 5
8. Subjects with any of the following cardiac abnormalities:
a. Underlying cardiomyopathy or clinically significant aortic or mitral valve disease in the opinion of the investigator
b. Left ventricular systolic dysfunction (LVSD), i.e., left ventricular ejection fraction (LVEF) < 40% or left ventricular shortening fraction (LVSF) < 22%, as determined by local reading
c. Current symptomatic coronary artery disease, myocardial infarction within 1 year, or any coronary artery interventions within 6 months
9. Systemic hypertension defined as systolic blood pressure (SBP) > 160 mmHg and/or diastolic blood pressure (DBP) > 100 mmHg persistent at Screening after a period of rest (treated or untreated)
10. Subjects with a history of deep vein thrombosis, pulmonary embolism/infarction or prothrombotic disorder must have had chronic thromboembolic pulmonary hypertension (CTEPH) excluded by ventilation/perfusion lung (V/Q) scan
11. Severe obstructive lung disease defined as both a forced expiratory volume in 1 second/forced vital capacity (FEV1/FVC) < 70% and FEV1 < 55%of predicted value
12. Moderate to severe restrictive lung disease: total lung capacity (TLC) < 60% of predicted; if TLC 60% to 70% predicted, a high resolution CT scan showing diffuse disease or more than mild patchy disease
13. Any subject who develops or has developed a PCWP > 20 mmHg during acute vasodilator testing (AVT)
14. Systemic hypotension defined as SBP < 90 mmHg persistent at Screening after a period of rest
15. Moderate to severe hepatic impairment, i.e., Child-Pugh Class B or C
16. On dialysis
17. Acute or chronic physical impairment (other than dyspnea due to PAH) that would limit the ability to comply with study procedures or adherence to therapy (i.e., 6MWT), including carrying and wearing the pulsed delivery device per study protocol, or medical problem(s) likely to preclude completion of the study
18. Pregnant or breastfeeding females at Screening
19. Administered L-arginine within 1 month prior to Screening
20. Known concomitant life-threatening disease with a life expectancy less than 1 year
21. Atrial septostomy within 3 months preceding randomization
22. The concurrent use of the INOpulse device with a continuous positive airway pressure (CPAP), Bilevel positive airway pressure BiPAP, or any other positive pressure device.
23. Use of investigational drugs or devices within 1 month prior to Screening (other than acute vasodilator testing with iNO)
24. Any underlying medical or psychiatric condition that, in the opinion of the Investigator, makes the subject an unsuitable candidate for the study
25. Any subject who has been enrolled in any previous clinical study with inhaled NO administered through pulse delivery.;Exclusion Criteria Part 2 Open Label Period:
1. Subject has initiated therapy with Riociguat

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):	28-09-2017
Enrollment:	3
Type:	Actual

Medical products/devices used

Generic name:	iNOpulse
Registration:	Yes - CE intended use
Product type:	Medicine
Brand name:	iNOmax
Generic name:	inhaled nitric oxide & INOpulse delivery
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	05-09-2016
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-01-2017

Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-08-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-08-2017
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	EUCTR2015-005223-90-NL
ClinicalTrials.gov	NCT02725372
CCMO	NL56626.029.16