A Phase 2, Dose-Ranging, Randomized, Double-Blind, Placebo-Controlled Study of GS-4997 in Subjects with Pulmonary Arterial Hypertension

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The primary objective of this study is to:Evaluate the effect of GS-4997 on pulmonary vascular resistance (PVR), as measured by right heart catheterization (RHC) in subjects with pulmonary arterial hypertension (PAH).

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

Summary

ID

NL-OMON41720

Source
ToetsingOnline

Brief title
0035/0100 (GS-US-357-1394)

Condition

- Pulmonary vascular disorders

Synonym
increase of blood pressure in the pulmonary artery, Pulmonary Arterial Hypertension

Research involving
Human

Sponsors and support

Primary sponsor: Gilead Sciences

Source(s) of monetary or material Support: Gilead Sciences;Inc.

Intervention

Keyword: Pulmonary Arterial Hypertension

Outcome measures

Primary outcome

The primary objective of this study is to:

Evaluate the effect of GS-4997 on pulmonary vascular resistance (PVR), as measured by right heart catheterization (RHC) in subjects with pulmonary arterial hypertension (PAH)

Secondary outcome

The secondary objectives of this study are to evaluate, in subjects with PAH, the effect of GS-4997 on the following:

- Cardiac index (CI), mean pulmonary artery pressure (mPAP), mean right atrial pressure (mRAP), mixed venous oxygen saturation (SvO2), and right ventricular cardiac power
- Clinical measures of PAH, including the 6-minute walk distance (6MWD), Borg Dyspnea index (BDI), heart rate recovery (HRR), WHO Functional Class, and N-terminal pro-brain natriuretic peptide (NT-proBNP)
- Quality of life (QoL) as measured by the SF-36® Health Survey and the emPHasis-10 questionnaire
- Time to clinical worsening (TTCW)
- Echocardiographic measures of right ventricular function
- Safety and tolerability

The additional objectives of this study are to evaluate the following in

subjects with PAH:

- The pharmacokinetics of GS-4997 and its metabolite, GS-607509

- The effect of GS-4997 on disease- and target-specific biomarkers

Study description

Background summary

Pulmonary arterial hypertension is a progressive pulmonary vascular disease characterized by profound vasoconstriction and pulmonary arterial obstruction that lead to increased pulmonary vascular resistance (PVR), elevated pulmonary arterial pressures (PAP)s, right ventricular (RV) dysfunction, and ultimately, right heart failure. Group 1 PAH includes idiopathic pulmonary arterial hypertension (IPAH), heritable pulmonary arterial hypertension (HPAH), and PAH associated with various conditions such as connective tissue disease (CTD), congenital
systemic-to-pulmonary shunts, drug or toxin use, and human immunodeficiency virus (HIV) infection. All of these disorders share similar proliferative and obstructive changes of the pulmonary microcirculation, including plexiform lesions.
First- and second-generation therapies for PAH primarily target the vasoconstrictive component of this disease, although anti-proliferative effects have been hypothesized for all approved treatments. Despite therapy with pulmonary vasodilators, patients with PAH still face a poor
prognosis (68% survival at 3 years), because underlying remodeling processes (e.g., cellular hyperplasia, hypertrophy, inflammation, migration, and extracellular matrix deposition) in the pulmonary vasculature and RV myocardium continue unchecked to promote disease progression.
There remains an unmet medical need for novel, effective and safe treatments that go beyond
vasodilation by targeting maladaptive remodeling processes in the pulmonary vasculature and
RV myocardium.

Study objective

The primary objective of this study is to:
Evaluate the effect of GS-4997 on pulmonary vascular resistance (PVR), as measured by right heart catheterization (RHC) in subjects with pulmonary

arterial hypertension (PAH).

Study design

This study will compare the efficacy, safety, and tolerability of 3 doses of GS-4997 to placebo in subjects with PAH. Study drug will be administered on the background of stable PAH therapy. The study will consist of screening followed by a 24-week blinded placebo-controlled treatment period (Period 1), and a long-term blinded GS-4997 treatment period (Period 2).
Eligible subjects will be stratified based on the underlying etiology of PAH (idiopathic PAH [IPAH]/heritable PAH [HPAH] or Non-IPAH/HPAH) and the number of background PAH therapies they are receiving (1, 2 or * 3) and randomized 1:1:1:1 to placebo, 2, 6 or 18 mg GS-4997 administered once daily.
In Period 2, subjects randomized to active GS-4997 in Period 1 will remain on their current dose of study drug; subjects randomized to placebo in Period 1 will be rerandomized 1:1:1 to 2, 6 or 18 mg GS-4997 administered once daily.

Intervention

PERIOD 1: Screening & 24-Week Placebo-Controlled Treatment
Subjects will be screened for study eligibility within 4 weeks prior to randomization. Subjects who meet all entry criteria other than the hemodynamic criteria will be scheduled to return to clinic for the screening RHC.
Returning subjects will hold their doses of oral and/or inhaled background PAH treatments such that these medications are at approximately trough concentrations prior to the RHC procedure. If prior approval is obtained, the screening RHC may be performed on the same day as the randomization procedures, provided that all blood draws and other efficacy assessments are conducted prior to the RHC procedure, and the RHC is performed prior to randomization and study drug dosing.
Eligible subjects will be stratified based on the underlying etiology of PAH (IPAH/HPAH or Non-IPAH/HPAH) and the number of background PAH therapies they are receiving (1, 2 or * 3) and randomized 1:1:1:1 to placebo or 2, 6, or 18 mg GS-4997 administered once daily (qd) for 24 weeks.
Subjects must remain on their randomized treatment regimen (GS-4997 or placebo) and background PAH therapies throughout Period 1; therefore, the investigator should ensure that the subject is at a stable dose as defined by the inclusion exclusion criteria. No increases in current background oral PAH doses or addition of a new PAH medications will be allowed during Period 1. Decreases in background oral PAH therapy dosing should only be considered in the event of suspected drug-related adverse effects. The sponsor should be notified of any change to background PAH therapy during Period 1.
During Period 1, subjects will be seen in the clinic for Screening, Randomization, and then at Weeks 4, 8, 16 and 24. In addition,

subjects will be contacted at Weeks 2, 12 and 20 for assessment of adverse events (AEs) and concomitant medications.
Cardiopulmonary hemodynamics will be assessed by RHC performed during the 4 weeks between the Screening and Randomization Visits
(or at the Randomization Visit) and again at Week 24. All required RHC parameters must be collected using the same methods at Screening/Randomization and Week 24.
The assessments of 6MWT, BDI, WHO Functional Class, HRR and NT-proBNP will be conducted at Screening, Randomization, and Weeks 4, 8, 16 and 24.
Echocardiography assessments will be conducted at Randomization and Weeks 8, 16 and 24. Evaluation of QoL by the SF-36 Health Survey will be conducted at Randomization and Weeks 16 and 24. The criteria for clinical worsening will be evaluated at Weeks 4, 8, 16 and 24.
A pharmacokinetic (PK) blood sample will be collected from all subjects at Weeks 4, 8, 16 and 24.
A PK substudy with intensive PK sampling will be performed in up to 6 subjects per treatment arm at selected sites. Samples will be
collected at 0 (pre-dose) and 1, 2, 4, 6, 10, and 24 hours postdose at any time between Week 4 and Week 20 (inclusive).
During the placebo-controlled treatment period, clinical assessments will be conducted at trough concentrations of study drug (GS-4997 or
placebo) and background oral/inhaled PAH medications at all clinic visits. Plasma concentrations of study drug and background PAH
medications will be considered to be at trough levels for the purposes of clinical assessments when dosed at specified times.
On the day of each clinic visit, subjects will be asked to hold their doses of study drug and concomitant oral PAH treatments (excluding oral treprostinil) until all efficacy and PK assessments have been completed. For subjects receiving inhaled or oral prostanoid treatments, the morning dose may be administered on the day of the clinic visit, provided efficacy and PK assessments are not initiated until after the appropriate length of time has passed.
Safety will be monitored at all study visits with assessments of vital signs, AEs, 12-lead ECG, and clinical laboratory tests, and
echocardiography at specified visits. Blood and urine samples for biomarker analysis will be also drawn at all clinic visits.

Period 2: Long-Term Blinded GS-4997 Treatment
Subjects who complete the 24 week placebo-controlled period will be eligible to continue blinded study drug treatment and will attend clinical visits at Weeks 28, 32, 40, 48 and then every 24 weeks. In addition, subjects will be contacted at Weeks 26 and 36 for assessment of adverse events and concomitant medications. Subjects enrolled in the United States may continue treatment with GS-4997 for a maximum of 7 years or when GS-4997 becomes commercially available, whichever comes sooner, or until such time when the Sponsor elects to terminate the study. Subjects enrolled in all countries outside of the United States may continue treatment with GS-4997 for a maximum of 2.5 years or

until such time when the Sponsor elects to terminate the study.
Subjects randomized to active GS-4997 in the blinded placebo-controlled treatment period will remain on their current dose of study drug; subjects randomized to placebo in the blinded placebo-controlled treatment period will be rerandomized 1:1:1 to 2 mg GS-4997, 6 mg GS-4997 or 18 mg GS-4997 administered once daily (qd). Changes in or additions of new PAH medications will be allowed during Period 2.
The assessments of 6MWT, BDI, WHO Functional Class, HRR and NT-proBNP will be conducted at every clinic visit. Echocardiography
assessments will be conducted at Weeks 32, 40 and 48. Evaluation of QoL by the SF-36® Healthy Survey will be conducted at Weeks 40,
48 and every 24 weeks thereafter. The criteria for clinical worsening will be evaluated at every clinic visit.
Safety will be monitored at all study visits with assessments of vital signs, AEs, 12-lead ECG, and clinical laboratory tests, and echocardiography at specified visits. Blood and urine samples for biomarker analysis will be also drawn at select clinic visits.

Study burden and risks

See section E9.

Contacts

Public
Gilead Sciences

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Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Subjects must meet all of the following inclusion criteria to be eligible
for participation in this study:;1) Have the ability to understand and sign a written informed consent form, which must be obtained prior to initiation of study procedures
2) Man or woman age 18 through 75 years
3) Diagnosis of one of the following:
a) IPAH
b) HPAH
c) Drug- and toxin-induced PAH
d) PAH associated with one of the following:
i) Connective tissue disease (CTD; e.g. limited scleroderma, diffuse scleroderma, mixed CTD systemic lupus erythematous or overlap syndrome),
ii) HIV infection
iii) Congenital heart defects, repaired greater than 1 year prior to screening (atrial septal defects, ventricular septal defects, and patent ductus arteriosus)
4) Confirm the diagnosis of PAH and meet all of the following hemodynamic criteria by means of a screening RHC completed prior to randomization:
a) Mean pulmonary artery pressure (mPAP) of * 25 mmHg
b) Pulmonary vascular resistance (PVR) * 400 dyne*sec/cm5
c) Pulmonary capillary wedge pressure (PCWP) or left ventricular end diastolic pressure (LVEDP) of * 12 mmHg if PVR * 400 and < 500 dynes*sec/cm5, or PCWP/LVEDP * 15 mmHg if PVR * 500 dynes*sec/cm5
5) Be able to walk a distance of at least 100 m during the screening visit 6-minute walk test (6MWT) and have screening and randomization visit 6MWD that do not vary by more than 10%
6) Have WHO Functional Class II or III symptoms at the screening visit, as assessed by the investigator
7) Meet the following criteria determined by pulmonary function tests completed no more than 24 weeks prior to screening, performed with or without bronchodilation:
a) Forced expiratory volume in one second (FEV1) * 55% of predicted normal
b) FEV1:FVC ratio * 0.60
8) Currently on a stable treatment regimen with one or more drugs approved for PAH. Stable therapy is defined as dosing of the same treatments for * 12 weeks prior to the screening RHC and at a stable dose for * 8 weeks prior to the screening RHC. Any instances where doses have been missed prior to RHC must be discussed with the medical monitor prior to performing the RHC.
9) If diagnosed with HIV, must have stable disease status. For this study, stable HIV status is defined as follows:

a) Stable treatment with HIV medications for at least 8 weeks prior to screening,
b) No active opportunistic infection during the screening period, and
c) No hospitalizations due to HIV for at least 4 weeks prior to screening
10) Have documented evidence of the exclusion of chronic thromboembolic pulmonary hypertension (CTEPH) by a negative or low probability lung ventilation/perfusion (V/Q) scan or negative pulmonary arteriogram
11) Women of childbearing potential must have a negative serum pregnancy test at Screening
12) If engaged in heterosexual activity and of child-bearing potential, must agree to use protocol-specified method(s) of contraception
13) If participating in an exercise program for pulmonary rehabilitation, the program must have been initiated *12 weeks prior to screening, and subjects must agree to maintain the current
level of rehabilitation for the first 24 weeks of study treatment
14) If not participating in an exercise training program for pulmonary rehabilitation, must agree not to enroll in an exercise training program for pulmonary rehabilitation during the screening period and the first 24 weeks of study treatment

Exclusion criteria

Subjects who meet any of the following exclusion criteria are not to
be enrolled in this study:
15) Diagnosis of PAH associated with:
a) Significant venous or capillary involvement (PCWP > 15 mm Hg)
b) Pulmonary capillary hemangiomatosis
c) Portal hypertension
d) Unrepaired congenital heart defects
16) Pulmonary hypertension (PH) belonging to groups 2 to 5 of the 2013 NICE classification.
a) Group 2: PH due to left heart disease
b) Group 3: PH due to lung diseases and/or hypoxia
c) Group 4: Chronic thromboembolic pulmonary hypertension
d) Group 5: PH with unclear multifactorial mechanisms
17) Evidence of * 3 of the following left ventricular disease/dysfunction risk factors (a-d):
a) Body mass index (BMI) * 30
b) Established diagnosis of essential hypertension and active treatment during the 2 years prior to screening
c) Diabetes mellitus * any type
d) Historical evidence of significant coronary artery disease (CAD) established by any one of the following:
i) History of myocardial infarction
ii) History of percutaneous intervention
iii) Angiographic evidence of CAD (> 50% stenosis in at least one vessel), either by invasive angiography or by CT angiography
iv) Positive stress test with imaging (either pharmacologic or with exercise)
v) Previous coronary artery surgery

vi) Chronic stable angina
18) Left ventricular ejection fraction (LVEF) * 40% or clinically significant ischemic, valvular or constrictive heart disease
19) Receiving intravenous inotropes within 4 weeks prior to the screening visit (e.g. dopamine, dobutamine)
20) Receiving treatment with a strong CYP3A4 inhibitor (e.g. protease inhibitors, systemic ketoconazole or systemic itraconazole) within 2 weeks prior to randomization.
21) Receiving treatment with a strong CYP3A4 inducer (e.g. rifampin). within 2 weeks prior to randomization.
22) Uncontrolled hypertension (*180/110 mm Hg) at screening
23) End stage renal disease (receiving peritoneal dialysis, hemodialysis, or status after renal transplantation)
24) Severe liver disease (Child-Pugh Class C, with or without cirrhosis)
25) Severe arthritis, musculoskeletal problems, or morbid obesity that, in the opinion of the investigator, is the cause of the subject*s functional limitation and would affect the subject*s ability to perform or complete the 6MWT
26) History of malignancies within the past 5 years, except for a subject with localized, nonmetastatic basal or squamous cell carcinoma of the skin, in situ carcinoma of the cervix, or prostate cancer who is not currently or expected (during the study) to undergo radiation therapy, chemotherapy, hormonal treatment, and/or surgical intervention
27) Pregnant or breastfeeding; lactating females must agree to discontinue nursing before the study drug is administered
28) Demonstrated noncompliance with previous medical regimens
29) Current alcohol or substance abuse judged by the Investigator to potentially interfere with subject compliance or subject safety
30) Participation in a clinical study involving another investigational drug or device within 4 weeks before the screening visit. Current participation in a drug access study for an eligible PAH therapy in a country where the therapy is approved but not yet commercially available to the subject is allowed.
31) Known hypersensitivity to the study drug, the metabolites, or formulation excipients.

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):	22-10-2015
Enrollment:	2
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	GS-4997
Generic name:	GS-4997

Ethics review

Approved WMO Date:	05-03-2015
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-07-2015
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-08-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-12-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-12-2015
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	EUCTR2014-002131-34-NL
ClinicalTrials.gov	NCT02234141
CCMO	NL51267.029.15