IMPAHCT: A Phase 2b/3, Randomized, Double-Blind, Placebo-Controlled, 24-Week Dose Ranging and Confirmatory Study to Evaluate the Safety and Efficacy of AV-101 in Patients with Pulmonary Arterial Hypertension (PAH).

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The objective of the study is to establish an optimal dose of AV-101 based primarily upon the change in PVR but also other efficacy, safety, and tolerability findings from the Phase 2b Part of the study. The optimal dose will be taken into the Phase...

Ethical review	Approved WMO
Status	Pending
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON54466

Source
ToetsingOnline

Brief title
IMPAHCT

Condition

- Other condition

Synonym
Pulmonary Arterial Hypertension

Health condition

Pulmonary Arterial Hypertension (PAH)

Research involving
Human

Sponsors and support

Primary sponsor: Aerovate Therapeutics, Inc
Source(s) of monetary or material Support: Aerovate Therapeutics;Inc.

Intervention

Keyword: AV-101 (imatinib), Pulmonary Arterial Hypertension (PAH)

Outcome measures

Primary outcome

Phase 2b

* Placebo corrected change from baseline at Week 24 in PVR, as measured by RHC

in subjects with PAH

Phase 3

* Placebo corrected change from baseline at Week 24 in the 6MWD

Secondary outcome

Phase 2b

* Change from baseline at Week 24 in 6MWD

* Change from baseline at Week 24 in NT-proBNP

* Change from baseline at Week 24 in hemodynamic measures (CI, mPAP, mRAP, and

Sv02)

* Incidence of Clinical Worsening events through 24 weeks

* Achieving the multi-component improvement parameters

o Percent of subjects who achieve the multi-component parameters by visit

o Time to achieving the multi-component improvement parameters

* Improvement at Week 24 in WHO Functional Class status

* Change from baseline at Week 24 in REVEAL Lite 2.0 risk score

* Change from baseline at Week 24 in QoL (emphasis-10) Questionnaire score

Other Phase 2b endpoints

* Change from baseline at Week 24 in Transthoracic Echo Parameters of right ventricular (RV) function

* Change from baseline at Week 24 in Borg Dyspnea Index (BDI) immediately following exercise

* Pharmacokinetic parameters (Cmax,ss, Cmin,ss, Cavg, Tmax,ss, AUC0-tau, CL/F,ss, MRCmax,ss, and MRAUC0-tau)

* Safety and tolerability of AV-101

Phase 3

* Change from baseline at Week 24 in NT-proBNP

* Time to Clinical Worsening events

* Achieving the multi-component improvement parameters

o Percent of subjects who achieve the multi-component parameters by visit

o Time to achieving the multi-component improvement parameters

* Improvement at Week 24 in WHO Functional Class

* Change from baseline at Week 24 in REVEAL Lite 2.0 risk score

* Change from baseline at Week 24 in QoL (PAH-SYMAPACT) Questionnaire score

Other Phase 3 endpoints

* Change from baseline at Week 24 in Transthoracic Echo Parameters of right ventricular function

* Change from baseline at Week 24 in Borg Dyspnea Index (BDI) immediately following exercise

* Pharmacokinetic parameters

* Safety and tolerability of AV-101

Study description

Background summary

PAH includes a group of rare, chronic cardiopulmonary diseases with various etiologies that share the common pathologic features of inappropriate cell growth resulting in the increased resistance to blood flow through the pulmonary vasculature. WHO classification Group 1 PAH has an estimated prevalence of 15-50 cases per million individuals and is characterized by the presence of pre-capillary pulmonary hypertension (mPAP >= 20 mmHg), a pulmonary artery wedge pressure <= 15 mmHg, and PVR > 3 Wood units (Simonneau et al., 2019). In the United States, approximately 500 to 1000 new cases of PAH are diagnosed each year (National Organization for Rare Disorders, 2018).

The currently approved therapies for PAH are all primarily direct acting pulmonary vasodilators (Badlam and Bull, 2017) that do not address the underlying cause of the disease itself. While approved therapies administered as a monotherapy or combination therapy have demonstrated improvements in exercise capacity and pulmonary hemodynamics and attenuate disease progression with long-term treatment, these agents do not specifically address the proliferation of multiple lung cell types and the subsequent vascular remodeling that causes PAH. In addition, the functional limitation and survival of PAH patients on current therapies remain unsatisfactory (Galiè et al., 2016). Data from the REVEAL registry demonstrate that, from the time of diagnostic right heart catheterization and even with treatment, patients with PAH had 1-, 3-, 5-, and 7-year survival rates of 85%, 68%, 57%, and 49%, respectively (McGoon and Miller, 2012). This reflects the serious nature of the disease and the need for alternative PAH treatments with new mechanisms of action that directly target the proliferative nature of the vasculopathy, with the ultimate goal being to halt or reverse disease progression.

Imatinib mesylate (Gleevec® oral tablets), a tyrosine kinase inhibitor currently approved for the treatment of patients with chronic myeloid leukemia, has demonstrated therapeutically significant improvements on meaningful measures in clinical trials of PAH patients. Clinical efficacy of oral imatinib mesylate in the treatment of PAH was observed in a subset of PAH patients in a Phase 2 trial (Ghofrani et al., 2010) and confirmed in Functional Class II-IV patients in the Phase 3 IMPRES trial, in which the primary endpoint, 6MWD, as well as secondary endpoints measuring PVR, mPAP, cardiac output, and NT-proBNP all showed statistically significant and therapeutically relevant improvements on top of the maximal standard of care (Hoeper 2013). However, a high discontinuation rate coupled with intolerable adverse events and side effects were observed with oral administration and imatinib was never approved for PAH.

At therapeutic concentrations, imatinib is an inhibitor of the Abelson murine leukemia viral oncogene homolog (ABL), Colony Stimulating Factor 1 Receptor (CSF1 R), KIT Proto-Oncogene Receptor Tyrosine Kinase (cKIT), Discoidin Domain Receptor (DDR), Lymphocyte-Specific Protein Tyrosine Kinase (LCK) and Platelet-derived growth factor receptor (PDGFR) kinases (Davis et al., 2011). Signaling through each of these kinases has been implicated in histopathologic remodeling in PAH including PDGFR mediated proliferation and apoptotic resistance of vascular smooth muscle and endothelial cells, KIT expression directly in the vasculature and its influence on precursor cells, fibrotic signaling and recovery mediated by DDR and ABL, as well as immune dysregulation via LCK, CSF1 Rand KIT (Schermuly et al., 2005; Montani 2011 ; Rojo et al., 2019; Leitinger et al., 2014; and Rossy et al., 2012). Due to its anti-proliferative effects, imatinib has the potential to be a disease modifying therapy for PAH.

Given the demonstrated clinical efficacy of oral imatinib mesylate in PAH, Aerovate is developing AV-101 to target the delivery of imatinib to the diseased organ, the lungs. Inhaled administration of AV-101 is expected to provide rapid local exposure of respiratory tissue to imatinib with a lower dose and lower systemic exposure compared to Gleevec® oral tablets. Aerovate expects that inhaled AV-101 administration will result in a more favorable benefit/risk profile than that observed with oral Gleevec administration. Thus AV-101 is expected to provide an effective and safe therapeutic option for PAH patients, distinguished from vasodilatory agents by virtue of a mechanism of action that addresses the core proliferative cause of the disease.

Study objective

The objective of the study is to establish an optimal dose of AV-101 based primarily upon the change in PVR but also other efficacy, safety, and tolerability findings from the Phase 2b Part of the study. The optimal dose will be taken into the Phase 3 Part of the study where the placebo-corrected change in 6MWD after 24 weeks of treatment will be used as the primary

endpoint. Except for PVR (RHC) and 6MWD, all secondary endpoints will be similar across the Phase 2b and 3 Parts of the study. All subjects will be given the opportunity to enter into a LTE study following completion of the placebo-controlled parts of Study AV-101-002. Subjects who were on placebo in the Phase 2b Part of the study and who enter the LTE study will be re-randomized to one of the 3 active doses until such time as the optimal dose has been selected. They will then be transitioned to the optimal dose while they continue in the LTE.

Study design

Study AV-101-002 consists of three parts with continuous recruitment:
• Phase 2b Part - A Phase 2b placebo-controlled dose response part to evaluate 3 doses of AV-101 (10 mg, 35 mg, and 70 mg BID) and placebo in patients with PAH over 24 weeks, with PVR as the primary endpoint. Subjects will continue to be enrolled until there are approximately 40 evaluable subjects in each treatment arm with RHC data who have completed the week 24 Visit. The database will be locked, and an optimal dose will be selected to take forward into the Phase 3 Part of the study.
• Intermediate Part - A placebo-controlled part to evaluate 3 doses of AV-101 (10 mg, 35 mg, and 70 mg BID) and placebo in patients with PAH over 24 weeks, with 6MWD as the primary endpoint. Recruitment will be continuous between completing enrollment of approximately 160 evaluable subjects in the Phase 2b Part and selecting the optimal dose.
• Phase 3 Part - A confirmatory Phase 3 placebo-controlled part to evaluate 1 dose of AV-101 (optimal dose) and placebo in patients with PAH over 24 weeks, with 6MWD as the primary endpoint. The Phase 3 primary analysis on change in 6MWD will also include subjects on the optimal dose who were enrolled during the Intermediate Part.

Enrollment criteria for all study Parts will be the same, except for the following:
• For the Intermediate and Phase 3 Parts, RHC procedures performed within 12-months of screening may be accepted provided the subject has NOT changed PAH medications since the historical RHC.

The schedule of activities will be the same for all study Parts except that there will be no requirement for a week 24 RHC at the end of the Intermediate and Phase 3 Parts of the study. In addition, the study QoL questionnaire will be conducted in the Phase 2b Part of the study using emPHasis-10 survey, whereas PAH-SYMPACT will be used in the Intermediate and Phase 3 parts of the study.

Intervention

Subjects will be followed by the Investigator according to clinical practice,

with formal (per protocol) assessments conducted at the Screening/Enrollment Visit and at Clinic Visits. Study visits will occur at Screening, Day 1, Weeks 1, 4, 8, 12, 16, and 24. There will be a 4-week follow up visit (by telephone) after the subject*s end of treatment (EOT) Week 24 Visit if they do not enter the LTE.

Subjects discontinuing study treatment prior to Week 24 must return to the site as soon as possible for safety assessments. If this assessment does not correspond with a scheduled study visit, then an Early Discontinuation (ED) Visit will be performed. Subjects will then be required to continue with study visits and assessments through to Week 24 as well as the Safety Follow-Up (FU).

Should a subject withdraw consent to be followed through to Week 24, they should return for an ED Visit as soon as possible following the last dose and will also have a Safety FU 4 weeks after the ED Visit.

Test Product, Dose, and Mode of Administration:
Capsules of AV-101 or placebo inserted into a dry powder inhaler device for administration to subjects* lungs by inhalation
Phase 2b: Capsule strength: 5 mg, 17.5 mg, or 35 mg AV-101, or placebo
Administered Doses (2 capsules): 10 mg, 35 mg or 70 mg AV-101, or placebo, BID

Phase 3: AV-101 optimal dose or placebo

Study burden and risks

The burden and risks mainly consist out of extra time spent and the subject may suffer from the measurements during the study.
No serious adverse events were reported by healthy volunteers who were administered AV-101 in a Phase 1 study.

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

To be eligible, a participant is required to be or have:
1• Male or female adults between 18 and 75 years of age at the screening visit within 28 days
prior to Day 1.
2• Subject with a diagnosis of PAH belong to one of the subgroups of the NICE classification of
Group 1*:
a. I/HPAH, PAH-CTD,
b. PAH due to drugs and toxins (having been in the care of the investigator for
at least one year with no relapses of drug or toxin/chemical abuse),
c. HIV associated or
d. PAH due to repaired congenital heart disease (at least 1 year since repair).
*Excluding patients with Portopulmonary Hypertension.
3• World Health Organization (WHO) Functional Class II, III or IV symptoms
4• Meets all of the following hemodynamic criteria by means of an RHC at study Screening: mPAP
>= 25 mmHg, PVR > 400 dynes.sec/cm5 and PCWP <= 15 mmHg.
* For the Phase 2b part: subjects who have had an RHC within 30 days of the Screening visit
to assess for pulmonary hypertension, with all the protocol required variables collected, and
was performed at the same institution as the Investigator*s site do not require the

Screening/Baseline RHC to be performed.
* For the Intermediate and Phase 3 Parts: RHC procedures performed within 12-months of screening may be accepted provided the subject meets the Inclusion Criteria #5 requirements for stable background PAH medication.
5• On a stable background of at least two PAH approved medications at the Screening Visit, i.e., the same PAH medications for at least 90 days and each PAH medication at a stable dose for at least 30 days. Approved PAH medications include phosphodiesterase type 5 (PDE-5) inhibitors, endothelin receptor antagonists (ERA), soluble guanylate cyclase (sGC) stimulators, and parenteral and oral prostacyclins (including prostanoids and prostacyclin receptor agonists). Stability of parenteral prostacyclins means a change of no more than 10% in the previous 30 days from the Screening Visit.
6• A history of ventilation/perfusion (V/Q) scan, CT angiogram or pulmonary arteriogram negative for chronic thromboembolic pulmonary hypertension (CTEPH) at the time of their Group 1 PAH diagnosis (if results from a historical scan are unavailable then one of the specified imaging procedures may be performed at Screening).
7• Must meet all of the following criteria for pulmonary function (spirometry) tests completed no more than 24 weeks before the Screening Visit: Forced Expiratory Volume in 1 second (FEV1) >= 60% of predicted normal and FEV1:Forced Vital Capacity (FVC) ratio >= 0.60.
8• Must have a resting arterial oxygen saturation (SaO2) >= 90%, with or without supplemental oxygen, as measured by pulse oximetry at the Screening Visit.
9• Must be able to walk a distance of at least 100 m but no more than 475 m during the Screening 6-minute walk tests. In addition, the subject must be able to demonstrate a stable baseline for the 6-minute walk tests between the Screening and Randomization Visits.
10• Able to understand the study procedures and be willing to comply with the study restrictions.
Willing and able to sign a written informed consent prior to all study-related procedures.
11• Female subjects of childbearing potential must agree to use a highly effective form of

contraception for at least 28 days prior to when they will receive the first dose of study
drug, and for at least 30 days after completing or discontinuing study treatment (highly effective
forms of contraception are described in the protocol.
12• Evidence of negative test for SARS-CoV-2, by PCR, at the Screening Visit; Subjects with
previous COVID-19 infection may be included provided the PCR test is negative for SARS
CoV-2 and they do not have chronic symptoms as a result of COVID-19. COVID-19 testing may
be performed at local lab, per site/local guidelines, or via the study Central Lab.
13• Has not enrolled in an exercise training program for pulmonary rehabilitation within 12 weeks
prior to the Screening Visit and must agree not to enroll in an exercise training program for
pulmonary rehabilitation during the Screening Period and the first 24 weeks of the study.
14• If currently enrolled in an exercise training program for pulmonary rehabilitation for more than
12 weeks at the time of the Screening Visit, must agree to maintain their current level of
rehabilitation for the first 24 weeks of the study.

Exclusion criteria

1• Taking warfarin (or any vitamin K antagonists), direct oral anticoagulant (DOAC) therapy, or
dual antiplatelet therapy within 2 weeks prior to Day 1/Randomization
2• Pulmonary hypertension (PH) belonging to Groups 2 to 5 of the 2018 NICE classification and
Group 1 diagnosed with Portopulmonary Hypertension.
3• History of left ventricular ejection fraction (LVEF) <= 40% on echocardiogram within 12 months
of screening, or clinically significant ischemic, mitral or aortic valve disease, or constrictive
heart disease in the opinion of the Investigator.
4• Evidence of three or more (>= 3) of the following left ventricular disease/dysfunction risk factors:
o Body mass index (BMI) >= 30 kg/m2 at the Screening Visit
o History of essential hypertension
o Diabetes mellitus - any type
o Historical evidence of significant coronary artery disease (CAD) established by any one of

the following:
- History of myocardial infarction
- History of percutaneous coronary intervention (PCI)
- Angiographic evidence of CAD (> 50% stenosis in at least one vessel), by angiography
- Positive stress test with imaging
- Previous coronary artery surgery
- History of chronic stable angina or unstable angina
5• Taking inhaled prostacyclins within the past 3 months prior to the Screening Visit
6• History of chronic uncontrolled asthma (subjects on corticosteroids will be allowed into the study)
7• History of any illness or condition that, in the opinion of the Investigator could confound the results of the study or pose an additional risk to the subject through their participation in the study
8• Inability to use or may have potential difficulties using an inhaler device during each dosing period
9• Participating in a clinical study (e.g., attending follow-up visits) or who have received an investigational drug (new chemical entity) in the past 30 days prior to the Screening Visit.
Involvement in strictly observational studies (Registries) is allowed provided this is approved by the Contract Research Organization (CRO) Medical Monitor.
10• Donated blood, plasma, or platelets in the month prior to screening or who have made donations on more than two occasions within the 12 months preceding the first dose administration of study drug or have had a loss of >= 400 mL of blood within 2 months prior to Day 1/Randomization
11• Deficient thrombocyte function, Thrombocytopenia < 50 x10^9/L (50 x 10^3/µL) at the Screening Visit
12• Uncontrolled systemic arterial hypertension, systolic > 180 mm Hg or diastolic >110 mm Hg at the Day 1/Randomization Visit
13• QTcF > 450 msec for males and > 470 msec for females at the Screening Visit in the absence of right bundle branch block. (If there is prolongation of the QTcF interval in the presence of bundle branch block, the Investigator should use their clinical

judgement as to whether to
include the subject. These cases should be discussed with the Medical
Monitor).
14• History of Long QT Syndrome or Torsade de Pointes
15• Hemoglobin of < 80 g/L (8 g/dL) at the Screening Visit
16• Serum ALT or AST lab value that is >3 x upper limit of normal (ULN) at the
Screening Visit
17• Severe renal impairment (eGFR <30 mL/min/1.73 m^2 at screening based on the
CKD-EPI
equation)
18• Severe hepatic impairment (Child-Pugh Class C with or without cirrhosis) at
the Screening Visit
19• Known deficiencies of blood coagulation, inherited, or acquired blood
coagulation disorders,
factor XII, factor XIII; decreased generation of coagulation factors
due to acute or chronic liver
diseases, inefficient coagulation e.g., due to autoantibodies against
coagulation factors such as
in lupus anticoagulant, disseminated intravascular coagulation (DIC)
etc.
20• Evidence or history of major bleeding or intracranial hemorrhage
21• History of elevated intracranial pressure
22• Significant history or drug allergy as determined by the Investigator
23• Known or suspected drug hypersensitivity to any component of the trial
drug (lactose
intolerant subjects are allowed into the study)
24• Clinically relevant history or current psychological abnormality
(including alcohol abuse),
psychiatric or neurological illness or autonomic neuropathy, which in
the opinion of the
Investigator could jeopardize or would compromise the subject*s
ability to participate in
the trial
25• Recent major surgical intervention which in the opinion of the
Investigator would
compromise the subject*s ability to participate in the trial
26• Pregnant or breast-feeding females
27• Receiving the SARS-CoV-2 vaccination from 1 week prior to Screening and
through 4 weeks
post-Day1/Randomization.
28• Post COVID-19 chronic symptoms (*Long Haulers*) at Screening

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:	Pending
Start date (anticipated):	15-05-2023
Enrollment:	14
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	N/A
Generic name:	imatinib

Ethics review

Approved WMO Date:	16-02-2022
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-12-2022
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-05-2023
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-06-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-07-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-08-2023
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	EUCTR2021-001910-13-NL
ClinicalTrials.gov	NCT05036135
CCMO	NL79435.029.22