IMPAHCT-FUL: A Long-Term Extension, Multi-Center Safety Study of AV-101 in Subjects With Pulmonary Arterial Hypertension (PAH) Who Have Completed Study AV-101-002

Published: 17-11-2022
Last updated: 07-04-2024

The objective of the study is to establish the long-term safety and tolerability of AV-101. The long-term effects of AV-101 on efficacy measures will also be assessed.

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

Summary

ID

NL-OMON53603

Source
ToetsingOnline

Brief title
IMPAHCT-FUL

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

Safety and tolerability of AV-101

Other Pre-specified Outcome Measures:

-Change from baseline in the 6MWD (Time Frame: Baseline, up to study completion)

-Change from baseline in NT-proBNP (Time Frame: Baseline, up to study completion)

-Change from baseline in Transthoracic Echo parameters of right ventricular (RV) function (Time Frame: Baseline, up to study completion)

-Time to Clinical Worsening events (Time Frame: up to study completion)

Secondary outcome

Not applicable

Study description

Background summary

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.

Clinical efficacy of oral imatinib mesylate in the treatment of PAH was observed in Functional Class II-IV patients in the Phase 3 IMPRES trial, in which the primary endpoint, six minute walk distance (6MWD), as well as secondary endpoints measuring pulmonary vascular resistance (PVR), mean pulmonary arterial pressure (mPAP), cardiac output (CO), and N-Terminal Prohormone-B Natriuretic Peptide (NT-proBNP) all showed statistically significant and therapeutically relevant improvements on top of the maximal standard of care (Hoeper et al., 2013). However, oral imatinib was not well tolerated and further clinical development was halted.

At therapeutic concentrations, imatinib is an inhibitor of the Abelson murine leukemia viral oncogene homolog (ABL), Colony Stimulating Factor 1 Receptor (CSF1R), 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, CSF1R and 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 in PAH, Aerovate is developing a dry powder inhaled imatinib, 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. Therefore, subjects who successfully complete the 24-week placebo-controlled trial (AV-101-002) will be offered the opportunity to continue into this long-term extension (LTE) study.

Study objective

The objective of the study is to establish the long-term safety and tolerability of AV-101. The long-term effects of AV-101 on efficacy measures will also be assessed.

Study design

Study AV-101-003 is a long-term extension (LTE) follow up study where recruitment of subjects will continue as the parent study (AV-101-002) progresses from Phase 2b to Phase 3. Subjects who were on placebo in Phase 2b and the Intermediate Part of the study who enroll in the LTE study will be re-randomized to one of the 3 active AV-101 doses until such time as the optimal dose has been selected. Once the optimal dose of AV-101 has been selected, all subjects will be transitioned to the optimal dose while they continue in the LTE, and subjects completing the Intermediate Part or parent study Phase 3 will enroll into the LTE study at the optimal dose.

Subjects enrolling into the LTE study will be closely followed for the first 24 weeks given that those who transition from placebo will be receiving AV-101 for the first time. Study visits will be every 3 months after completing the first 24-week period. Investigators and subjects will remain blinded to the randomization in the parent study until the optimal dose has been selected for the Phase 3 part in AV-101-002.

Intervention

Subjects will be followed by the Investigator according to clinical practice, with formal (per protocol) assessments conducted at the Screening/Baseline and at other protocol Clinic Visits. Study visits will occur at Screening/Baseline, Weeks 1 (phone), 4, 8, (phone) 12, 16 (phone), week 20 (phone) and 24. After the Week 24 visit subjects will return to the clinic every 12 weeks for study assessments. There will be a 4-week follow up by telephone after the subject*s End of Treatment (EOT) Visit.
Week 20 phone visit is only for females of childbearing potential as the main purpose is to provide a reminder to perform home pregnancy testing.

If a subject withdraws consent, they should return for an ED Visit as soon as possible following the last dose and they should have a Safety Follow-Up (FU) Visit 4 weeks after the ED Visit. Subjects will then be contacted for Vital Status every 24 weeks after the Safety Follow Up Visit by telephone until study completion.

Test Product, Dose, and Mode of Administration:
Capsules of AV-101 inserted into a dry powder inhaler device for administration to subjects* lungs by inhalation.

Subjects entering the LTE study from the Phase 2b and Intermediate Parts of AV-101-002: Capsule strength: 5 mg, 17.5 mg, or 35 mg AV-101. Administered Doses (2 capsules): 10 mg, 35 mg, or 70 mg AV-101, BID.
Subjects entering the LTE study from the Phase 3 Part of AV-101-002: AV-101 optimal dose, BID.

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

1. Subjects who have consented to participate.
2. Subjects who have successfully completed the placebo-controlled 24-week study AV-101-002 without a treatment-limiting toxicity resulting in discontinuation of study drug.
3. Female subjects of childbearing potential who have agreed to continue to use a highly effective form of contraception during the LTE and for at least 30 days after completing or discontinuing study treatment.

Exclusion criteria

1. Subjects for whom the investigator believes that it would not be in the best interest of the subject to be included in the LTE e.g., for clinical or social reasons.
2. Subjects who were not compliant with study medication in AV-101-002 as assessed by the Investigator.
3. 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.
4. Recent major surgical intervention which in the opinion of the Investigator would compromise the subject*s ability to participate in the trial.
5. Pregnant or breast-feeding females

Study design

Design

Study phase:	3
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL
Recruitment status: Pending

Start date (anticipated):	01-11-2023
Enrollment:	9
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	n.a.
Generic name:	imatinib

Ethics review

Approved WMO Date:	17-11-2022
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-08-2023
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-08-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-11-2023
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	EUCTR2021-006864-25-NL
ClinicalTrials.gov	NCT05557942
CCMO	NL82159.029.22