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RESEARCH ARTICLE

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IMPAHCT: A randomized phase 2b/3 study of inhaled imatinib for pulmonary arterial hypertension

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Abstract

AV-101 (imatinib) powder for inhalation, an investigational dry powder inhaled formulation of imatinib designed to target the underlying pathobiology of pulmonary arterial hypertension, was generally well tolerated in healthy adults in a phase 1 single and multiple ascending dose study. *I*nhaled I*m*atinib *P*ulmonary *A*rterial *H*ypertension *C*linical *T*rial (IMPAHCT; NCT05036135) is a phase 2b/3, randomized, double-blind, placebo-controlled, dose-ranging, and confirmatory study. IMPAHCT is designed to identify an optimal AV-101 dose (phase 2b primary endpoint: pulmonary vascular resistance) and assess the efficacy (phase 3 primary endpoint: 6-min walk distance), safety, and tolerability of AV-101 dose levels in subjects with pulmonary arterial hypertension using background therapies. The study has an operationally seamless, adaptive design allowing for continuous recruitment. It includes three parts; subjects enrolled in Part 1 (phase 2b dose–response portion) or Part 2 (phase 3 intermediate portion) will be

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randomized 1:1:1:1 to 10, 35, 70 mg AV-101, or placebo (twice daily), respectively. Subjects enrolled in Part 3 (phase 3 optimal dose portion) will be randomized 1:1 to the optimal dose of AV-101 and placebo (twice daily), respectively. All study parts include a screening period, a 24-week treatment period, and a 30-day safety follow-up period; the total duration is ~32 weeks. Participation is possible in only one study part. IMPAHCT has the potential to advance therapies for patients with pulmonary arterial hypertension by assessing the efficacy and safety of a novel investigational drug-device combination (AV-101) using an improved study design that has the potential to save 6-12 months of development time. ClinicalTrials.gov Identifier: NCT05036135.

KEYWORDS
dry powder inhaler, effectiveness, study design, tolerability, tyrosine kinase inhibitor

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a rare, chronic cardiopulmonary disease characterized by abnormal vascular remodeling and proliferation of pulmonary vascular endothelial cells and smooth muscle cells, resulting in elevated pulmonary vascular resistance (PVR), right ventricular heart failure, and death.[1–3] Pulmonary vasodilators (e.g., prostacyclin analogs and receptor agonists, phosphodiesterase-5 inhibitors, endothelin receptor antagonists, and guanylate cyclase stimulators), used alone or in combination, comprise the current primary therapies for PAH,[1,3] and improve PAH symptoms, but do not fully address PAH pathobiology.

Multiple tyrosine kinase-mediated signaling pathways are implicated in PAH pathobiology, including platelet-derived growth factor, vascular endothelial growth factor, epidermal growth factor, c-kit, and SRC.[4–7] Activation of these pathways leads to sustained proliferation and apoptotic resistance in both malignancies and PAH, suggesting similarities in pathobiology; thus, therapies targeting such pathways might be leveraged to treat PAH.[8] Several tyrosine kinase inhibitors (e.g., imatinib, nilotinib, sorafenib, and seralutinib), some of which are approved to treat malignancies, have been investigated for PAH treatment[4] with variable effectiveness and safety in preclinical and clinical studies, suggesting their distinct target profiles are important.[9–15]

Platelet-derived growth factor signaling has been extensively studied for its role in PAH pathogenesis.[5,16–21] Imatinib has been shown to attenuate downstream platelet-derived growth factor receptor-mediated signaling effects, affecting cellular growth, differentiation, proliferation, survival, inflammation, and metabolism, as well as restoring proper apoptotic signaling,[22,23] in PAH preclinical models. In in vitro and in vivo PAH models, imatinib reversed evidence of pulmonary vascular remodeling, reduced right ventricular hypertrophy and pressure, and improved hemodynamics.[5,16–19]

In a phase 2 study, oral imatinib improved hemodynamics in symptomatic patients with PAH using stable PAH medications, suggesting the efficacy of imatinib as an add-on therapy.[24] The subsequent phase 3 IMPRES trial further evaluated oral imatinib as an add-on therapy in patients with advanced PAH using ≥2 background PAH therapies.[14] However, there was no difference in the time to clinical worsening between imatinib and placebo. This was related to an excess of hospitalizations leading to discontinuations due to adverse events (AEs; 20 vs. 7 in the imatinib and placebo groups, respectively) during the first 8 weeks of the study. The AEs were mainly gastrointestinal (nausea, vomiting, and diarrhea) or peripheral edema.[25] Even though IMPRES achieved its primary outcome, a 6-minute walk distance (6MWD), the regulatory agencies were concerned about the high rate of AEs with imatinib, including subdural hematomas, and considered the benefit/risk balance as unfavorable; thus, the development of oral imatinib for the treatment of PAH was halted.

AV-101 design and development

AV-101, a novel inhaled dry powder formulation of imatinib was developed (Figure 1) with aim to deliver therapeutically relevant imatinib concentrations to the lungs while reducing systemic AEs, potentially resulting in a more favorable benefit/risk profile.[26] Following inhalation, the size and properties of AV-101 particles facilitate their deposition throughout the respiratory tract.[27,28] Once deposited, the particles undergo dissolution and concentration gradient-driven diffusion to the

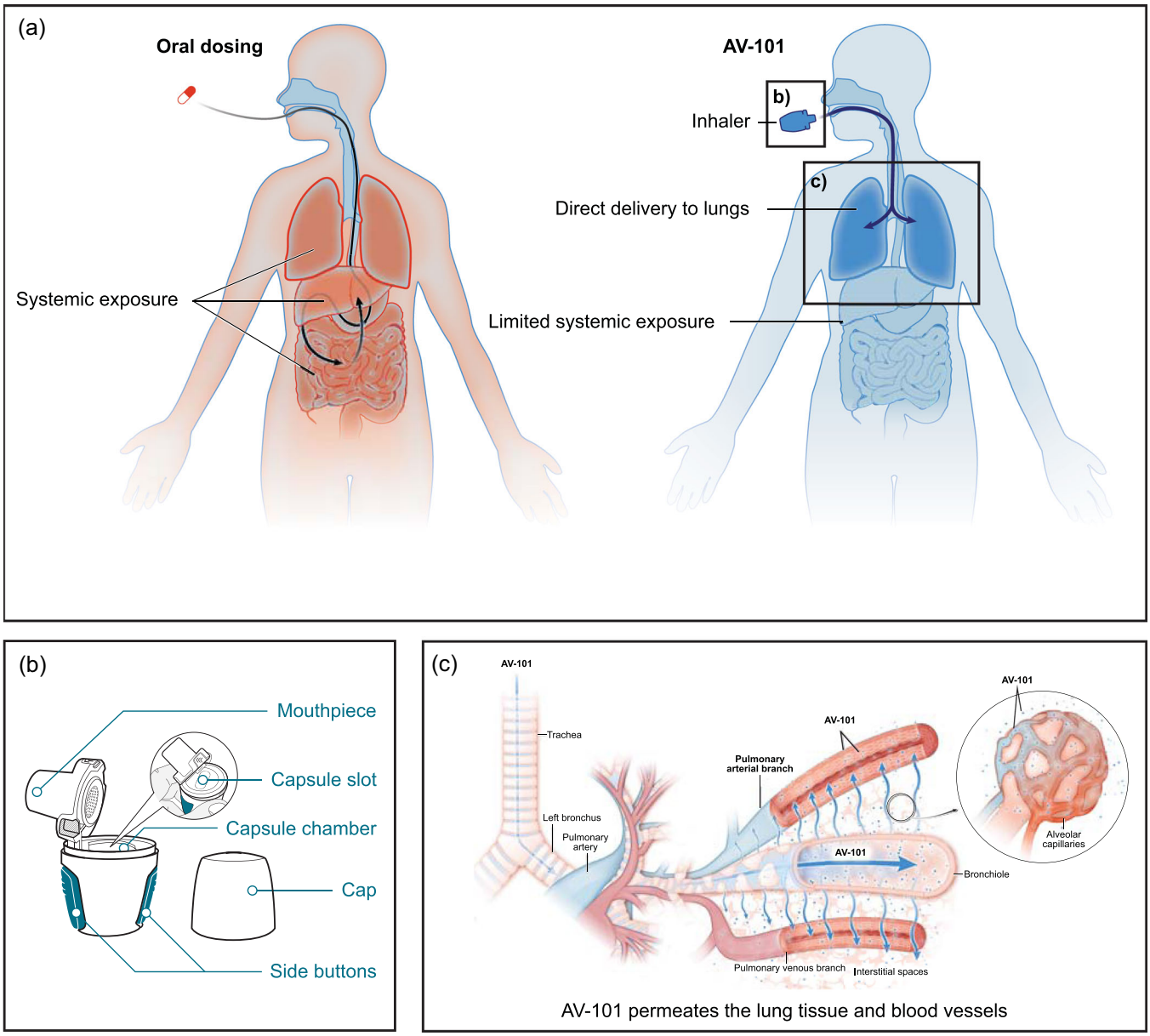

FIGURE 1 Targeted delivery of AV-101 to diseased respiratory tissue. (a) AV-101 is a novel, investigational drug-device combination that is designed to deliver a dry powder formation of imatinib directly to the lungs via a dry powder inhaler, limiting the off-target effects from systemic exposure to oral imatinib. (b) AV-101 capsules are inserted into the dry powder inhaler and delivered to the subject's lungs via inhalation through the device mouthpiece. (c) Following inhalation, AV-101 particles rapidly diffuse to the surrounding pulmonary vasculature.

surrounding pulmonary vasculature. Intratracheal instillation of imatinib in rats demonstrated high lung-to-plasma concentration ratios. Six-month chronic toxicity studies have been conducted in nonhuman primates with no important clinical or laboratory observations (data on file).

A phase 1 study was conducted to evaluate AV-101 doses ranging from 1 to 90 mg in healthy participants. In the single-ascending dose portion, AV-101 significantly reduced systemic imatinib exposure compared with oral imatinib 400 mg ($p < 0.001$).[26] In the multiple-ascending dose portion, AV-101 (10, 30, or 90 mg) or placebo was administered twice daily (BID) for 7 days, except for a single morning dose on Day 7. Dose-dependent increases in imatinib concentration were observed after multiple AV-101 administrations, but steady-state plasma concentrations were substantially lower at the maximum AV-101 dose (90 mg) compared with the simulated, steady-state plasma concentration following daily oral administration of imatinib 400 mg ($p = 0.0002$). Across all doses, AV-101 was generally well tolerated, with no reported serious treatment-emergent AEs.[26] Results from

the phase 1 study in healthy volunteers, together with lung modeling data and the 6-month toxicity studies, supported the doses selected for the phase 2b/3 *I*nhaled I*m*atinib *P*ulmonary *A*rterial *H*ypertension *C*linical *T*rial (IMPAHCT) study.

IMPAHCT STUDY DESIGN AND METHODS

The IMPAHCT (ClinicalTrials.gov Identifier: NCT05036135) was designed to address some of the challenges of historical PAH clinical trials with continuous recruitment and an adaptive study design comprising a 24-week treatment period for each subject. The key objectives of IMPAHCT are to identify an optimal AV-101 dosage (phase 2b primary endpoint: PVR) and assess the efficacy (phase 3 primary endpoint: 6MWD), safety, and tolerability of the optimal AV-101 dosage in subjects with PAH using background PAH therapies.

Study population

Assuming a conservative discontinuation rate of 20%, an estimated 400–500 subjects will be enrolled across ~140 sites in ≥28 countries (Supporting Information S1: Figure 1). All study phases will enroll adults aged 18–75 years with Group 1 pulmonary hypertension[29] and a PVR > 400 dynes s/cm^5 who are currently using background PAH medications and no inhaled prostacyclins. Detailed eligibility criteria are provided in Table 1. Although enrollment criteria are similar between study phases, each subject can participate in only one study part.

Study design

IMPAHCT is a phase 2b/3, randomized, double-blind, placebo-controlled, dose-ranging, and confirmatory study with an operationally seamless adaptive design, consisting of three parts: the phase 2b dose–response portion (Part 1), the multiple dose intermediate portion (Part 2), and the optimal dose portion (Part 3). Parts 2 and 3 comprise the confirmatory phase 3 portion (Figure 2). This design allows for continuous recruitment throughout the study, with an evaluation of primary endpoints at Week 24 (phase 2b: PVR; phase 3: 6MWD). Part 2 enrollment will begin immediately upon completion of Part 1 enrollment. The phase 2b and phase 3 data will be evaluated separately. Subjects will have the opportunity to enter a long-term, open-label extension study (IMPAHCT-FUL). Each of the three study parts of IMPAHCT consists of a screening period (≤30 days), a 24-week treatment period, and a 30-day safety follow-up period, for a total duration of up to ~32 weeks.

An interactive web-based randomization system will be used to assign subjects to treatment groups. Following enrollment, subjects will be stratified based on underlying PAH etiology (idiopathic/heritable or nonidiopathic/heritable PAH) and Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL) Lite 2 risk scores (low/intermediate or high risk). Each subject will be randomly assigned to a unique randomization number that is associated with the treatment assignment per the randomization list, and the interactive web-based randomization system will allocate a study drug to each subject. Subjects, study site personnel, and sponsor personnel will be blinded to treatment assignments.

Part 1: Phase 2b dose response

Part 1 uses a dose–response design to evaluate the benefits and risks of AV-101 at 3 doses (10, 35, and 70 mg BID) versus placebo, with 180-200 subjects randomized 1:1:1:1 to parallel dose groups. Part 1 enrollment will continue until there are 50 randomized subjects per treatment group. Based on the results of Part 1, an optimal AV-101 dose will be selected for Part 3.

Part 2: Phase 3 intermediate

While Part 1 matures to obtain Week 24 PVR data, IMPAHCT will transition to the phase 3 portion of the study, beginning with the intermediate Part 2 until the optimal AV-101 dosage from Part 1 is identified. Subjects will be randomized 1:1:1:1 to the same 4 parallel treatment arms as in Part 1. Subjects randomized to the to-be-identified optimal dose and placebo arms will contribute to the phase 3 efficacy analyses, while all subjects in Part 2 will contribute to the safety and tolerability analyses for phase 3.

Part 3: Phase 3 optimal-dose confirmation

Once the optimal AV-101 dosage is identified, enrollment will continue into Part 3, where subjects will be randomized 1:1 to the optimal AV-101 dosage or placebo. Parts 2 and 3 (combined) will comprise the phase 3 data set, with 6MWD as the primary endpoint to confirm the efficacy and safety of the optimal AV-101 dosage versus placebo.

TABLE 1 Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
1. Male or female (18–75 years old) at the screening visit (≤28 days before Day 1) 2. Diagnosis of Group 1 PAH • Idiopathic PAH/heritable PAH • Drug- and toxin-induced PAH (≥1 year with no relapse and in the care of the investigator) • PAH associated with HIV infection • PAH associated with repaired congenital heart disease (≥1 year since repair) 3. WHO functional class II, III, or IV symptoms 4. Hemodynamic criteria, as measured by right heart catheterization at screening[a]: • mPAP ≥ 25 mmHg • PVR > 400 dynes s/cm^5 • PCWP ≤ 15 mmHg 5. Stable (≥90 days) background PAH medications • Parenteral and oral prostacyclins (including prostanoids and prostacyclin receptor antagonists) are permitted • Stability of parenteral prostacyclins means a change of ≤10% in the previous 30 days from the screening visit 6. History of ventilation/perfusion scan, pulmonary arteriogram, or CT angiogram negative for chronic thromboembolic pulmonary hypertension at the time of Group 1 PAH diagnosis 7. Pulmonary function (spirometry; ≤24 weeks before screening visit): • FEV_1 ≥ 60% of predicted normal • FEV_1:FVC ≥ 0.60 8. Resting arterial oxygen saturation ≥ 90% with or without supplemental oxygen, as measured by pulse oximetry at the screening visit 9. Walk 100–475 m for the 6MWD test at the screening visit and demonstrate a stable baseline for the 6MWD tests between the screening and randomization visits 10. Understand and comply with the study procedures and restrictions; sign a written informed consent before all study-related procedures 11. Highly effective forms of contraception (≥28 days before the first dose of study drug and ≥30 days after completing or discontinuing study treatment) for female subjects 12. Negative SARS-CoV-2 PCR test at the screening visit; subjects with prior COVID-19 infection are eligible provided that their PCR test is negative and they do not have chronic symptoms as a result of COVID-19 13. Not enrolled in an exercise training program for pulmonary rehabilitation (≤12 weeks before the screening visit); agrees to not enroll in an exercise training program for pulmonary rehabilitation (during the screening period and for ≤24 weeks of the study) 14. If the subject is currently enrolled in an exercise training program for pulmonary rehabilitation for >12 weeks at the time of the screening visit, the subject must agree to maintain the current level of rehabilitation for the first 24 weeks of the study	1. Taking warfarin (or any vitamin K antagonist), DOACs, or dual antiplatelet therapy (≤2 weeks before Day 1/randomization) 2. Diagnosis of Group 2–5 PH; Group 1 diagnosed with portopulmonary hypertension 3. LVEF ≤ 40% on echocardiogram (≤12 months of screening visit); history of clinically significant ischemic, mitral, or aortic valve disease; or constrictive heart disease in the opinion of the investigator 4. Evidence of ≥3 of the following left ventricular disease/dysfunction risk factors: • BMI ≥ 30 at the screening visit • History of essential hypertension • Diabetes mellitus (any type) • Historical evidence of significant coronary artery disease, as established by: ○ Myocardial infarction ○ Percutaneous coronary intervention ○ Angiography of coronary artery disease (>50% stenosis in ≥1 vessel) ○ Positive stress test with imaging ○ Previous coronary artery surgery ○ Chronic stable angina or unstable angina 5. Taking inhaled prostacyclins (≤3 months before the screening visit) 6. Inability/difficulty using an inhaler device 7. Participating in a clinical study (e.g., attending follow-up visits) or receiving an investigational drug (≤30 days before the screening visit) • Involvement in strictly observational studies (e.g., registries) is permitted and must be approved by the contract research organization medical monitor 8. Lost ≥400 mL of blood within 2 months before Day 1/randomization or donated blood, plasma, or platelets: • ≤1 month before the screening visit • ≥2 occasions within 12 months before the first dose of the study drug 9. Uncontrolled systemic arterial hypertension (systolic: >180 mmHg or diastolic: >110 mmHg) at the screening visit or Day 1/randomization 10. Thrombocytopenia (platelets $<50 \times 10^9$/L), QTcF (males: >450 ms; females: >470 ms) in the absence of right bundle branch block, hemoglobin (<80 g/L), serum ALT or AST lab value (>3 × ULN), severe renal impairment (eGFR < 30 mL/min/1.73 m^2), severe hepatic impairment (Child–Pugh Class C with or without cirrhosis) at the screening visit 11. History of long QT syndrome or Torsade de Pointes, chronic uncontrolled asthma (subjects taking corticosteroids are eligible), any illness or condition that could confound study results or pose additional risk to the subject through study participation (in the opinion of the investigator) 12. 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

(Continues)

TABLE 1 (Continued)

Inclusion criteria	Exclusion criteria
	autoantibodies against coagulation factors such as in lupus anticoagulant, DIC, etc.) 13. History or evidence of major bleeding or intracranial hemorrhage; history of elevated intracranial pressure 14. Significant history or drug allergy as determined by the investigator 15. Known or suspected drug hypersensitivity to any component of the trial drug (lactose-intolerant subjects are eligible) 16. Clinically relevant history or current psychologic abnormality (including alcohol abuse), psychiatric or neurologic illness, autonomic neuropathy, or recent major surgical intervention that could or would jeopardize or compromise a subject's study participation (in the opinion of the investigator) 17. Females who are pregnant or breastfeeding 18. SARS-CoV-2 vaccination (≤1 week before the screening visit and through 4 weeks post-Day 1/randomization) 19. Chronic COVID-19 symptoms at the screening visit

Abbreviations: 6MWD, 6-minute walk distance; ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; COVID-19, coronavirus disease 2019; CT, computed tomography; DIC, disseminated intravascular coagulation; DOAC, direct-acting oral anticoagulant; eGFR, estimated glomerular filtration rate; FEV1, forced expiratory volume; FVC, forced vital capacity; HIV, human immunodeficiency virus; LVEF, left ventricular ejection fraction; mPAP, mean pulmonary arterial pressure; PAH, pulmonary arterial hypertension; PCR, polymerase chain reaction; PCWP, pulmonary capillary wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; QTcF, QT interval corrected using Fridericia's formula; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; ULN, upper limit of normal; WHO, World Health Organization.

[a]For the phase 3 intermediate and optimal dose parts of the study, right heart catheterization procedures performed within 6 months of screening may be accepted if conducted consistent with the protocol.

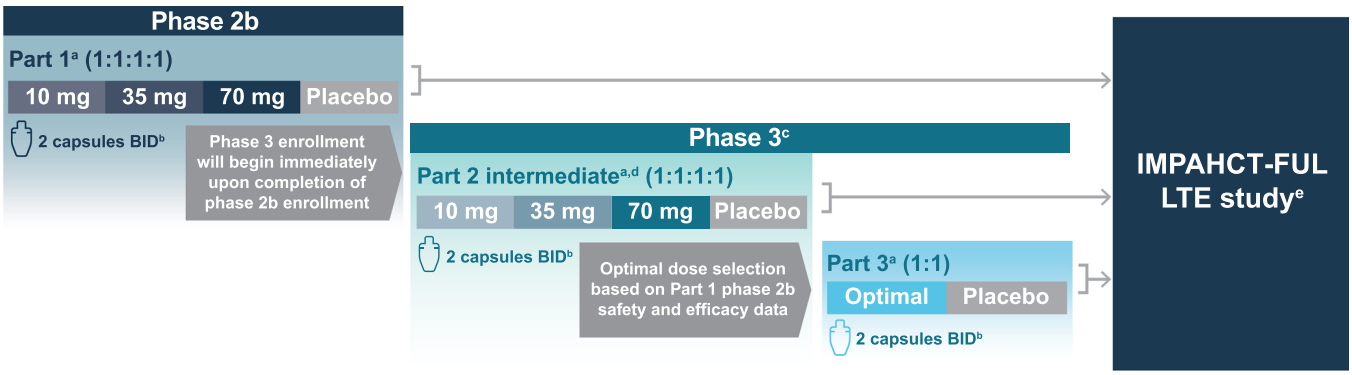

FIGURE 2 Study design. IMPAHCT (ClinicalTrials.gov Identifier: NCT05036135) is a randomized, double-blind, phase 2b/3 study being conducted in three parts. Part 1 is the phase 2b portion that will assess the safety, tolerability, and efficacy of three AV-101 doses (10, 35, and 70 mg) and placebo to determine the optimal dose of AV-101 in subjects with PAH who are on PAH background therapies. Parts 2 and 3 constitute the phase 3 portion and allow for continuous recruitment. Phase 3 will confirm the safety, tolerability, and efficacy of AV-101 compared to the placebo. [a]Participation is possible in only one part of the study, which includes a screening period (up to 30 days), a 24-week treatment period, and a 30-day safety follow-up period. [b]AV-101 will be supplied at three capsule strengths: 5, 17.5, and 35 mg. The AV-101 dry powder inhaler is a single capsule-use, reusable device. Each dose will require two capsules and will be administered BID, once in the morning and once in the evening. [c]All subjects from Parts 2 and 3 will contribute to the phase 3 safety analysis, while subjects treated at the subsequently determined optimal dose and placebo from Parts 2 and 3 will contribute to the phase 3 efficacy analysis. [d]Recruitment into Part 2 (intermediate) will be continuous beyond the number of subjects required for the phase 2b primary endpoint; these additional subjects will be enrolled into four arms until the completion of the optimal dose is identified. [e]Once the optimal dose has been identified, subjects enrolled in the IMPAHCT-FUL LTE study from phase 2b and intermediate parts of the study will be transitioned to the optimal dose. BID, twice daily; LTE, long-term extension; PAH, pulmonary arterial hypertension.

Special committees and ethical conduct of the trial

An independent data safety monitoring board (DSMB), consisting of two pulmonologists, one cardiologist, and one statistician, will be utilized to ensure external objective medical and/or statistical review of safety and/or efficacy issues, protect the ethical and safety interests of subjects, and protect the scientific validity of the study. On a predefined quarterly basis, the DSMB will review unblinded data, including discontinuation rates due to AEs in the AV-101 and placebo arms using test-based confidence intervals and the benefit/risk of AV-101 treatment.

Clinical worsening events, including serious AE hospitalizations, will be adjudicated by a treatment-blinded independent clinical event adjudication committee to determine if an event meets the definition of clinical worsening of PAH.

The study protocol will be approved by an independent ethics committee or institutional review board at all participating sites and is being conducted in accordance with the International Council for Harmonisation Good Clinical Practice, applicable laws, and regulations. Legal informed consent must be obtained from all participating subjects before enrollment.

Investigational product and treatment administration

On Day 1, subjects will be given a 4-week supply kit containing four bottles of AV-101 capsules at their respective randomized dose or placebo and four inhaler devices. AV-101 capsules will contain a proprietary dry powder of imatinib in one of three strengths (5, 17.5, or 35 mg) or placebo. Subjects will be trained to insert the drug capsules into the reusable inhaler device and on proper inhalation, maintenance, and storage techniques. Using the device, subjects will inhale the contents of two AV-101 or placebo capsules BID (morning and evening, ~10–12 h apart) and ideally within 30 min of food, for a total of 4 capsules inhaled daily.

Study endpoints and schedule of assessments

Primary and secondary endpoints for IMPAHCT were guided by the phase 3 IMPRES trial, where the change in 6MWD was the primary endpoint, and changes in PVR, mean pulmonary arterial pressure, cardiac output, and

TABLE 2 IMPAHCT study endpoints.

Phase 2b
Primary endpoint
• The placebo-corrected change from baseline in PVR[a] at Week 24
Key secondary endpoints (placebo-corrected change from baseline at Week 24)
• 6MWD
• NT-proBNP
• Hemodynamic measures (CI, mPAP, mRAP, and SvO_2)
• Clinical worsening through 24 weeks
• Multicomponent improvement parameters (% of subjects and time to achievement of parameters)
• Improvement in WHO functional class
• REVEAL Lite 2 score
• QoL (EmPhasis-10) questionnaire score
Other endpoints
• Change from baseline at Week 24 in transthoracic echo parameters of RV function
• Change from baseline at Week 24 in the Borg Dyspnea Index score
• Pharmacokinetics ($C_{max,ss}$, $C_{min,ss}$, C_{avg}, $T_{max,ss}$, $AUC_{0\text{-}tau}$, CL/F_{ss}, $MRC_{max,ss}$, and $MR_{AUC0\text{-}tau}$)
• Safety and tolerability
Phase 3
Primary endpoint
• The placebo-corrected change from in 6MWD at Week 24
Key secondary endpoints (placebo-corrected change from baseline at Week 24)
• NT-proBNP
• Clinical worsening through 24 weeks
• Multicomponent improvement parameters (% of subjects and time to achievement of parameters)
• Improvement in WHO functional class
• REVEAL Lite 2 score
• QoL (PAH-SYMPACT) questionnaire score
Other endpoints
• Change from baseline at Week 24 in transthoracic echo parameters of RV function
• Change from baseline at Week 24 in the Borg Dyspnea Index score

(Continues)

TABLE 2 (Continued)

Phase 3
• Pharmacokinetics
• Safety and tolerability

Abbreviations: 6MWD, 6-min walk distance; $AUC_{0\text{-}tau}$, area under the plasma concentration-time curve from time 0 to the end of the dosing internal; C_{avg}, average concentration during a dosing interval at steady state calculated as $AUC_{0\text{-}tau}$/tau; CI, cardiac index; CL/F_{ss}, apparent plasma clearance at steady state; $C_{max,ss}$, maximum concentration at steady state; $C_{min,ss}$, minimum concentration at steady state; mPAP, mean pulmonary arterial pressure; mRAP, mean right atrial pressure; $MR_{AUC0\text{-}tau}$, metabolite (CGP-74588) to parent AV-101 ratio for $AUC_{0\text{-}ss}$; $MRC_{max,ss}$, metabolite (CGP-74558) to parent AV-101 ratio for $C_{max,ss}$; NT-proBNP, N-terminal pro-brain natriuretic peptide; PAH, pulmonary arterial hypertension; PVR, pulmonary vascular resistance; QoL, quality of life; REVEAL, Registry to Evaluate Early and Long-Term PAH Disease Management; RV, right ventricle; SvO_2, mixed venous oxygen saturation; $T_{max,ss}$, time to reach maximum concentration at steady state ($C_{max,ss}$); WHO, World Health Organization.

[a]Assessed via right heart catheterization.

N-terminal pro-brain natriuretic peptide (NT-proBNP) were secondary endpoints.[14]

Endpoints for each IMPAHCT study part are detailed in Table 2. The primary endpoint for the phase 2b study is a placebo-corrected change from baseline in PVR at 24 weeks, assessed via right heart catheterization. The primary endpoint for the phase 3 portion is a placebo-corrected change in 6MWD at 24 weeks. Except for PVR, 6MWD, and hemodynamic measurements, secondary endpoints are the same across the phase 2b and phase 3 studies. Used in conjunction with symptom, hemodynamic, and biomarker assessments, the 6MWD test is useful for direct measurement of functional capacity and indirect assessment of common PAH symptoms (i.e., shortness of breath and fatigue).[30] It is an accepted primary endpoint for phase 3 registration trials for PAH therapies.

During the study, subjects will participate in 4 in-clinic and 3 telephone visits to reduce participation burden. A schedule of efficacy and safety assessments at each visit is provided in Figure 3. Investigator- and subject-reported AEs will be recorded throughout the study. Additional safety assessments include physical examinations, vital signs, electrocardiograms, clinical laboratory tests, and pulmonary function tests (e.g., spirometry; forced expiratory volume and forced vital capacity, peripheral oxygen saturations, and diffusing capacity of the lungs for carbon monoxide).

Clinical worsening events, a composite endpoint, will be defined as death, or hospitalization for worsening PAH, or the initiation of parenteral prostanoids, or ≥15% decline from baseline in 6MWD with continued or worsening to World Health Organization (WHO) functional class III or IV symptoms, similar to prior PAH studies. Clinical improvement will be assessed by the proportion of subjects achieving all of the following components after 24 weeks: (1) WHO functional class improvement or maintenance of class II status, (2) NT-proBNP ≥30% improvement or <300 pg/mL, and (3) ≥30 m improvement in 6MWD. REVEAL Lite 2 risk scores are derived from the following variables: estimated glomerular filtration rate, WHO functional class, systolic blood pressure and heart rate, 6MWD, and NT-proBNP.

Permitted and prohibited concomitant medications

Subjects may receive required concomitant medications not specifically prohibited by protocol. PAH therapies (endothelin receptor antagonists, phosphodiesterase-5 inhibitors, guanine cyclase stimulators, or prostacyclin derivatives [subcutaneous, oral, or intravenous]) not used at the time of enrollment should only be added if a subject has a clinical worsening event. Prohibited medicines include inhaled prostacyclins, SARS-CoV-2 vaccination (from 1 week before screening through 4 weeks after randomization), vitamin K antagonists, direct oral anticoagulants, and dual antiplatelet therapy.

Statistical analyses

Sample size and power determinations were calculated using PVR (for phase 2b) and 6MWD (for phase 3) results from the IMPRES trial. The phase 2b sample size is calculated to test the null hypothesis that the difference in change from baseline in PVR at Week 24 between each AV-101 dose and placebo is ≥0 versus the alternative hypothesis that the difference in change from baseline is <0. The global power of the study is >90% to detect that ≥1 of the doses differs statistically from placebo with a sample size of 40 subjects per treatment arm. The phase 2b portion will enroll 200 subjects (50 per treatment arm), which accounts for potential discontinuations. A closed testing method for multiple comparisons will be used to control the overall type 1 error rate ($\alpha = 0.025$).

The phase 3 sample size is calculated to test the null hypothesis that the difference in change from baseline in 6MWD at Week 24 between the optimal AV-101 dose and placebo arms is ≤0 versus the alternative that the difference is >0. The final phase 3 analysis will consist of Parts 2 and 3. The total sample size will be informed by the phase 2b data and calculated using a two-sample, independent, one-sided z test with a 0.025 significance

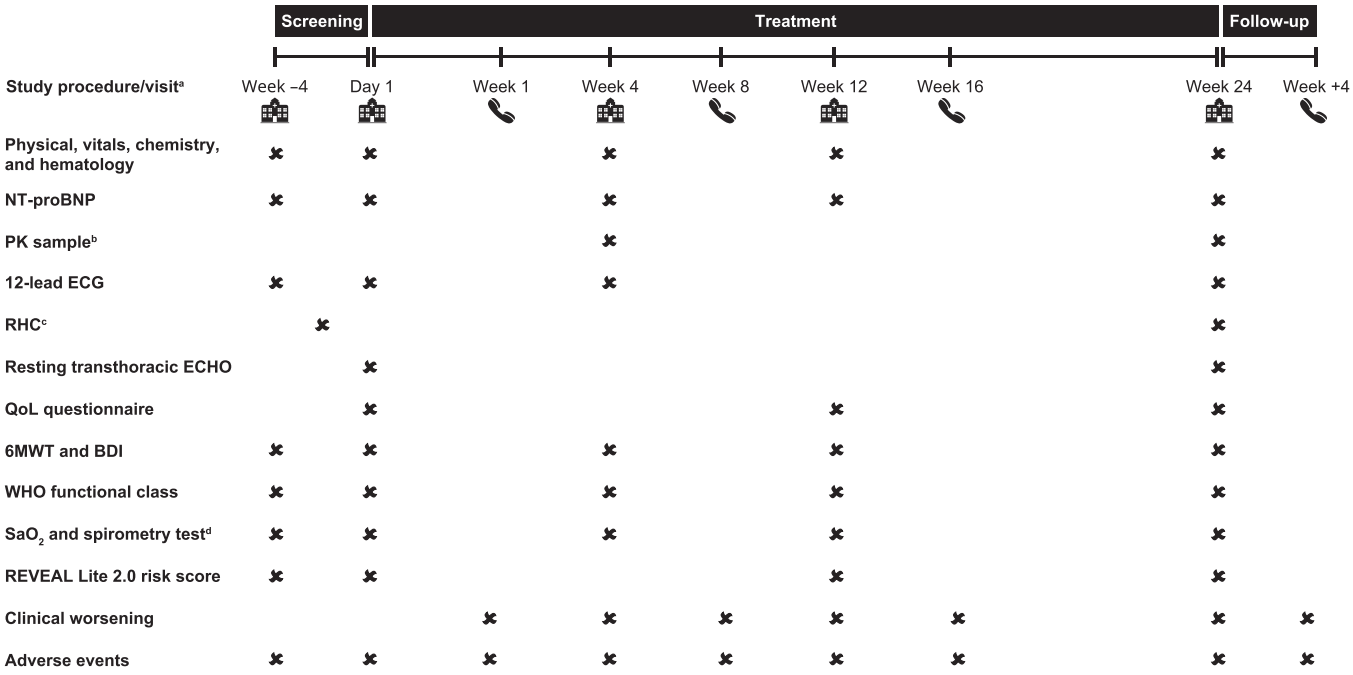

FIGURE 3 Schedule of assessments. For an individual subject, participation is possible in only one part of the 32-week study (inclusive of screening and follow-up periods). A minimum of nine study visits are planned, with three of the on-treatment visits and the 30-day safety follow-up visits being remote telephone visits. An additional phone visit is scheduled at Week 20 for women of childbearing potential to provide a reminder to perform home pregnancy testing. [a]Subjects who discontinue study treatment before Week 24 must complete an early discontinuation visit, which includes all procedures performed at Week 24 (except PK sample collection). Subjects will then be required to continue with study visits and assessments through Week 24, as well as the 30-day safety follow-up visit. [b]In the phase 2b part of the study, PK samples will be taken from subjects at Week 4 (±7 days) predose and at 5 min, 30 min, 1 h, 2 h, 4 h, 6 h, 8 h, and 12 h postdose. In the phase 3 portion of the study, PK samples will be taken at Week 4 in all subjects at predose and at T_{max} (to be determined from the phase 2b PK data). In all parts of the study, a predose trough PK sample will be taken before performing visit procedures. [c]Subjects enrolled in the phase 3 portion of the study do not require a screening RHC for eligibility if they have the results from an RHC within the previous 6 months. There will be no Week 24 RHC required for these subjects. [d]Testing includes FEV_1, FVC, and peripheral oxygen saturation. For screening, a historical assessment (≤24 weeks before the screening visit) may be used. 6MWT, 6-min walk test; BDI, Borg Dyspnea Index; ECG, electrocardiogram; ECHO, echocardiography; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; NT-proBNP, N-terminal pro-brain natriuretic peptide; PAH, pulmonary arterial hypertension; PK, pharmacokinetic; QoL, quality of life; REVEAL, Registry to Evaluate Early and Long-Term PAH Disease Management; RHC, right heart catheterization; SaO_2, arterial oxygen saturation; T_{max}, time of peak plasma concentration; WHO, World Health Organization.

level at 90% power. The effect size for calculation of the sample size for the optimal dose in phase 3 is estimated based on published data on the minimal clinically important difference for 6MWD (~33 m) in subjects with PAH,[31,32] and the sample size will be further refined based on the phase 2b data. In more typical inferential adaptive design studies, phase 2b and phase 3 data are combined and analyzed using a controlled type 1 error rate. For this study, however, which uses an operational adaptive design to continuously enroll subjects between phases, statistical analyses for phase 2b and phase 3 will be performed separately, as if the phases are 2 separate studies.

All treated subjects in each study phase (i.e., phase 2b and phase 3) will be included in safety and tolerability analyses for that phase of the study.

For the phase 2b primary endpoint of change in PVR, analysis of covariance (ANCOVA) will be performed using the Week 24 change from baseline PVR data from all dose groups and the placebo group, with randomization stratification factors and baseline PVR as covariates. Randomization strata include the underlying etiology of PAH (idiopathic/heritable or nonidiopathic/heritable PAH) and the baseline REVEAL Lite 2 risk score in lieu of risk (low/intermediate or high) category.

For secondary endpoints, a similar model will be used. For continuous variables, such as 6MWD and NT-proBNP, ANCOVA will be utilized with the same covariates as for the PVR analysis. For time-to-clinical worsening, a log-rank test stratified by randomization stratification factors and Kaplan–Meier analysis will be performed. For binary variables, such as achieving

multicomponent improvement and maintenance of or improvement in the WHO functional class, logistic regression with the same covariates will be performed. Analysis of the phase 3 data will be similar; however, the phase 2b data will be used to further refine these analyses.

Optimal dose selection

When the database for the phase 2b portion has been locked, the study team, including the steering committee, the chair of the DSMB, and the sponsor, will review the data. There is no predetermined threshold that will dictate which dose is chosen; however, the data will be assessed in their totality, with the primary focus being on the change in PVR across dose groups and considering the overall benefit/risk profile. If there is a clear dose response, then the most effective dose with acceptable safety and tolerability will likely be chosen.

IMPAHCT-FUL long-term extension study

Following completion of their participation in the phase 2b or phase 3 portions of IMPAHCT, eligible subjects (including those randomized to placebo) will be given the opportunity to enter the long-term extension study (IMPAHCT-FUL; NCT05557942) and transition to the optimal AV-101 dosage. IMPAHCT-FUL will evaluate long-term (i.e., over ~3 years) safety and tolerability of AV-101 and further assess key efficacy outcomes, including 6MWD, NT-proBNP, right ventricular function, and time to clinical worsening.

DISCUSSION

AV-101, imatinib powder for inhalation is expected to achieve therapeutic lung concentrations of imatinib at lower doses than oral administration by directly delivering imatinib to respiratory tissue, thereby potentially limiting adverse effects of systemic exposure and improving tolerability. IMPAHCT is designed to determine the optimal AV-101 dosage, maximizing its potential benefit/risk profile for subjects with PAH using background PAH therapies. Moreover, primary endpoint assessments (phase 2b: PVR; phase 3: 6MWD) will provide data on the potential effectiveness of AV-101 to attenuate disease progression and improve functional exercise capacity, while secondary endpoint assessments will provide a holistic understanding of impacts on biomarkers, hemodynamics, cardiac function, clinical improvement, quality of life, and safety and tolerability. We chose to keep the clinical worsening composite endpoint similar to previous PAH studies; however, composites are statistically only as strong as the weakest component (e.g., initiation of parenteral prostacyclins). Outside of the objective hard components (e.g., death), it has been acknowledged that this composite endpoint in PAH clinical studies needs further scrutiny.

IMPAHCT's operationally seamless design supports the potential for expedited drug development and the need for innovative trial design. Clinical trial designs for evaluating PAH therapies have evolved over time.[33] The current paradigm of phase 2 and phase 3 studies in PAH generally has PVR (requiring fewer patients) and 6MWD (requiring more patients) as the primary endpoint, respectively,[34,35] with a break between the phases that extends drug development timelines. By employing continuous recruitment and an adaptive study design, IMPAHCT is estimated to save 6–12 months versus conducting separate phase 2 and phase 3 studies. IMPAHCT uses remote telephone visits to reduce the burden of in-clinic study visits, and the total expected study duration for each subject is only ~32 weeks, including screening and follow-up. Limitations of this design include that it potentially exposes additional subjects to ineffective doses during the intermediate part and, similarly, that it may also expose additional subjects to doses that might be poorly tolerated. In this respect, the role of the DSMB is significant as a safeguard to protect subjects from harm, and its timely review of the safety data is important, particularly toward the end of the phase 2b portion of the study. Despite increasing use, globally not all stakeholders are familiar with seamless adaptive trial designs. This potentially may complicate negotiations and approvals from ethics and regulatory bodies.

However, given the increasing complexity of PAH clinical trials (to account for background therapies and long-term composite outcomes), the innovative design of IMPAHCT may serve as a model for future PAH clinical study designs.

Overall, the IMPAHCT study has the potential to help advance therapies for patients with PAH by utilizing an adaptive trial design to enable a shorter drug development timeline and by assessing the efficacy and safety of a novel investigational drug-device combination (AV-101) that is designed to target the underlying pathobiology of PAH. Moreover, the IMPAHCT-FUL long-term extension study will evaluate the safety and tolerability of AV-101, as well as provide critical data on clinical and quality-of-life measures and long-term disease progression in patients with PAH treated with AV-101.

AUTHOR CONTRIBUTIONS

Hunter Gillies, Benjamin T. Dake, Jonathan Langley, Ralph W. Niven, and Xiaosha Zhang are employees of Aerovate Therapeutics and have contributed to the original study concept and design, the protocol development, and the planning of analyses, and are responsible for the ongoing conduct of the study. Hunter Gillies additionally acts as the guarantor and takes responsibility for the integrity of this work. Murali M. Chakinala, Marius M. Hoeper, Marc Humbert, Zhi-Cheng Jing, Vallerie V. McLaughlin, and Nicholas S. Hill are members of the IMPAHCT Study Advisory Committee, have contributed to the elaboration of the study concept and design, the protocol development, the planning of the analyses, the acquisition of data in his/her clinical department, and support the ongoing conduct of the study. Jeremy P. Feldman and Stephan Rosenkranz are members of the IMPAHCT Study Advisory Committee and have contributed to the elaboration of the study concept and design, the protocol development, the planning of the analyses, and support the ongoing conduct of the study. Hunter Gillies acts as the guarantor for the manuscript content. All authors critically reviewed, revised, and approved the manuscript for submission.

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CONFLICTS OF INTEREST STATEMENT

Hunter Gillies, Benjamin T. Dake, Jonathan Langley, Ralph W. Niven, and Xiaosha Zhang are employees of Aerovate Therapeutics Inc. Murali M. Chakinala received research grants/funding from Acceleron Pharma, Actelion, Gossamer Bio, Medtronic, Respira Therapeutics, and United Therapeutics Corporation; and served as a consultant for Actelion, Altavant Sciences Inc., Express Scripts Holding Company, Liquidia Technologies Inc., PhaseBio Pharmaceuticals, United Therapeutics Corporation, and WebMD LLC (Medscape). Jeremy P. Feldman received honoraria from Acceleron Pharma, Altavant Sciences, Bayer, Gilead Sciences, and United Therapeutics Corporation. Marius M. Hoeper received fees for lectures/consultations from Acceleron, Actelion, AOP Health, Bayer, Ferrer, Gossamer Bio, Janssen, Merck, and Pfizer. Marc Humbert received research grants/funding from Acceleron Pharma, Aerovate Therapeutics Inc., Altavant Sciences Inc., Bayer, Janssen Pharmaceuticals, Merck, Morphogen-IX Limited, and United Therapeutics Corporation; and received honoraria from Acceleron Pharma, Actelion, Bayer, GSK, Merck, and United Therapeutics Corporation. Vallerie V. McLaughlin received research grants/funding from Aerovate Therapeutics Inc., Altavant Sciences, Gossamer Bio, Janssen Pharmaceuticals, Merck, and SoniVie; and served as a consultant for Aerami Therapeutics, Aerovate Therapeutics Inc., Altavant Sciences, Bayer, Caremark LLC, CorVista, Gossamer Bio, Janssen Pharmaceuticals, Merck, and United Therapeutics Corporation. Stephan Rosenkranz received fees for lectures/consultations from Abbott, Actelion, Acceleron, AstraZeneca, AOP, Bayer, Boehringer Ingelheim, Ferrer, Gossamer, Janssen Pharmaceuticals, MSD, UT, and Vifor; and received institutional research grants from AstraZeneca, Bayer, and Janssen Pharmaceuticals. Nicholas S. Hill served as a consultant for Acceleron/Merck, Aerovate Therapeutics Inc., Altavant Sciences, Gossamer Bio, Insmed, and United Therapeutics Corporation. Zhi-Cheng Jing declares no conflict of interest.

ETHICS STATEMENT

The study protocol will be approved by an independent ethics committee or institutional review board at all participating sites and is being conducted in accordance with the International Council for Harmonisation Good Clinical Practice, applicable laws, and regulations. Legal informed consent must be obtained from all participating subjects before enrollment.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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