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Baseline Characteristics From the IMPAHCT Trial of AV-101, Inhaled Imatinib, in Subjects With Pulmonary Arterial Hypertension

Hunter Gillies,[1,*] Murali M. Chakinala,[2] Benjamin T. Dake,[1] Jeremy P. Feldman,[3] Marius M. Hoeper,[4] Marc Humbert,[5] Zhi-Cheng Jing,[6] Jonathan Langley,[1] Vallerie V. McLaughlin,[7] Ralph W. Niven,[1] Stephan Rosenkranz,[8] Xiaosha Zhang,[1] Nicholas S. Hill[9]

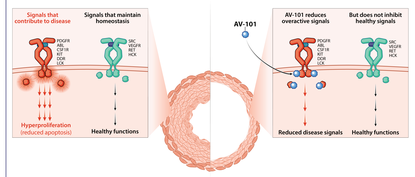
[1]Aerovate Therapeutics, Waltham, MA, USA; [2]Division of Pulmonary and Critical Care Medicine, Washington University, St. Louis, MO, USA; [3]Summit Health/BMC, Bend, OR, USA; [4]Department of Respiratory Medicine and Infectious Diseases, Hannover Medical School, and Member of the German Center for Lung Research (DZL), Biomedical Research in Endstage and Obstructive Lung Disease Hannover (BREATH), Hannover, Germany; [5]Université Paris-Saclay, INSERM UMR_S 999, Assistance Publique Hôpitaux de Paris, Service de Pneumologie et Soins Intensifs Respiratoires, Hôpital Bicêtre, Le Kremlin Bicêtre, France; [6]Department of Cardiology, Guangdong Cardiovascular Institute, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Southern Medical University, Guangzhou, China; [7]University of Michigan, Ann Arbor, MI, USA; [8]Department of Internal Medicine III and Cologne Cardiovascular Research Center, Heart Center, University of Cologne, Cologne, Germany; [9]Pulmonary Critical Care and Sleep Division, Tufts Medical Center, Boston, MA, USA.

*Presenting author.

INTRODUCTION

- Imatinib is an antiproliferative agent that targets kinase signaling believed to cause aberrant cell growth in the pulmonary vasculature while not interfering with signals needed for healthy cellular function (**Figure 1**)

Figure 1. Kinase signaling in PAH.

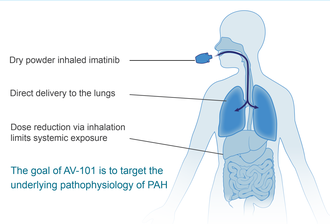


AV-101 selectively inhibits overactive kinases implicated in driving PAH, which restores balance

PAH, pulmonary arterial hypertension.

- The potential therapeutic benefits of imatinib in treating adult patients with pulmonary arterial hypertension (PAH) have been observed in randomized controlled trials and case studies[1-3]
  - In prior investigations, imatinib 400 mg was administered orally; despite clinical efficacy, tolerability concerns emerged, primarily systemic side effects[1,2]
- AV-101 is administered as 2 capsules twice daily via a passive dry powder inhaler, with the intent of achieving equivalent or higher lung exposure at a reduced total dose compared with oral imatinib 400 mg, thereby limiting systemic exposure and improving tolerability (**Figure 2**)
  - A phase 1 trial in healthy volunteers showed AV-101 to be generally well tolerated, with no report of treatment-emergent serious adverse events[4]
- With its seamless, phase 2b/3, adaptive design, the IMPAHCT trial is intended to expedite the development timeline while maintaining scientific rigor

Figure 2. AV-101 inhaled delivery of imatinib.



PAH, pulmonary arterial hypertension.

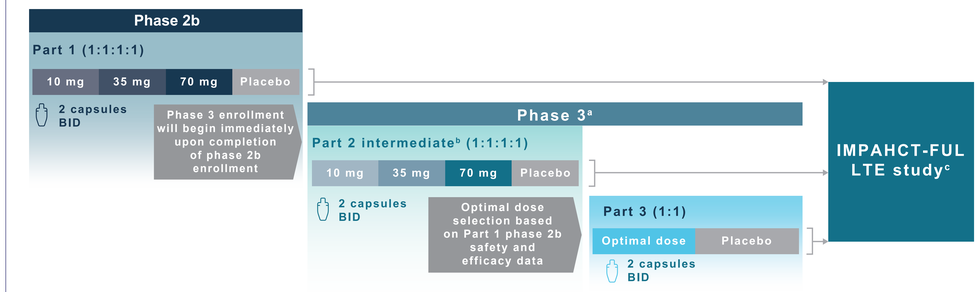
OBJECTIVE

- To detail the baseline characteristics of the IMPAHCT phase 2b study population
  - While the submitted abstract reported data for the first 147 subjects, this presentation reports data for the fully enrolled phase 2b population of 202 subjects

METHODS

- IMPAHCT (NCT05036135) is a phase 2b/3, randomized, double-blind, placebo-controlled, dose-ranging and confirmatory trial to establish the optimal dose, safety, efficacy, and tolerability of AV-101 in patients with PAH
- The IMPAHCT trial uses an operationally seamless, adaptive design that employs continuous recruitment throughout the 3 study parts (**Figure 3**):
  - Part 1: phase 2b dose response
  - Part 2: phase 3 intermediate multiple dose
  - Part 3: phase 3 optimal dose
- The AV-101 optimal dose will be selected based on phase 2b results and will be used in comparison to placebo within the confirmatory phase 3 part
- Subjects participate in only 1 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
- In Parts 1 and 2, AV-101 is supplied at 3 capsule strengths (5, 17.5, and 35 mg; requiring 2 capsules per dose) and is administered twice daily using a reusable, single capsule–use dry powder inhaler
- Recruitment is taking place in >27 countries, thus representing a geographically diverse population of subjects with PAH

Figure 3. IMPAHCT trial design.



BID, twice daily; LTE, long-term extension.
[a]All subjects from Parts 2 and 3 will contribute to the phase 3 safety analysis, while subjects who were administered the subsequently determined optimal dose and placebo from Parts 2 and 3 will contribute to the phase 3 efficacy analysis.
[b]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 4 arms until the optimal dose is identified.
[c]Once the optimal dose has been identified, subjects enrolled in the IMPAHCT-FUL LTE study from Part 1 (phase 2b) and Part 2 (intermediate) will be transitioned to the optimal dose.
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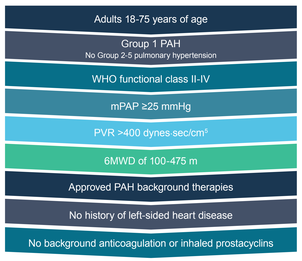
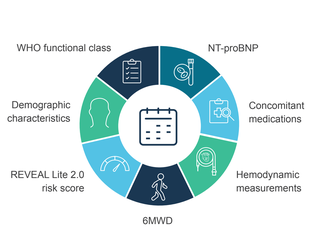
Figure 4. IMPAHCT key eligibility criteria.



6MWD, 6-minute walk distance; mPAP, mean pulmonary arterial pressure; PAH, pulmonary arterial hypertension; PVR, pulmonary vascular resistance; WHO, World Health Organization.

Figure 5. IMPAHCT phase 2b baseline measurements.



6MWD, 6-minute walk distance; NT-proBNP, N-terminal pro-brain natriuretic peptide; WHO, World Health Organization.

- The primary endpoint for phase 2b is the placebo-corrected change from baseline at 24 weeks in pulmonary vascular resistance; key secondary endpoints for phase 2b include:
  - Placebo-corrected change from baseline at 24 weeks in 6-minute walk distance (6MWD), N-terminal pro-brain natriuretic peptide (NT-proBNP), hemodynamic measurements, REVEAL Lite 2.0 risk score, and emPHasis-10 questionnaire score
  - Time to clinical worsening through 24 weeks
  - Improvement at Week 24 in WHO functional class
- The primary endpoint for phase 3 is the placebo-corrected change in 6MWD at 24 weeks; key secondary endpoints for phase 3 are consistent with phase 2b except for the omission of hemodynamic measurements and the use of the Pulmonary Arterial Hypertension–Symptoms and Impact (PAH-SYMPACT) questionnaire in place of the emPHasis-10 questionnaire

RESULTS

- Enrollment into the phase 2b part of IMPAHCT was completed with a total of 202 randomized subjects
- Subject demographic characteristics are shown in **Table 1**, and baseline clinical characteristics are shown in **Table 2**

Table 1. Demographic Characteristics of Subjects Randomized in the Phase 2b Dose-response Part of the IMPAHCT Trial

Characteristic	N = 202
Age, years	
Mean (SD)	46.8 (13.03)
Median (range)	45 (22-75)
Female, n (%)	165 (81.7)
Race, n (%)	
White	130 (64.4)
Asian	47 (23.3)
Black or African American	8 (4.0)
American Indian or Alaska Native	4 (2.0)
Other[a]	3 (1.5)
Not reported	10 (5.0)
Ethnicity, n (%)	
Hispanic or Latino	45 (22.3)
Not Hispanic or Latino	145 (71.8)
Not reported	12 (5.9)
BMI, mean (SD), kg/m^2	25.5 (5.75)

BMI, body mass index; SD, standard deviation.
Date of data cut for analysis: March 11, 2024. Data cleaning is ongoing.
[a]"Other" included unknown race (n = 2) and multiple races (n = 1).

Table 2. Baseline Clinical Characteristics of Subjects Randomized in the Phase 2b Dose-response Part of the IMPAHCT Trial

Characteristic	N = 202
Time since PAH diagnosis, median (range), years	5.9 (0.3-35.3)
Primary PAH etiology, n (%)	
IPAH or HPAH	143 (70.8)
Non-IPAH and non-HPAH	59 (29.2)
PAH background treatment, n (%)	
Dual therapy	86 (42.6)
Triple therapy	116 (57.4)
Prostacyclin therapy, n (%)	133 (65.8)
Intravenous/subcutaneous	73/133 (54.9)
Oral	60/133 (45.1)
REVEAL Lite 2.0 risk score, n (%)	
Low risk	109 (54.0)
Intermediate risk	53 (26.2)
High risk	39 (19.3)
Missing	1 (0.5)
French risk score, n (%)	
Low risk[a]	32 (15.8)
6MWD, mean (SD), m	395.7 (70.91)
WHO functional class, n (%)	
Class II	105 (52.0)
Class III	97 (48.0)
Hemoglobin, mean (SD), g/dL	13.9 (1.90)
NT-proBNP, mean (SD), pg/mL	738.4 (1233.64)
Hemodynamic measurements, mean (SD)	
PCWP, mmHg	9.3 (3.25)
mPAP, mmHg	50.9 (13.18)
Cardiac output, L/min	4.6 (1.22)
PVR, dynes·sec/cm^5	791.7 (413.27)
Cardiac index, L/min/m^2	2.7 (0.67)
Medical history, n (%)	
Hypertension	24 (11.9)
Diabetes mellitus	12 (5.9)
Coronary artery disease	6 (3.0)

6MWD, 6-minute walk distance; HPAH, heritable pulmonary arterial hypertension; IPAH, idiopathic pulmonary arterial hypertension; mPAP, mean pulmonary arterial pressure; NT-proBNP, N-terminal pro-brain natriuretic peptide; PAH, pulmonary arterial hypertension; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; SD, standard deviation; WHO, World Health Organization.
Date of data cut for analysis: March 11, 2024. Data cleaning is ongoing.
[a]Subjects with a WHO functional class of I or II, 6MWD >440 m, and NT-proBNP <300 pg/mL.

Conclusions

- The baseline characteristics, including hemodynamic measurements, 6MWD, WHO functional class, age, and sex, are consistent with recently published phase 3 PAH studies[5-7]
- Although the majority of subjects in the IMPAHCT population are treated with 3 PAH medications, they continue to experience impaired function, reduced exercise capacity, and persistent, significant hemodynamic impairment. This is typical of current PAH study populations and underscores the limitations of current therapies and the persistent unmet need for new PAH therapies
- There is a low prevalence of cardiovascular comorbidities
- The IMPAHCT trial, which is currently enrolling the phase 3 intermediate part, is designed to provide robust clinical data on dose response and the overall safety and efficacy of AV-101 in patients with PAH

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FUNDING

This study is funded by Aerovate Therapeutics.

ACKNOWLEDGMENTS

Medical writing and editorial assistance were provided by Meaghan Paganelli, PhD, of Lumanity Communications Inc. (Yardley, PA, USA), under the direction of the authors, and were financially supported by Aerovate Therapeutics.

DISCLOSURES

H.G., B.T.D., J.L., R.W.N., and X.Z. are employees of Aerovate Therapeutics. M.M.C. 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, Express Scripts Holding Company, Liquidia Technologies, Inc., PhaseBio Pharmaceuticals, United Therapeutics Corporation, and WebMD, LLC (Medscape). J.P.F. received honoraria from Acceleron Pharma, Altavant Sciences, Bayer, Gilead Sciences, and United Therapeutics Corporation. M.M.H. received fees for lectures/consultations from Acceleron Pharma, Actelion, AOP Health, Bayer, Ferrer, Gossamer Bio, Janssen Pharmaceuticals, Merck, and Pfizer. M.H. received research grants/funding from Acceleron Pharma, Aerovate Therapeutics, Inc., Altavant Sciences, 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. Z.-C.J. has no disclosures to declare. V.V.M. 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. S.R. received fees for lectures/consultations from Abbott, Actelion, Acceleron Pharma, AstraZeneca, AOP Health, Bayer, Boehringer Ingelheim, Ferrer, Gossamer Bio, Janssen Pharmaceuticals, MSD, UT, and Vifor; and received institutional research grants from AstraZeneca, Bayer, and Janssen Pharmaceuticals. N.S.H. served as a consultant for Acceleron Pharma/Merck, Aerovate Therapeutics, Inc., Altavant Sciences, Gossamer Bio, Insmed, and United Therapeutics Corporation.

Poster presented at the American Thoracic Society (ATS) International Conference; May 17-22, 2024; San Diego, CA, USA.