Inhaled iMatinib for Pulmonary Arterial Hypertension Clinical Trial: Design of the IMPAHCT Phase 2b/3 Study

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INTRODUCTION

Orally administered imatinib, a tyrosine kinase inhibitor, has demonstrated improvements in pulmonary hemodynamics and exercise capacity as add-on therapy for pulmonary arterial hypertension (PAH), but safety and tolerability issues have been observed.[1]

Aerovate Therapeutics has developed AV-101, a novel dry-powder inhaled imatinib, which is designed to maximize efficacy while limiting toxicity.

Results of a recent Phase 1 trial in healthy volunteers showed AV-101 to be generally well tolerated with no reported treatment-emergent serious adverse events.[2]

The clinical efficacy and safety of AV-101 in adults with PAH is being investigated in the phase 2b/3 IMPAHCT trial, which is designed to expedite the development timeline while maintaining scientific rigor.

OBJECTIVES

Phase 2b assesses safety, tolerability, and efficacy of three AV-101 doses and placebo to establish the optimal AV-101 dose.

- Change in pulmonary vascular resistance (PVR) at 24 weeks is the primary endpoint for phase 2b.
- Secondary endpoints include the change at 24 weeks in additional hemodynamic measures and 6-minute walk distance (6MWD).

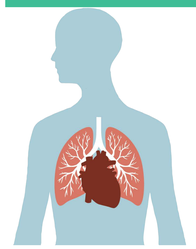
Phase 3 further assesses safety, tolerability, and efficacy of AV-101 optimal dose and placebo.

- Change in 6MWD at 24 weeks is the primary endpoint for phase 3.

Additional endpoints for both phase 2b and 3 include:

- WHO functional class
- REVEAL Lite 2.0 risk score
- Clinical worsening
- Clinical improvement
- NT-pro-BNP
- Quality of Life
- Safety and tolerability
- Pharmacokinetics

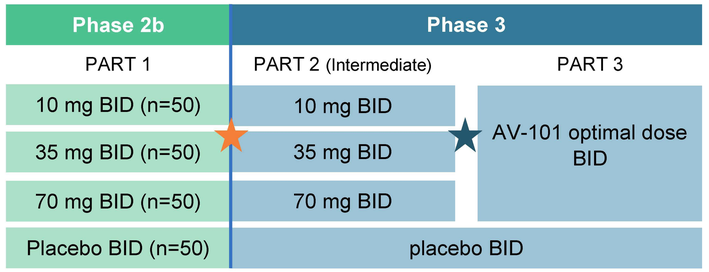
POPULATION



- Idiopathic or heritable PAH, or PAH associated with CTD, HIV, drugs and toxins, or CHD (NICE Group I)
- WHO Functional Class II, III or IV symptoms
- PVR >400dynes.sec.cm^{-5}
- 6MWD of 100m - 475m
- On stable concomitant therapy of at least two PAH approved medications
- Must not be on inhaled prostacyclins within 3 months of screening
- Must not have PH corresponding to NICE Groups 2-5

METHODS

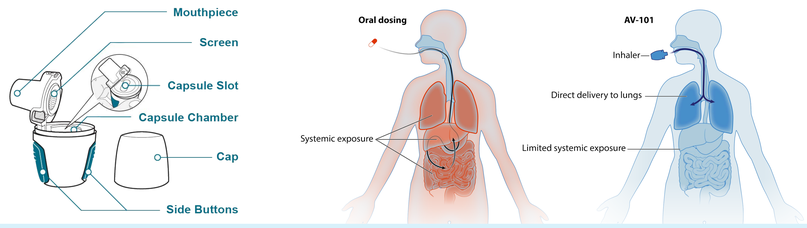
IMPAHCT (NCT05036135) is a randomized, double-blind study with 3 parts: i) phase 2b, ii) phase 3 intermediate, and iii) phase 3 optimal dose. Phase 2b assesses 3 BID doses of AV-101: 10 mg, 35 mg, and 70 mg, and placebo with each dose consisting of 2 capsules. The phase 3 intermediate part allows for continuous recruitment and an operationally seamless adaptive design for optimal AV-101 dose selection.



- An independent data safety monitoring board (DSMB) will periodically evaluate trial data, and advise on whether continued conduct is safe and ethical.
- Participation is possible in only one part, and includes a screening period (up to 30 days), treatment period (24 weeks), and a 30-day safety follow-up.
- Participants who successfully complete the IMPAHCT trial will be eligible to continue AV-101 treatment in the long-term extension study, IMPAHCT-FUL.

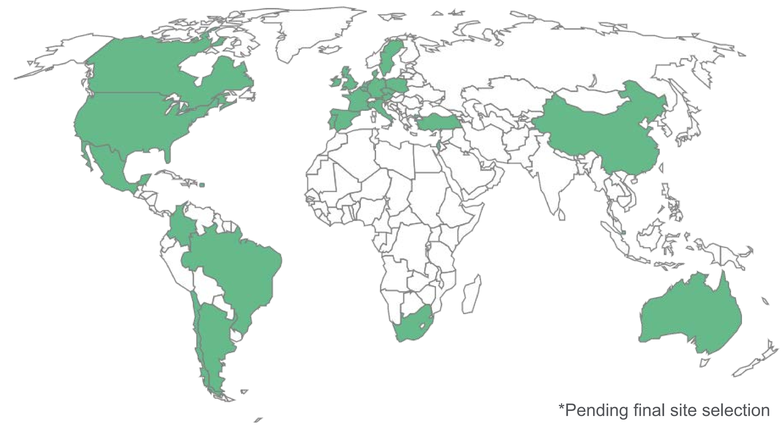
INVESTIGATIONAL PRODUCT

AV-101 is a drug-device combination product, comprised of a proprietary dry powder imatinib in a capsule delivered by a dry powder inhaler. AV-101 is designed to: i) deliver imatinib to the lungs, ii) limit systemic exposure, and iii) be easily administered.



IMPAHCT COUNTRIES

The IMPAHCT trial plans to have over 100 clinical sites participating in approximately 27 countries*. The extensive global presence will help provide a diverse patient population in a variety of clinical settings.



*Pending final site selection

Conclusions

- Direct administration of imatinib to the lungs is expected to achieve therapeutic lung concentrations using doses that limit systemic exposure and improve tolerability.
- We estimate that the operationally seamless adaptive design of IMPAHCT will save at least 6 to 12 months compared to separate Phase 2 and 3 studies, allowing for an efficient development timeline.
- The design of IMPAHCT may ultimately demonstrate to be an improved and innovative approach for PAH drug development.

REFERENCES

1. Hoeper, MM, et al.*Circulation*.2013;127:1128-1138.
2. Gillies, H. et al. Poster presentation. ATS International Conference, May 13-18, 2022. https://doi.org/10.1164/ajrccm-conference.2022.205.1_MeetingAbstracts.A3594

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DISCLOSURES

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