IMPROVE-PAH: An Adaptive, 2-Part, Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of IKT-001in Pulmonary Arterial Hypertension (PAH)

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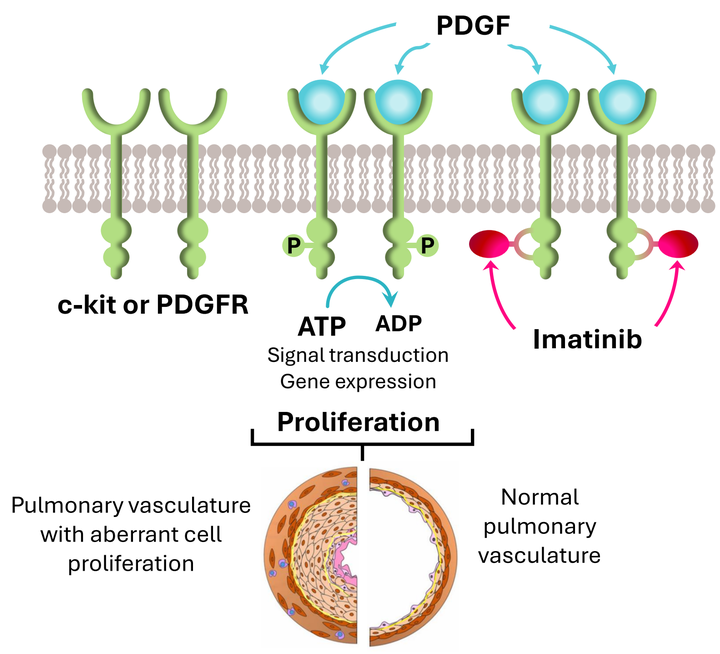
Background

- Pulmonary arterial hypertension (PAH) is a rare, progressive, and life-threatening disease with significant unmet need.[1,2]
- PAH is characterized by progressive pulmonary vascular remodeling and elevated pulmonary vascular resistance (PVR) leading to right ventricular heart failure and ultimately death.[1,2]
- Aberrant signaling through platelet-derived growth factor receptor (PDGFR)α, PDGFRβ, and c-KIT tyrosine kinases drives cellular proliferation/migration and plays a key role in PAH pathophysiology (**Figure 1**).[2,3]
- Imatinib mesylate, a tyrosine kinase inhibitor (TKI), has shown efficacy in PAH patients; however, further clinical development was limited by discontinuations and adverse events (AEs).[3-5]
- IKT-001, an investigational oral prodrug of imatinib, is designed to improve tolerability while inhibiting PDGFR and c-Kit signaling involved in abnormal vascular remodeling.

Figure 1. Imatinib Mechanism of Action in PAH Targets the Underlying Cause of PAH



Abbreviations: ADP, adenosine diphosphate, ATP, adenosine triphosphate, P, phosphate; PDGF, platelet-derived growth factor; PDGFR, platelet-derived growth factor receptor.

Objective

- Evaluate the efficacy and safety of IKT-001 versus placebo in addition to background PAH therapy in adults with World Health Organization (WHO) Group 1 PAH.

Methods

Study Design

- IMPROVE-PAH (EU CT number: 2024-520218-23-00) is an adaptive, 2-part, randomized, double-blind, placebo-controlled study (**Figure 2**).
- Overall, approximately 486 adult participants with PAH will be enrolled at approximately 180 sites globally with an expected duration of study participation of up to 52 weeks.
- Part A will include the first 140 patients, and Part B will include the following 346 patients.
- The overall study design, dosing regimen, and assessments will be the same across both parts.

Endpoints

- For Part A, the primary endpoint is change from baseline in PVR at Week 24.
- For Part B, the primary endpoint is change from baseline in in 6-minute walk distance (6MWD) at Week 24.
- Key secondary endpoints include time to clinical worsening and change from baseline in WHO functional class.
- Safety and tolerability of IKT-001 will be evaluated by the incidence and nature of treatment-emergent AEs, serious AEs, AEs leading to discontinuation, and AEs leading to dose modification.

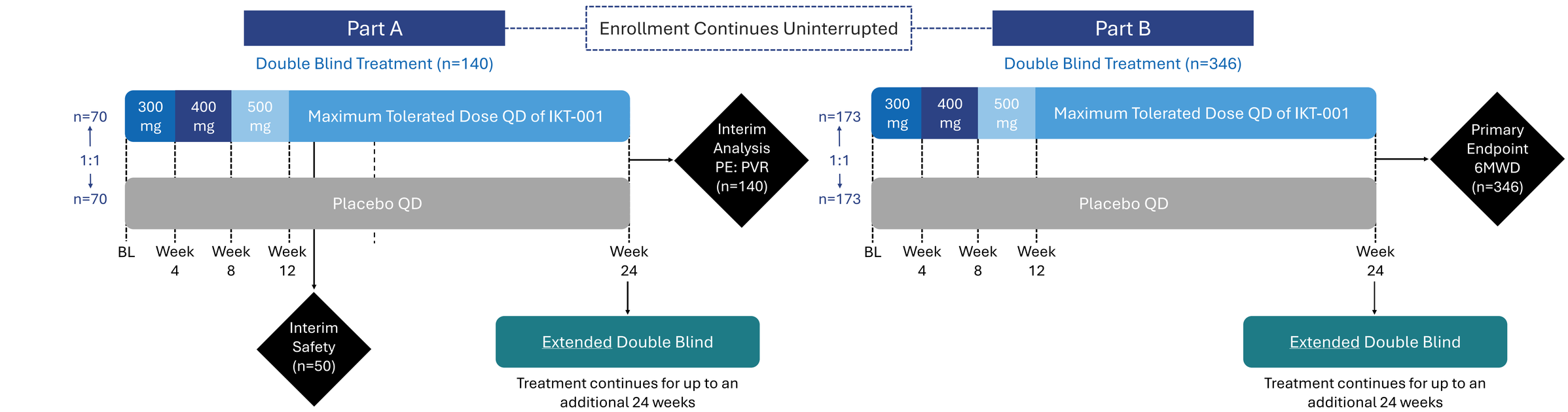
Patient Population

- IMPROVE-PAH will enroll approximately 486 adult participants with WHO Group 1 PAH, with a baseline 6MWD ≥100 m and ≤475 m and the following hemodynamic criteria, measured by right heart catheterization during the screening period:
  - Mean pulmonary arterial pressure >20 mmHg;
  - Pulmonary capillary wedge pressure ≤15 mmHg;
  - PVR ≥400 dynes/sec/cm^{-5}.
    - PVR enrichment criteria are in place to ensure population mean baseline PVR >700 dynes/sec/cm^{-5}.
- Stable doses of background PAH therapy (≤3 PAH specific medications) are permitted, including endothelin receptor antagonists, phosphodiesterase-5 inhibitors, prostacyclin pathway agents, and soluble guanylate cyclase stimulators, with no dose changes for ≥90 days prior to screening.
- Current use of sotatercept is not permitted; however, participants who previously received sotatercept may be considered if the last dose administered was >6 months before screening with no significant bleeding events while on sotatercept.
- Stratification factors include PAH etiology and baseline European Respiratory Society/European Society of Cardiology risk score

Study Drug

- Part A and Part B participants will be randomized 1:1 to once daily IKT-001 or matched placebo.
- Dose modifications are permitted during the first 12 weeks. The goal of the dose titration period is to reach the highest tolerated dose.

Figure 2. IMPROVE-PAH Study Design



Abbreviations: 6MWD, 6-minute walk distance; BL, baseline; PE, primary endpoint; PVR, pulmonary vascular resistance; QD, once daily.

Conclusion

- IMPROVE-PAH will assess whether IKT-001 offers a clinically meaningful reduction in PVR and improvement in 6MWD with acceptable tolerability in adult participants with PAH.
- This single, pivotal, adaptive study design has important advantages including: (1) permitting a 12-week dose-titration phase to get patients to the highest tolerable dose of IKT-001; (2) uninterrupted enrollment between Part A and Part B; and (3) the ability to, if necessary, undertake a sample size re-estimation for Part B based on Part A findings.[6]
- Results from IMPROVE-PAH will inform the potential of IKT-001 as a novel, oral, once-daily anti-proliferative TKI treatment option targeting vascular remodeling pathways in PAH.

References and Notes

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