Pharmacokinetic/pharmacodynamic (PK/PD) sub-study of UNISUS in pulmonary arterial hypertension (PAH): Characteristics of enrolled patients

Ioana R. Preston[1], Neli Boyanova[2], Dénes Csonka[2], Marc Humbert[3], Hilke Kracker[2], Vallerie V. McLaughlin[4], Yuichi Tamura[5], Marius Hoeper[6]

[1]Lahey Hospital and Medical Center, UMass Chan Medical School, Burlington, MA, USA; [2]Johnson & Johnson, Allschwil, Switzerland; [3]Université Paris-Saclay, Hôpital Bicêtre, Assistance Publique Hôpitaux de Paris, Le Kremlin-Bicêtre, France; [4]University of Michigan, Ann Arbor, MI, USA; [5]Pulmonary Hypertension Center, International University of Health and Welfare Mita Hospital, Tokyo, Japan; [6]Hannover Medical School, Hannover, Germany

Background

- Despite improvements in survival with therapies for pulmonary arterial hypertension (PAH), there remains an unmet need to further improve long-term outcomes.[1]
- Macitentan is an oral, dual endothelin receptor (ET_A/ET_B) antagonist (ERA) with proven efficacy at a once-daily dose of 10 mg.[2,3] Macitentan 10 mg is indicated for the treatment of PAH in adults to reduce risk of disease progression and hospitalization for PAH.[4]
- As clearance of endothelin-1 (ET-1) from the circulation is primarily mediated by the ET_B receptor, ET-1 plasma levels can serve as pharmacodynamic (PD) marker of ET_B receptor inhibition.[5]
- Enhanced ET_B receptor inhibition via increased macitentan dose is of therapeutic interest in PAH. Modelling suggests that macitentan 75 mg will provide potent blockade of both ET_A and ET_B receptors.[5]
- UNISUS, the first head-to-head superiority study in PAH, aims to demonstrate superior efficacy of macitentan 75 mg versus macitentan 10 mg on time to first morbidity/mortality event in patients with PAH.[6]
- UNISUS includes a pharmacokinetic (PK)/PD sub-study to evaluate plasma levels of macitentan and ET-1 following macitentan 75 mg treatment.

Objective

- Here, we describe the UNISUS PK/PD sub-study design and the preliminary baseline characteristics of included patients.

Methods

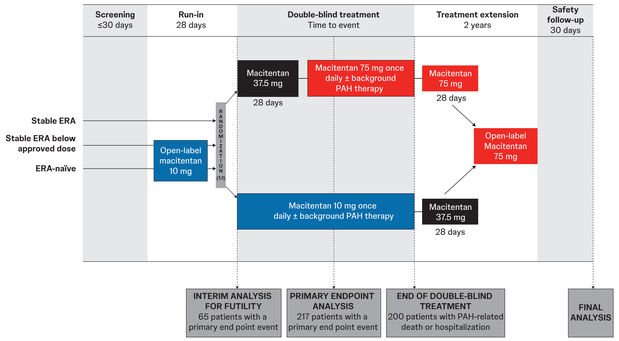
UNISUS study design

- UNISUS (NCT04273945) is an ongoing, phase 3, prospective, multicenter, double-blind, double-dummy, randomized, active-controlled, parallel-group, group-sequential, adaptive, event-driven superiority study in patients with PAH.
- Following screening, a total of 935 patients from 229 study sites were randomized 1:1 to receive either oral macitentan 75 mg or 10 mg once-daily (**Figure 1**).
- Eligible patients were aged 18–75 years, had PAH and were in World Health Organization (WHO) functional class II–III.
  - Stable (≥3 months) background PAH therapy could be maintained, except for ERA.
  - After review of unblinded safety and tolerability data from the initial 60 recruited patients, the independent data-monitoring committee recommended to expand the study population to also include patients aged >75 years, in WHO functional class IV, with portopulmonary hypertension, or who were treatment-naïve or receiving prostanoid analogs.

PK/PD sub-study design

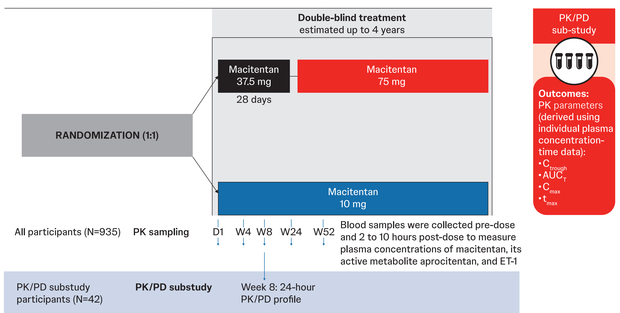
- Participants taking part in the PK/PD sub-study were included in the analysis set if they received study intervention and provided at least one evaluable 24-hour PK/PD sample during Week 8 (**Figure 2**).
- Analyses will include derivation of PK parameters from individual plasma concentration–time data and population PK/PD modelling.

Figure 1: Design of the UNISUS event-driven study



Patients who were ERA treatment-naïve or on a dose of macitentan or ambrisentan lower than 10 mg once daily, or dose of bosentan lower than 125 mg twice daily entered a 4-week run in period prior to randomization where they received open-label macitentan 10 mg once daily. Patients treated with an approved ERA dose on a stable regimen (≥3 months prior to screening) bypassed this run-in period. Eligible patients were randomly assigned in a 1:1 ratio to receive macitentan 75 mg or macitentan 10 mg once daily, and entered the event-driven double-blind treatment period.
ERA, endothelin receptor agonist; PAH, pulmonary arterial hypertension.

Figure 2: PK/PD sampling in UNISUS (N=935) and the PK/PD sub-study (n=42)

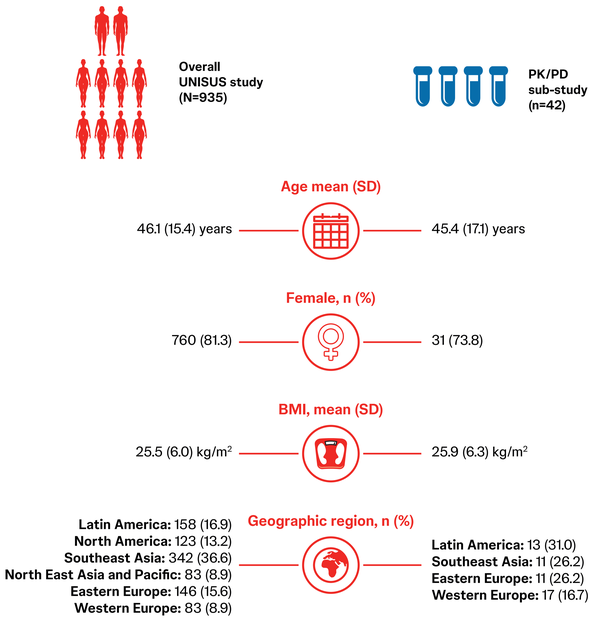


Plasma samples were analyzed to determine the concentrations of macitentan and aprocitentan using a validated, specific, and sensitive liquid chromatography-mass spectrometry/mass spectrometry method. The range of lower to upper quantification (ULOQ) limits for macitentan and aprocitentan in plasma were 1.00–2,000 ng/mL for both analytes. Concentrations of ET-1 were determined using a quantified cartridge-based Ella™ enzyme-linked immunosorbent assay. The range of ULOQ limits for ET-1 was 0.10–0.26 pg/mL (depending on cartridge lot) for the lower limit of quantification (LLOQ) to 1,000 pg/mL for the ULOQ.
AUC_τ, area under the plasma concentration–time curve over dosing interval; C_{max}, maximum concentration; C_{trough}, trough concentration; ET-1, endothelin-1; PD, pharmacodynamic; PK, pharmacokinetic; t_{max}, time to maximum concentration.

Results

- Patient recruitment to the UNISUS study is now complete, with 935 patients enrolled in the main study and 42 patients enrolled in the PK/PD sub-study (enrolled from July 2020). Patient demographics at baseline are shown in **Figure 3**.

Figure 3: Baseline patient demographics in the overall UNISUS study and PK/PD sub-study



BMI, body mass index; PD, pharmacodynamic; PK, pharmacokinetic; SD, standard deviation.

Key takeaway

- Changes in ET-1 levels following potent blockade of the ET_B receptor have not previously been characterized in PAH patients; these findings will enhance our understanding of the mechanistic impact of maximal dual ET_A and ET_B receptor inhibition in PAH.

Conclusions

- The UNISUS PK/PD sub-study will provide new insights into changes in ET-1 concentrations and ET_B receptor inhibition in patients with PAH following macitentan 10 mg and 75 mg treatment.
- As the first head-to-head superiority study in PAH, UNISUS uses a robust, adaptive, event-driven design to determine if macitentan 75 mg provides superior clinical benefit to patients with PAH over the established 10-mg dose.

Acknowledgments

Medical writing support was provided by Patrick Hoggard of Ashfield MedComms, an Inizio company, and funded by Johnson & Johnson.

Disclosures

This study was funded by Johnson & Johnson.

Ioana R. Preston served as a Scientific Committee member for Johnson & Johnson, Merck, Liquidia; received consulting fees and honoraria for lectures, presentations, manuscript writing or educational events from Johnson & Johnson, Altavant, Gossamer and United Therapeutics; received support for attending meetings and/or travel from Johnson & Johnson, Merck and United Therapeutics.

Vallerie V. McLaughlin serves as a Scientific Committee member for Johnson & Johnson; received research grants from Aerovate, Altavant, Gossamer Bio, Johnson & Johnson, Merck and SoniVie; and received consultant fees from Aerami, Aerovate, Altavant, Bayer, Caremark, Corvista, Gossamer Bio, Johnson & Johnson, L.L.C, Merck, and United Therapeutics.

Yuichi Tamura and Marc Humbert served as Scientific Committee members for Johnson & Johnson.

Marius Hoeper has received fees for consultations or lectures from Acceleron, Aerovate, AOP Health, Bayer, Ferrer, Gossamer, Johnson & Johnson, MSD, and Novartis.

Neli Boyanova, Dénes Csonka, and Hilke Kracker are employees of Johnson & Johnson.

Sponsored by Johnson & Johnson

Poster presented at American Thoracic Society (ATS) 2026 International Conference, May 17–20, 2026, Orange County Convention Center, Orlando, FL, USA.

REFERENCES:

1. Reinders S, et al. *Respir Res* 2024;25:373.
2. Humbert M, et al. *Eur Heart J* 2022;43:3618–713.
3. Pulido T, et al. *N Engl J Med* 2013;369:809–18.
4. Johnson & Johnson. Opsumit®. Highlights of prescribing information. https://www.opsumit.com/opsumit-prescribing-information.pdf (accessed March 2026).
5. Csonka D, et al. *Eur Respir J* 2025;66(Suppl 69):PA5154.
6. ClinicalTrials.gov. NCT04273945. Accessed May 2026. https://clinicaltrials.gov/study/NCT04273945.

Pulmonary Hypertension

Scan the QR code