Overall patient characteristics from UNISUS, a phase 3 superiority study comparing macitentan 75 mg vs macitentan 10 mg in patients with pulmonary arterial hypertension

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

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

Background

- Despite improvements in survival with therapies for pulmonary arterial hypertension (PAH), there remains an unmet need to further improve long-term outcomes for patients with PAH.[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]
- Enhanced ET_B receptor inhibition via increased macitentan dose is of therapeutic interest in PAH.
  - Preclinical data indicate that macitentan exerts dose-dependent effects through enhanced inhibition of ET_A/ET_B receptors.[5]
  - In Phase 1 clinical studies in cardiovascular healthy volunteers and patients with glioblastoma, doses of macitentan up to 300 mg have been administered.[3,6,7]
  - Modelling estimates that macitentan 10 mg predominantly blocks ET_A receptors, while increasing the macitentan dose to 75 mg also achieves substantial blockade of ET_A and ET_B receptors.[8,9]
- UNISUS, the first head-to-head superiority study in PAH, aims to show superior efficacy of macitentan 75 mg over 10 mg in adults with PAH.

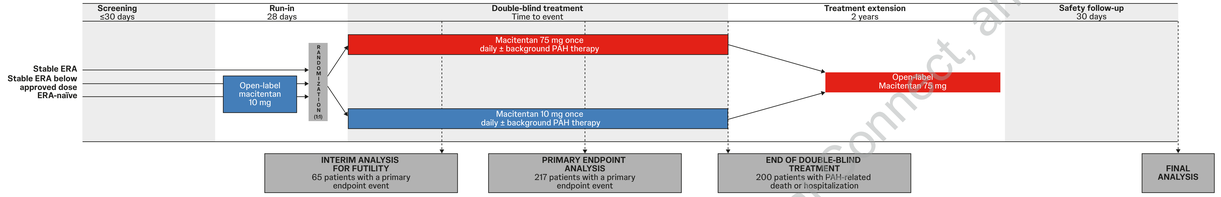
Objective

- Here, we describe preliminary findings for the baseline characteristics of all patients enrolled in the ongoing UNISUS study.

Methods

- UNISUS (NCT04273945) is an ongoing, phase 3, prospective, multicenter, double-blind, double-dummy, randomized, active-controlled, parallel-group, group-sequential, adaptive, event-driven study in adults with PAH.
- Following screening, patients were randomly assigned 1:1 to receive macitentan 75 mg or macitentan 10 mg once daily (**Figure 1**).
  - Patients who were treatment-naïve or receiving an ERA below the approved dose entered a run-in period where they received macitentan 10 mg once daily for 4 weeks prior to randomization.
  - Patients randomized to macitentan 75 mg received macitentan 37.5 mg for 4 weeks, and macitentan 75 mg thereafter.
- Eligible patients aged 18 to 75 years had PAH and were in World Health Organization (WHO) functional class II–III. PAH was: idiopathic; heritable or drug- or toxin-induced; or associated with connective tissue disease, human immunodeficiency virus or congenital heart disease.
  - 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, and who are treatment-naïve or receiving prostanoid analogs.
- The primary study endpoint is time to first on-treatment morbidity/mortality event (defined as PAH-related hospitalization, PAH progression, or all-cause death).
- Secondary study endpoints include hospitalizations for PAH or death due to PAH up to end of treatment, change from baseline in 6-minute walk distance and PAH-SYMPACT® symptom scores at Week 24, and time to all-cause death up to the end of the double-blind period.

Figure 1. Design of the UNISUS study

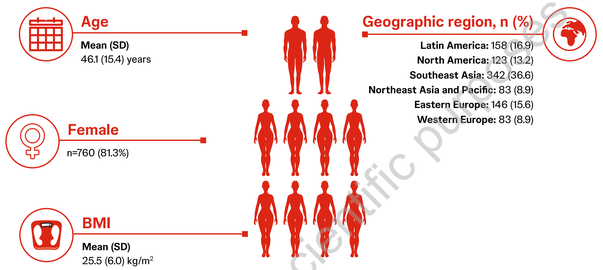


ERA, endothelin receptor agonist; PAH, pulmonary arterial hypertension.
Patients who were ERA treatment-naïve or on a dose of macitentan or ambrisentan lower than 10 mg once daily, or dose of bosentan lower than 125 mg twice daily entered a 4-week run-in period prior to randomization where they received 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.

Results

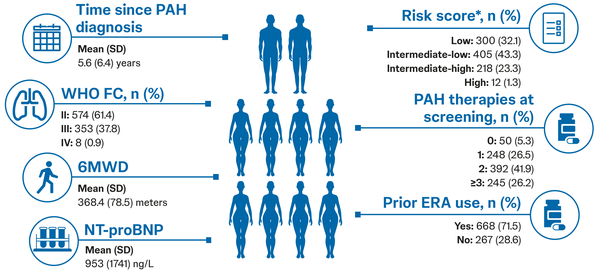
- Patient recruitment to UNISUS is now complete. As of July 2024, 935 adult patients were enrolled and randomized (**Figures 2–4**).

Figure 2. Baseline patient demographics (N=935)



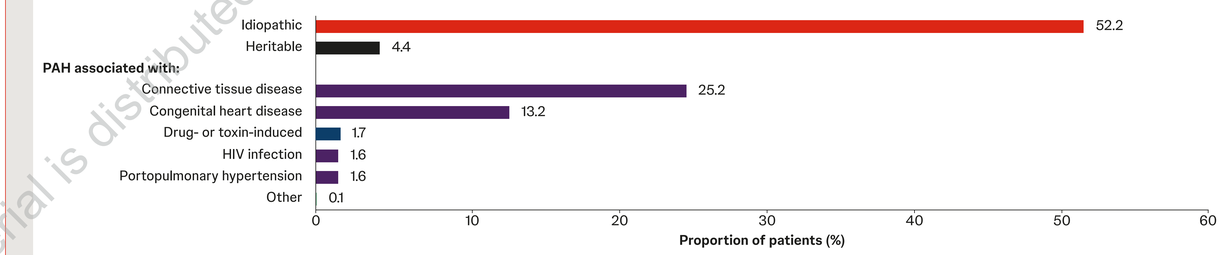
BMI, body mass index; SD, standard deviation.

Figure 3. Baseline patient PAH characteristics (N=935)



*Risk score according to the non-invasive risk criteria as per 2022 ESC and ERS guidelines.
6MWD, 6-minute walk distance; ERA, endothelin receptor agonist; ERS, European Respiratory Society; ESC, European Society of Cardiology; FC, functional class; IQR, interquartile range; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PAH, pulmonary arterial hypertension; SD, standard deviation; WHO, World Health Organization.

Figure 4. PAH etiologies (N=935)



HIV, human immunodeficiency virus; PAH, pulmonary arterial hypertension.

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Key takeaway

- UNISUS patients represent a broad PAH patient population, with diverse etiologies, geographical distribution, and background PAH therapies.

Conclusions

- UNISUS has met its enrolment target, with 935 adult patients fully enrolled and randomized.
- As the first head-to-head superiority study in PAH, UNISUS uses an adaptive, event-driven design and will provide robust evidence on the potential to optimize the foundational endothelin pathway with macitentan 75 mg.

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