Pre-planned study design adaptations in UNISUS: a Phase 3, randomized superiority study comparing the efficacy, safety and tolerability of macitentan 75 mg versus 10 mg in patients with pulmonary arterial hypertension (PAH)

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Introduction

Background and purpose

- Pulmonary arterial hypertension (PAH) is a progressive and fatal disease.[1] Despite progress in the treatment of PAH, it is still an area of high unmet clinical need.
- Macitentan is a dual endothelin receptor antagonist (ERA) indicated for the treatment of PAH to reduce the risks of disease progression and hospitalization for PAH.[2]
- The current recommended adult dose of macitentan is 10 mg once daily, the efficacy of which has been established in previous studies.[1,3] Analyses of clinical and non-clinical data suggest that a dose of 75 mg might provide further benefits to patients with PAH.[4–6]

Aim

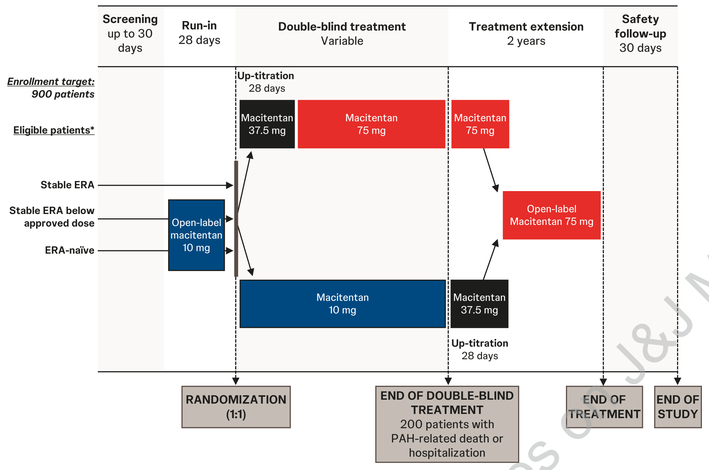
- The aim of UNISUS (NCT04273945) is to demonstrate the superiority of macitentan 75 mg versus macitentan 10 mg in adults with PAH.

Methods and Results

UNISUS study design

- UNISUS is an ongoing, multicenter, prospective, Phase III, superiority study of macitentan 75 mg versus 10 mg in adults with PAH (**Figure 1**).
- Primary (time to first morbidity/mortality [M/M] event) and secondary endpoints of the study are shown in **Figure 2**.
- Efficacy and safety are continuously assessed by the independent data monitoring committee (IDMC).
- Pre-defined adaptations to the protocol could be recommended by the IDMC based on unblinded data review of enrolled participants (**Figure 3**), including:
  - Expansion of the target population, which initially excluded patients with portopulmonary hypertension (PoPH) and those who were: aged ≥75 years, in World Health Organization functional class (WHO FC) IV, treatment-naïve or receiving a prostanoid analog.
  - Elimination of some or all of the four close safety monitoring visits.
  - Interim analysis for futility.
- The results of the unblinded reviews are presented in **Figures 3 and 4**.

FIGURE 1. UNISUS is an ongoing, multicenter, prospective, Phase III, superiority study of macitentan 75 mg versus 10 mg in adults with PAH.



*Stable non-ERA background therapy is maintained on top of the study intervention.

Figure first presented at the ESC congress 2022, Barcelona, Spain. Copyrights of this figure were transferred to the ESC, on a non-exclusive basis.

FIGURE 2. Primary and secondary endpoints of the UNISUS study.

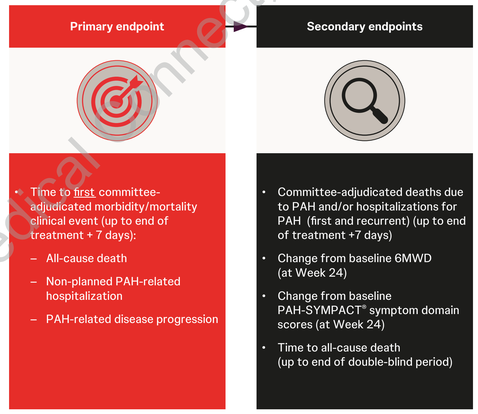


FIGURE 3. IDMC-recommended changes following unblinded review of safety/tolerability data and interim futility analysis.

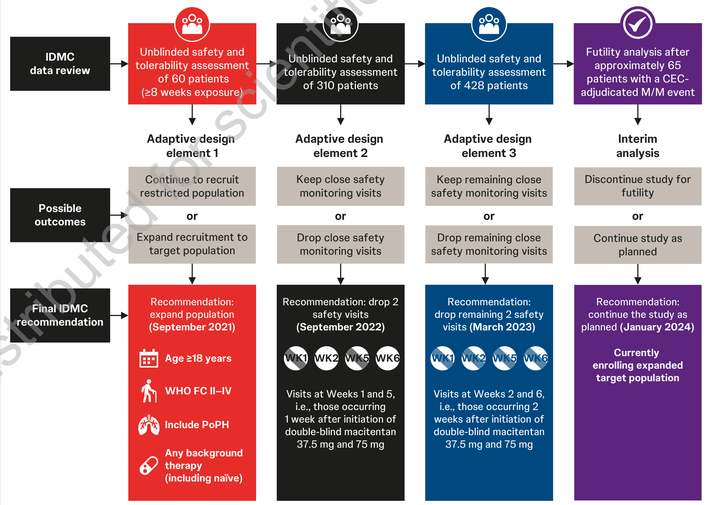
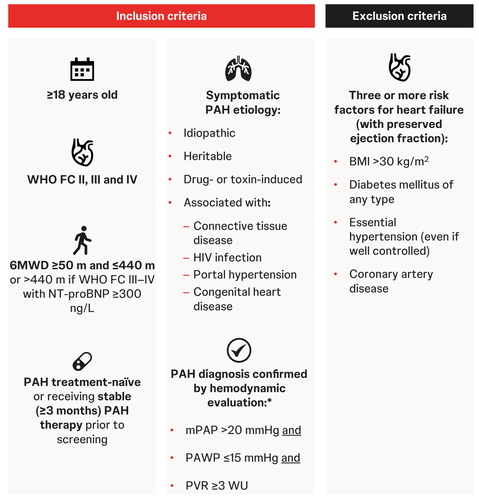


FIGURE 4. Eligibility criteria for target population currently being enrolled in UNISUS.



*Hemodynamic definition of PAH according to the 6th World Symposium on Pulmonary Hypertension (February 2018).[7]

Conclusions

UNISUS is a superiority study comparing macitentan 75 mg and macitentan 10 mg in PAH.

Regular unblinded review of ongoing safety and tolerability data by the IDMC led to pre-planned changes to the study design, including:

- An expanded patient population is now being enrolled in UNISUS;
- Less frequent safety monitoring visits during the up-titration phase.

The study is currently ongoing and recruiting globally, with a total enrollment target of approximately 900 patients.

Abbreviations

6MWD, 6-minute walk distance; BMI, body mass index; CEC, clinical event committee; ERA, endothelin receptor antagonist; HIV, human immunodeficiency virus; IDMC, independent data monitoring committee; m, meters; M/M, morbidity/mortality; mPAP, mean pulmonary arterial pressure; NT-proBNP, N-terminal pro-brain natriuretic peptide; PAH, pulmonary arterial hypertension PAH-SYMPACT, pulmonary arterial hypertension symptoms and impact; PAWP, pulmonary arterial wedge pressure; PoPH, portopulmonary hypertension; PVR, pulmonary vascular resistance; WHO FC, World Health Organization functional class; WU, wood units.

Acknowledgments

Medical writing support was provided by Lisa Berridge, MSc, of Ashfield MedComms, an Inizio company, and funded by Actelion Pharmaceuticals Ltd, a Johnson & Johnson Company.

Disclosures

This study was funded by Actelion Pharmaceuticals Ltd, a Janssen Pharmaceutical company of Johnson & Johnson.
Vallerie V McLaughlin served as a Scientific Committee member for Janssen Pharmaceutical Companies of Johnson & Johnson; received research grants from Aerovate, Altavant, Gossamer Bio, Janssen Pharmaceutical Companies of Johnson & Johnson, Merck and SoniVie; and consultant fees from Aerami, Aerovate, Altavant, Bayer, Caremark, Corvista, Gossamer Bio, Janssen Pharmaceutical Companies of Johnson & Johnson, L.L.C, Merck and United Therapeutics.
Marius Hoeper has received fees for consultations or lectures from Acceleron, Actelion, Aerovate, AOP Health, Bayer, Ferrer, Gossamer, Janssen, MSD and Novartis.

Presented at the American Thoracic Society (ATS) 2024, May 17-22, San Diego, CA, USA

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