UNISUS hemodynamic sub-study: Study design and patient characteristics from the first head-to-head superiority study in pulmonary arterial hypertension (PAH)

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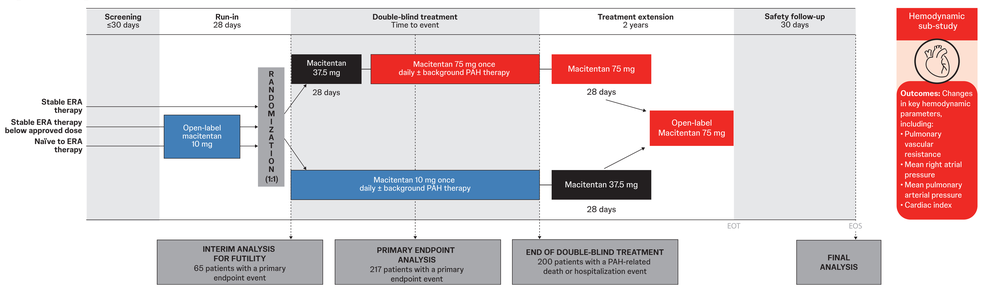
Background

- Despite improvements in survival with therapies for pulmonary arterial hypertension (PAH), median survival remains 5–7 years, highlighting an unmet need to further improve long-term outcomes for patients with PAH.[1–5]
- Macitentan 10 mg is an oral, dual endothelin receptor (ET_A/ET_B) antagonist (ERA) and is a guideline-recommended standard of care for adults with PAH.[6]
  - Its estimated ET_A:ET_B receptor selectivity is 50:1, suggesting a high degree of ET_A receptor occupancy prior to ET_B receptor inhibition.[7–9]
- Enhanced ET_B receptor inhibition via increased macitentan dose is of therapeutic interest in PAH. Pharmacokinetic/pharmacodynamic (PK/PD) modelling suggests that macitentan 75 mg will provide optimal blockade of both ET_A and ET_B receptors.[10,11]
  - In Phase 1 clinical studies in cardiovascular (CV) healthy volunteers and patients with glioblastoma, doses of macitentan up to 300 mg have been administered.[10,11]
- The phase 3 UNISUS trial aims to demonstrate superior efficacy of macitentan 75 mg versus macitentan 10 mg on time to first morbidity/mortality event in patients with PAH.[12]
- In PAH, assessment of the right heart function by right heart catheterization (RHC) is critical to understanding treatment response.[13] Macitentan 10 mg has demonstrated positive effects on hemodynamic outcomes.[14]
- UNISUS includes an elective RHC sub-study to assess hemodynamic changes in response to treatment with macitentan 75 mg.

Objective

- Here, we describe the study design and preliminary baseline characteristics of patients in UNISUS and its planned hemodynamic sub-study.

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.
EOS, end of study; EOT, end of treatment; ERA, endothelin receptor agonist; PAH, pulmonary arterial hypertension.

Methods

UNISUS:

- 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.
- Patients 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.

UNISUS hemodynamic sub-study:

- The hemodynamic sub-study was conducted at selected study sites based on their ability to perform RHC, experience with the procedure, and willingness to participate.
- Enrollment in the sub-study was mandatory in Japan and optional in other countries.
- Patients in the sub-study underwent RHC at baseline and Week 24 to evaluate changes in key hemodynamic parameters (**Figure 1**).
- Randomization was stratified by region rather than by site, and no mechanisms were used to ensure equal distribution of the study treatments in the sub-study.
- Data from participants of the hemodynamic sub-study were reviewed for quality control by a member of the UNISUS Steering Committee.

Results

- Patient recruitment to the UNISUS is complete.
  - In total, 935 patients from 229 study sites were randomized.
  - 128 patients from 52 study sites entered into the RHC sub-study.
- Patient demographics and PAH characteristics at baseline for the UNISUS study and hemodynamic sub-study are shown in **Figures 2 and 3**.
- A broad range of PAH etiologies were included (**Figure 4**).

Figure 2: Baseline patient demographics in the overall UNISUS study and hemodynamic sub-study

	Overall UNISUS study (N=935)	Hemodynamic sub-study (n=128)
Age, mean (SD)	46.1 (15.4) years	48.7 (16.8) years
Female, n (%)	760 (81.3)	101 (78.9)
BMI, mean (SD)	25.5 (6.0) kg/m^2	24.9 (5.0) kg/m^2
Geographic region, n (%)	**Latin America:** 158 (16.9) **North America:** 123 (13.2) **Southeast Asia:** 342 (36.6) **North East Asia and Pacific:** 83 (8.9) **Eastern Europe:** 146 (15.6) **Western Europe:** 83 (8.9)	**Latin America:** 37 (28.9) **North America:** 14 (10.9) **Southeast Asia:** 8 (6.3) **North East Asia and Pacific:** 46 (35.9) **Eastern Europe:** 7 (5.5) **Western Europe:** 16 (12.5)

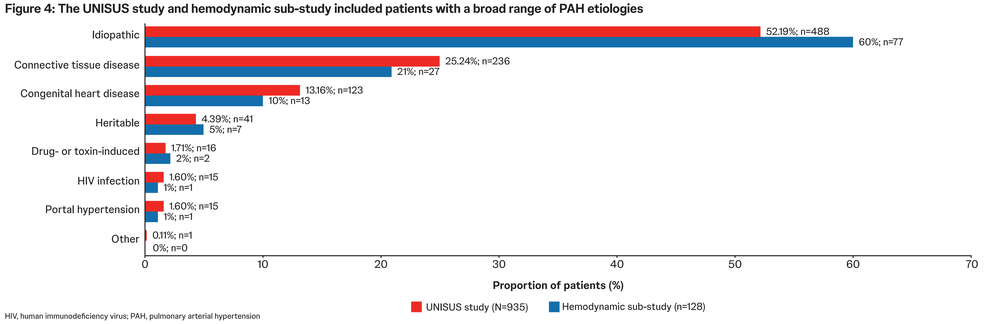
BMI, body mass index; SD, standard deviation.

Figure 3: Baseline PAH characteristics in the overall UNISUS study and the hemodynamic sub-study

	Overall UNISUS study (N=935)	Hemodynamic sub-study (n=128)
Time since PAH diagnosis, mean (SD)	5.6 (6.4) years	6.7 (8.1) years
WHO FC, n (%)	**II:** 574 (61.4) **III:** 353 (37.8) **IV:** 8 (0.9)	**II:** 85 (66.4) **III:** 43 (33.6)
6MWD, mean (SD)	368.4 (78.5) meters	367.3 (70.2) meters
NT-proBNP, mean (SD)	953 (1741) ng/L	682 (1517) ng/L
PAH therapies at screening, n (%)	**0:** 50 (5.3) **1:** 248 (26.5) **2:** 392 (41.9) **>2:** 245 (26.2)	**0:** 1 (0.8) **1:** 35 (27.3) **2:** 45 (35.2) **>2:** 47 (36.7)
Prior ERA use, (%)	**Yes:** 668 (71.5) **No:** 267 (28.6)	**Yes:** 91 (71.1) **No:** 37 (28.9)
RHC parameters, mean (SD)		**Pulmonary vascular resistance:** 644.5 (453.11) dyn.sec/cm^5 **Right atrial pressure:** 8.1 (8.03) mmHg **Pulmonary arterial pressure :** 42.6 (15.80) mmHg **Cardiac index**: 2.84 (0.820) L/min/m^2

6MWD, 6-minute walk distance; ERA, endothelin receptor agonist; FC, functional class; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PAH, pulmonary arterial hypertension; SD, standard deviation; WHO, World Health Organization.

Figure 4: The UNISUS study and hemodynamic sub-study included patients with a broad range of PAH etiologies



HIV, human immunodeficiency virus; PAH, pulmonary arterial hypertension

Key takeaway

- The UNISUS hemodynamic sub-study will provide critical insights into the effects of macitentan 75 mg on the right heart function in a diverse and broad PAH patient population, with similar characteristics to the overall UNISUS study

Conclusions

- The findings from the UNISUS hemodynamic sub-study may inform future therapeutic strategies by enhancing our understanding of the clinical impact of maximal dual ET_A and ET_B receptor inhibition in PAH.

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