Cardiac magnetic resonance imaging (CMR) sub-study of UNISUS in pulmonary arterial hypertension (PAH): Characteristics of enrolled patients

Francois Haddad[1], Neli Boyanova[2], Marius M. Hoeper[3], Marc Humbert[4], David Kiely[5], Hilke Kracker[2], Vallerie V. McLaughlin[6], Vivek Muthurangu[7], Ioana R. Preston[8], Lilian Sanna[2], Yuichi Tamura[9], Anton Vonk Noordegraaf[10]

[1]Division of Cardiovascular Medicine, Stanford University School of Medicine, Stanford, CA, USA; [2]Johnson & Johnson, Allschwil, Switzerland; [3]Hannover Medical School, Hannover, Germany; [4]Université Paris-Saclay, Hôpital Bicêtre, Assistance Publique Hôpitaux de Paris, Le Kremlin-Bicêtre, France; [5]Sheffield Pulmonary Vascular Disease Unit and NIHR Biomedical Research Centre, Royal Hallamshire Hospital, Sheffield, UK, and Department of Clinical Medicine, University of Sheffield, UK; [6]University of Michigan, Ann Arbor, MI, USA; [7]University College London, London, UK; [8]Lahey Hospital and Medical Center, UMass Chan Medical School, Burlington, MA, USA; [9]Pulmonary Hypertension Center, International University of Health and Welfare Mita Hospital, Tokyo, Japan; [10]Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam, Netherlands

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. PK/PD modelling suggests that macitentan 75 mg will provide potent 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]
- At 10 mg, macitentan has demonstrated clinically relevant improvements in right ventricular (RV) structure and function.[13]
- The UNISUS study includes a planned cardiac magnetic resonance imaging (CMR) sub-study to assess the effect of macitentan 75 mg on RV and pulmonary artery (PA) properties.

Objective

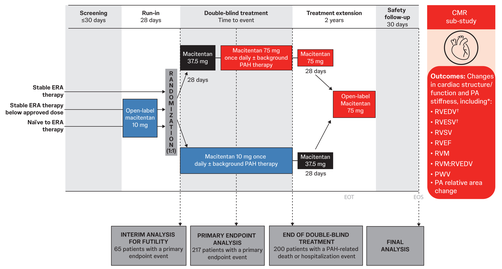
- Here, we describe the study design and preliminary baseline characteristics of patients in UNISUS and the CMR sub-study.

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**).

Figure 1: Design of the UNISUS event-driven study



*Papillary muscles and trabeculae will be included in the volumes calculations (ie. LVEDV, LVESV, RVESV, RVEDV), but not included in mass calculations; [1]Percentage predicted for mass will be calculated.

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.

CMR, cardiac magnetic resonance imaging; EOS, end of study; EOT, end of treatment; ERA, endothelin receptor antagonist; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; PA, pulmonary artery; PAH, pulmonary arterial hypertension; PWV, pulse wave velocity; RVEF, right ventricular ejection fraction; RVEDV, right ventricular end-diastolic volume; RVESV, right ventricular end-systolic volume; RVM, right ventricular mass; RVSV, right ventricular stroke volume.

- 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.

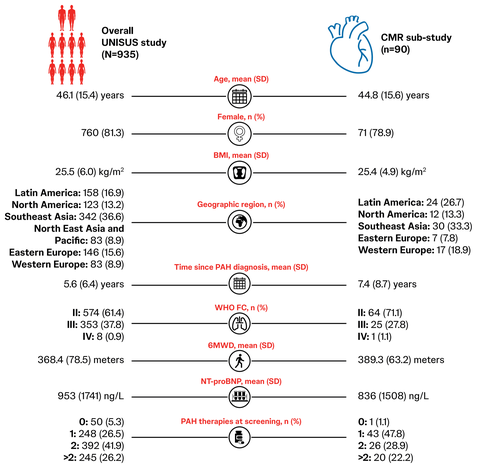
UNISUS CMR sub-study:

- The CMR sub-study was conducted at selected study sites based on access to CMR facility and interest.
- Patients in the CMR sub-study underwent imaging at baseline, Week 24, and Week 52 to assess changes in cardiac structure/function and in PA stiffness. Images were centrally assessed.
- Multiple cardiac measurements were captured (**Figure 1**).

Results

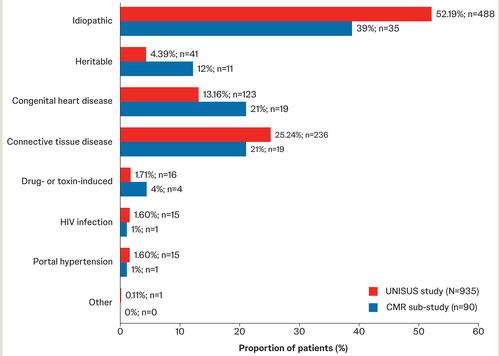
- Patient recruitment to the UNISUS study is complete.
  - In total, 935 patients from 229 study sites were randomized.
  - 90 patients from 20 study sites entered into the CMR sub-study.
- Patient demographics and PAH characteristics at baseline for the UNISUS study and CMR sub-study are shown in **Figure 2**.
  - A broad range of PAH etiologies was included (**Figure 3**).
- Baseline CMR parameters are shown in **Figure 4**.

Figure 2: Baseline patient demographics and PAH characteristics in the overall UNISUS study and CMR sub-study



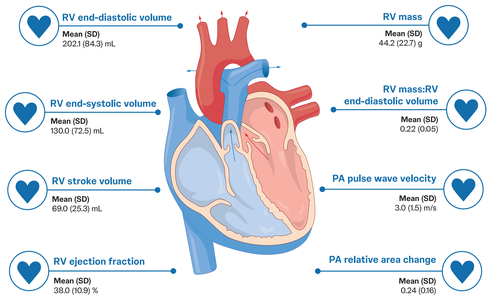
6MWD, 6-minute walk distance; BMI, body mass index; CMR, cardiac magnetic resonance imaging; FC, functional class; IQR, interquartile range; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PAH, pulmonary arterial hypertension; SD, standard deviation; WHO, World Health Organization.

Figure 3: PAH etiologies included in the UNISUS study and CMR sub-study



CMR, cardiac magnetic resonance imaging; HIV, human immunodeficiency virus; PAH, pulmonary arterial hypertension.

Figure 4: Baseline CMR parameters in the CMR sub-study (n=90)



CMR, cardiac magnetic resonance imaging; PA, pulmonary artery; RV, right ventricular; SD, standard deviation.

Key takeaway

- Baseline patient demographics and PAH characteristics in the CMR sub-study are representative of the main UNISUS study population.

Conclusions

- The UNISUS CMR sub-study will assess the impact of macitentan 75 mg versus macitentan 10 mg on RV and PA structure and function. Findings from the study may provide mechanistic insights into how maximal ET_A and ET_B blockade benefits patients with PAH.

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