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

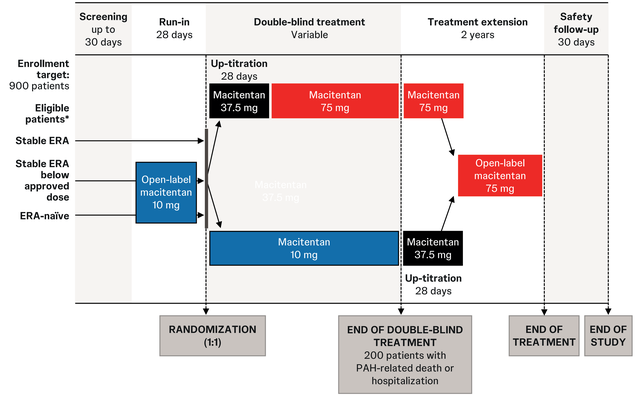
- The aim of UNISUS (NCT04273945) is to demonstrate the superiority of macitentan 75 mg versus macitentan 10 mg in adults with PAH

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.

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FIGURE 2. Primary and secondary endpoints of the UNISUS study

Primary endpoint	Secondary endpoints
• Time to **first** committee-adjudicated morbidity/mortality clinical event (up to end of treatment + 7 days): – All-cause death – Non-planned PAH-related hospitalization – PAH-related disease progression	• Committee-adjudicated deaths due to PAH and/or hospitalizations for PAH (first and recurrent) (up to end of treatment + 7 days) • Change from baseline 6MWD (at Week 24) • Change from baseline PAH-SYMPACT® symptom domain scores (at Week 24) • Time to all-cause death (up to end of double-blind period)

All events are adjudicated by an independent clinical event committee

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

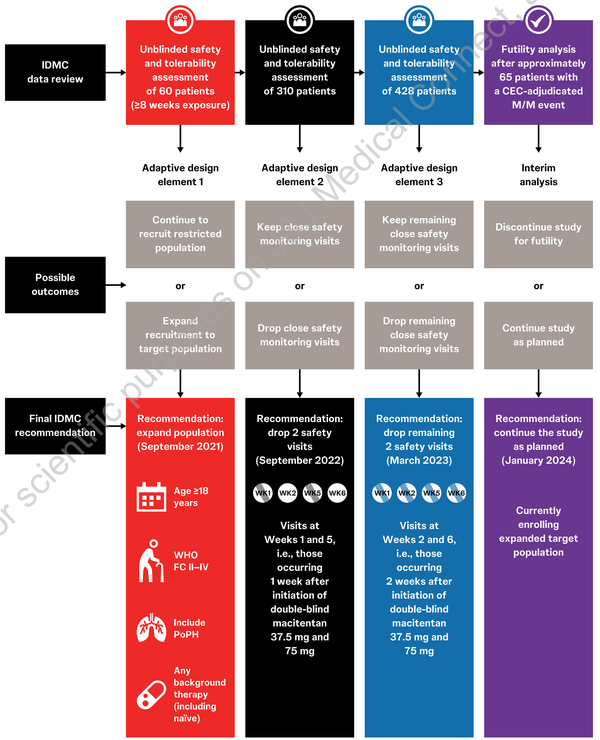

FIGURE 4. Eligibility criteria for target population currently being enrolled in UNISUS

Inclusion criteria	Exclusion criteria
≥18 years old WHO FC II, III and IV 6MWD ≥50 m and ≤440 m or >440 m if WHO FC III–IV with NT-proBNP ≥300 ng/L PAH treatment-naïve or receiving stable (≥3 months) PAH therapy prior to screening	Symptomatic PAH etiology: • Idiopathic • Heritable • Drug- or toxin-induced • Associated with: – Connective tissue disease – HIV infection – Portal hypertension – Congenital heart disease PAH diagnosis confirmed by hemodynamic evaluation:* • mPAP >20 mmHg and • PAWP ≤15 mmHg and • PVR ≥3 WU	Three or more risk factors for heart failure (with preserved ejection fraction): • BMI >30 kg/m² • Diabetes mellitus of any type • Essential hypertension (even if well controlled) • Coronary artery disease

*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.

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Disclosures

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REFERENCES:

1. Humbert M, et al. *Eur Heart J* 2022;43:3618–713; **2.** Actelion Pharmaceuticals US, Inc. Opsumit®. Highlights of prescribing information. https://www.opsumit.com/opsumit-prescribing-information.pdf (accessed Feb 2024); **3.** Pulido T, et al. *N Engl J Med* 2013;369:809–18; **4.** Iglarz M, et al. *J Pharmacol Exp Ther* 2008;327:736–45; **5.** Jasmin JF, et al. *Circulation* 2001;103:314–8; **6.** Kunita-Takanezawa M, et al. *J Cardiovasc Pharmacol* 2014;64:473–80; **7.** Galiè N, et al. *Eur Respir J* 2019;53:1802148.