UNISUS study design: a phase 3 superiority study comparing the efficacy, safety, and tolerability of macitentan 75 mg vs macitentan 10 mg in patients with pulmonary arterial hypertension (PAH)

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Background: While advances in PAH-specific therapies have substantially improved survival, there is still an unmet need to improve long-term outcomes in PAH.

Purpose: The UNISUS study is the first head-to-head superiority study in PAH, comparing the time to morbidity or mortality (M/M) with macitentan 75 mg vs macitentan 10 mg in PAH patients.

Methods: UNISUS, an ongoing multicentre, prospective, double-blind (DB), adaptive, event-driven superiority study randomises PAH patients 1:1 to receive macitentan 75 mg or macitentan 10 mg, with a target enrolment of ∼900 patients. Efficacy and safety are continuously assessed by an independent data monitoring committee (IDMC), who advises on pre-specified adaptive changes in study conduct, including expansion of the study population. An independent clinical event committee adjudicates all M/M events. The initial population was restricted to patients in functional class (FC) II/III, aged 18–75 years and excluded those with portopulmonary hypertension (PoPH) and those who were PAH treatment-naïve or receiving a prostanoid analogue. Stable (≥3 months) background PAH-therapy may be maintained, except for endothelin receptor agonists (ERAs), which must be stopped the day before initiating study drug. The study is comprised of a screening period, a 4-week run-in period (if ERA treatment-naïve or on sub-optimal ERA dose), and an event-driven DB treatment period, followed by a 2-year open-label extension with macitentan 75 mg. Initiation of macitentan 75 mg occurs after a 4-week up-titration step with macitentan 37.5 mg (Figure 1). The primary endpoint is time to first on-treatment M/M event, defined as first of: all-cause death, PAH-related hospitalisation, or PAH-related disease progression (confirmed ≥15% decrease in 6-minute walk distance (6MWD) and either FC worsening or addition of PAH therapy). Other endpoints include change from baseline to Week 24 in 6MWD and PAH-SYMPACT symptom scores; time to PAH-related hospitalisation or death; time to all-cause death (may be supplemented with data from an external control arm derived from the CARE PAH study [NCT04955990]); and the safety and tolerability of the study drugs. Figure 2 shows planned assessments and sub-studies. To maximise patient retention, add-on PAH therapies are allowed after a M/M event and, for patients at risk of withdrawing and unable to attend visits, the investigator may consider options for reduced follow-up.

Results: After 60 patients had been exposed for ≥8 weeks, the IDMC reviewed unblinded safety/tolerability data and recommended to expand recruitment from the restricted population to the target population (i.e., including patients: with PoPH, in FC II–IV, from any PAH therapy background [including naïve], aged ≥18 years).

Conclusion: UNISUS is the first head-to-head superiority study in PAH; with over 200 patients enrolled, it is currently recruiting the target population.

![Figure 1](https://academic.oup.com/eurheartj/article/43/Supplement_2/ehac544.1929/6744805)

![Figure 2](https://academic.oup.com/eurheartj/article/43/Supplement_2/ehac544.1929/6744805)