Dose rationale for UNISUS, an ongoing, event-driven, phase III superiority study evaluating macitentan 75 mg vs 10 mg in pulmonary arterial hypertension (PAH)

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Introduction

- Endothelin-1 (ET-1) pathway dysregulation is a hallmark of PAH[1,2] and leads to enhanced endothelin A (ET_A) and endothelin B (ET_B) receptor-mediated vasoconstriction, as well as inflammation, proliferation, pulmonary vascular remodeling, and fibroblast activation
- Macitentan is an endothelin receptor antagonist (ERA) approved for the treatment of PAH at 10 mg once daily (o.d.).[3,4] 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[5,6]
- ET_A receptor inhibition is considered maximal with currently available macitentan, as clinical effects mediated via ET_A receptor occupancy plateau at the 10 mg o.d. dose[7]
  - Blood pressure[8] and hemoglobin[9] decreases observed with both dual (bosentan and macitentan) and ET_A-selective (ambrisentan) ERAs suggest that these effects are mediated via ET_A inhibition
- Enhanced ET_B receptor inhibition via increased macitentan dose is of therapeutic interest in PAH
  - Preclinical studies suggest dose-dependent benefits on pulmonary fibrosis and right ventricular hypertrophy with macitentan via ET_B-mediated effects[10,11]
  - In phase I clinical studies in cardiovascular (CV) healthy volunteers and patients with glioblastoma, doses of macitentan up to 300 mg have been administered[12–14]

Objective

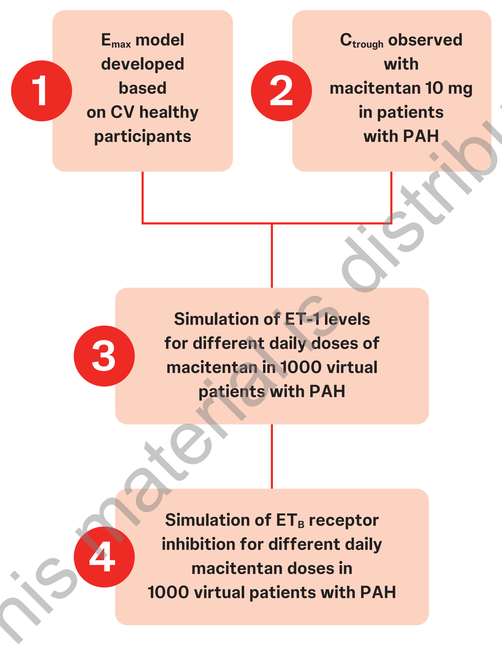
- To select doses of macitentan for the first head-to-head superiority study in PAH, the phase III UNISUS study (NCT04273945)[15]

Methods

Background

- ET_B receptors mediate clearance of ET-1 and their blockade leads to increased plasma levels of ET-1,[16] which can be used as a marker of ET_B receptor inhibition

FIGURE 1: Overview of the methodology



(1) E_{max} model

- A pharmacokinetic/pharmacodynamic analysis was performed using pooled data from three phase I studies in CV healthy participants (AC-055-102, n=32; NCT01499251, n=37; NCT02254954, n=6; overall, N=75) where macitentan was given for ≥5 days (steady-state) at doses ranging from 1 mg to 300 mg o.d.[12–14,17]
- Plasma macitentan and ET-1 concentrations were assessed
- To correlate macitentan and ET-1 plasma concentrations, an exposure-response analysis was performed using a time-matched, steady-state, macitentan and ET-1 concentration dataset
- An E_{max} model was fitted to the pooled dataset using a nonlinear least squares approach (**Box 1**)

(2) Calculation of C_{trough} achieved with macitentan 10 mg in patients with PAH

- Pharmacokinetic data from the SERAPHIN open-label extension study (NCT00667823, n=20)[18] were used to calculate the observed mean trough concentration (C_{trough}) for macitentan 10 mg in patients with PAH

(3) Simulation of ET-1 levels for macitentan doses >10 mg

- Based on these pharmacokinetic data for macitentan 10 mg in patients with PAH, C_{trough} values were simulated for 1000 virtual patients with PAH at macitentan daily doses of 37.5 mg, 75 mg, and 150 mg using a log-normal distribution, assuming dose linearity and the same standard deviation across doses evaluated

(4) Simulation of ET_B receptor inhibition for different macitentan doses

- The ET-1 concentration and corresponding level of ET_B inhibition receptor for each C_{trough} value were calculated
- The distribution of ET_B receptor inhibition values for each macitentan daily dose was plotted in the 1000 virtual patients
- The point at which 50% of the virtual patients, at trough, achieve the corresponding ET_B receptor inhibition for each daily dose was calculated and presented as the median ET_B receptor inhibition level for that dose

BOX 1: Essential pharmacodynamic concepts in drug development

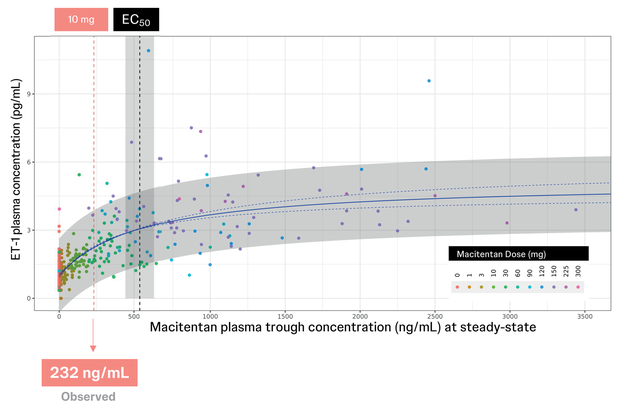
- **E_{max} model** is a pharmacodynamic model used to describe the dose-response relationship of a drug. It helps determine drug potency (EC_{50}) and efficacy (E_{max}), models pharmacological responses, and helps to optimize drug dosing regimens

$$Conc_{ET_1} \approx E_0 + \frac{(Conc_{macitentan} \cdot E_{max})}{(Conc_{macitentan} + EC_{50})}$$

  - **E_0** is the baseline ET-1 concentration
  - **E_{max}** is a key parameter of the E_{max} model that represents the **maximum effect** that a drug can achieve, provided sufficiently large exposure is achieved
  - **$Conc_{macitentan}$** and **$Conc_{ET1}$** are the steady-state, observed, time-matched, macitentan and ET-1 concentrations, respectively
  - **EC_{50}** refers to the concentration at which **half-maximal effect is achieved**
- **C_{trough}** is the lowest concentration of a drug in the bloodstream, reached before the next dose is administered. C_{trough} is dependent on the dose administered and, once the minimum effective drug concentration needed to achieve the desired therapeutic effect, while reducing the risk of toxicity, is identified, it helps in determining the optimal dosing regimens

Results

FIGURE 2: E_{max} curve derived from time-matched macitentan/ET-1 plasma concentration measurements (n=572) from CV healthy participants (n=75)



The dashed lines along the E_{max} curve are the 95% confidence interval, and the shaded area around the E_{max} curve is the model interval, estimated by linear approximation. The shaded area around the vertical EC_{50} line is the range of the EC_{50} value ± standard error.

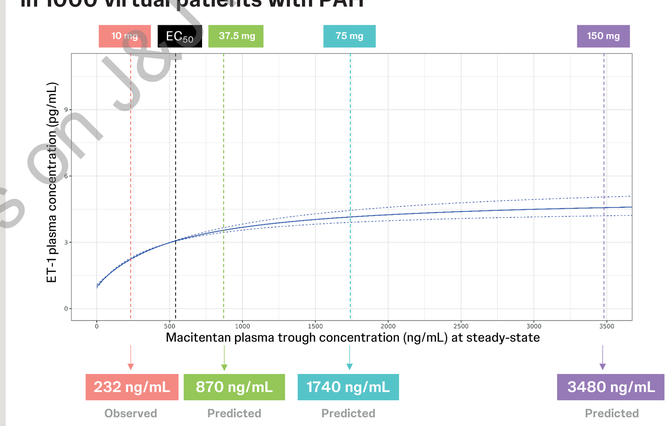
TABLE 1: Parameter estimates of the E_{max} model

Parameter	Estimate	Standard error
E_0 (pg/mL)	1.00	0.04
E_{max} (pg/mL)	4.12	0.30
EC_{50} (ng/mL)	538.55	95.5

E_0, baseline ET-1 concentration; **E_{max}**, maximum ET-1 concentration; **EC_{50}**, half-maximal effective concentration.

- ET-1 levels increased with increasing concentrations of macitentan and followed an E_{max} curve
- The observed mean C_{trough} (232 ng/mL) achieved with macitentan 10 mg o.d. in patients with PAH is below the estimated EC_{50} for ET_B inhibition
- These findings suggest that increasing the dose of macitentan beyond 10 mg o.d. could further enhance ET_B receptor inhibition

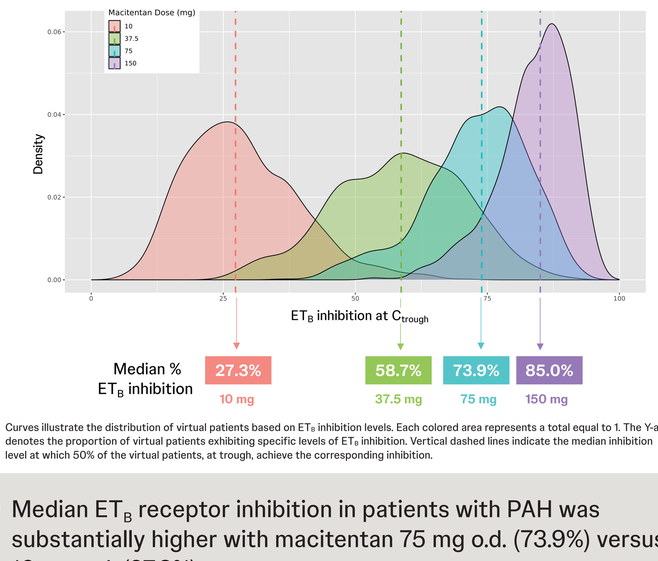
FIGURE 3: Predicted C_{trough} for macitentan daily doses >10 mg in 1000 virtual patients with PAH



The dashed lines along the E_{max} curve are the 95% confidence interval.

- At a 75 mg o.d. macitentan dose, the mean predicted C_{trough} for ET-1 plasma concentrations is close to the plateau region of the E_{max} curve
  - Therefore, no substantial increases in ET_B receptor inhibition are expected for doses above 75 mg o.d.

FIGURE 4: ET_B receptor inhibition in 1000 virtual patients with PAH

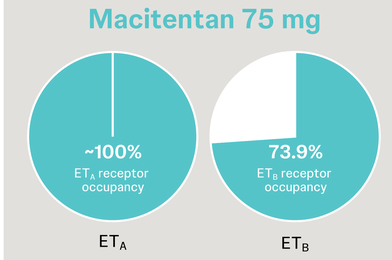


Curves illustrate the distribution of virtual patients based on ET_B inhibition levels. Each colored area represents a total equal to 1. The Y-axis denotes the proportion of virtual patients exhibiting specific levels of ET_B inhibition. Vertical dashed lines indicate the median inhibition level at which 50% of the virtual patients, at trough, achieve the corresponding inhibition.

- Median ET_B receptor inhibition in patients with PAH was substantially higher with macitentan 75 mg o.d. (73.9%) versus 10 mg o.d. (27.3%)
  - Overlap in ET_B receptor inhibition between these doses was minimal (6.8%), indicating greater capacity for ET_B receptor inhibition at 75 mg o.d. versus 10 mg o.d.
- Doubling the macitentan dose to 150 mg o.d. resulted in a minor increase (11.1%) in the median ET_B receptor inhibition level compared to the 75 mg o.d. dose
  - There was a 78.8% overlap in ET_B receptor inhibition between the 75 mg o.d. and 150 mg o.d. doses, indicating similar levels of ET_B inhibition
- The intermediate macitentan dose of 37.5 mg o.d. resulted in a median ET_B inhibition of 58.7%, with a considerable overlap with 10 mg o.d. (21.5%)

Key takeaways

Macitentan 75 mg is the once-daily dose estimated to provide near maximal ET_B inhibition in patients with PAH



- Macitentan 75 mg o.d. was selected for the phase III, event-driven UNISUS study, the first head-to-head superiority study in PAH
- UNISUS will evaluate the efficacy and safety of macitentan 75 mg o.d. versus macitentan 10 mg o.d.
- UNISUS is fully recruited with 935 patients with PAH treated for up to 5 years

Conclusions

- **A macitentan dose of 75 mg o.d. was selected for the phase III UNISUS study, as modeling and analysis estimated:**
  - **A substantially higher ET_B receptor inhibition in PAH patients compared to 10 mg o.d.**
  - **No substantial additional ET_B receptor inhibition beyond 75 mg o.d.**
- **UNISUS is the first head-to-head superiority study in PAH and aims to demonstrate safety, tolerability, and superior efficacy of macitentan 75 mg o.d. versus macitentan 10 mg o.d. This will support the use of macitentan 75 mg o.d. as foundational therapy in a broad PAH patient population**
- **Improved outcomes with macitentan 75 mg o.d. versus 10 mg o.d. in UNISUS will confirm the clinical importance of maximal ET_B receptor blockade for PAH treatment**

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Disclosures

Dénes Csonka, Gurinderpal Doad, and Juan José Pérez-Ruixo are employees of Johnson & Johnson.

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