Pharmacokinetics (PK) and Safety of Macitentan 75 mg: Phase I Data from Chinese and White Healthy Adults

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Background

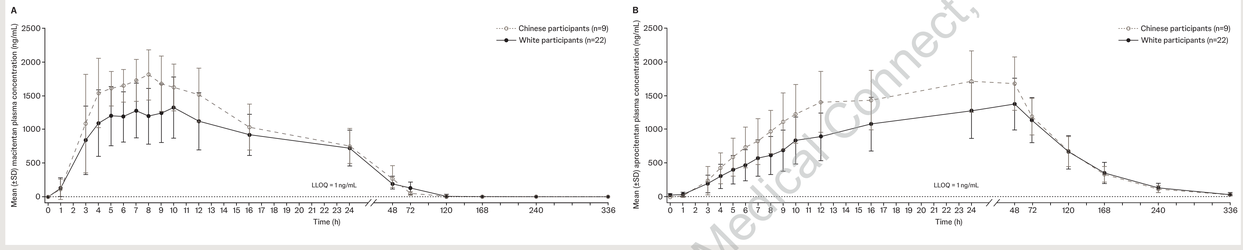
- Pulmonary arterial hypertension (PAH) is a progressive, currently incurable disease with a median survival of 5–7 years, despite available therapies.[1,2]
- In PAH, endothelial dysfunction, increases in vasoconstrictive substances, such as endothelin-1, and changes in endothelin (ET) receptor expression occur, with aberrant downstream effects mediated by both ET_A and ET_B receptors,[3,4] making the ET-1 pathway a key drug target.
- Macitentan 10 mg is a highly effective endothelin receptor antagonist and is a guideline-recommended standard of care (SOC) for PAH patients.[2]
  - 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.[4–6]
- Macitentan 75 mg is postulated to have superior efficacy compared to macitentan 10 mg due to its potent blockade of both ET_A and ET_B receptors, and with a safety profile consistent with macitentan 10 mg.[5–7]
- The Phase 3 UNISUS trial (NCT04273945) aims to demonstrate superior efficacy of macitentan 75 mg vs macitentan 10 mg on time to first morbidity/mortality event in patients with PAH.[8]
- Macitentan 10 mg has been studied across several racial and ethnic groups showing no clinically relevant differences in pharmacokinetics (PK) or safety.[9]
  - Real-world data have also demonstrated clinical benefits of macitentan 10 mg in Chinese patients with PAH treated in routine clinical practice.[10]
- In this analysis, the PK and safety of macitentan 75 mg was examined in healthy volunteers of White and Chinese ethnic groups.

Methods

- PK data for macitentan and its active metabolite aprocitentan, and safety data from two randomized, single-centre, Phase I studies of healthy volunteers were used for comparison.
  - The first study was a double-blind, placebo-controlled trial in 12 Chinese male adults (NCT05959941).
    - Healthy Chinese adult males aged 18–55 years with a BMI 18.0–27.9 kg/m^2 and body weight ≥50.0 kg were included.
    - Participants were randomized 3:1 to receive macitentan 75 mg or placebo under high-fat fed conditions. Only macitentan 75 mg data are reported (n=9).
  - The second study was an open-label, relative bioavailability trial in 23 White adults at a single-center in Belgium.
    - Healthy White adults aged 18–55 years with a BMI 18.5–30.0 kg/m^2 and body weight ≥50.0 kg, were included.
    - In a 3-way crossover design, participants received three different 75 mg formulations, one per treatment period. Only the reference formulation of 75 mg macitentan being evaluated in Phase III studies is reported.
    - Macitentan 75 mg was administered under fed conditions (high-calorie, high-fat meal).
- In each study, the PK of macitentan and aprocitentan were assessed using a validated liquid chromatography assay with a lower limit of quantification (LLOQ) of 1.0 ng/mL for macitentan and aprocitentan.
- The safety population were participants who received at least one dose of any study intervention, and contributed safety data after the start of study intervention.

Results

Figure 1. Mean (SD) plasma macitentan (A) and aprocitentan (B) concentration–time profiles (PK analysis set)



- A total of 9 healthy Chinese adults and 23 healthy White adults received macitentan 75 mg and were included in this analysis.
  - Overall, baseline characteristics were broadly comparable between the two study populations (**Table 1**).
    - BMI and age were numerically higher in the White participants group compared with Chinese participants group.
- Mean (SD) plasma concentration–time profiles for macitentan 75 mg and aprocitentan are depicted in **Figure 1**.
  - In both groups, a plateau in macitentan concentrations was observed between 4 and 5 hours and 10 hours post-dose. (**Figure 1A**).
  - Aprocitentan concentrations reached a maximum at 24 hours (Chinese participants) or 48 hours (White participants) post-dose and then slowly declined (**Figure 1B**).
- Macitentan 75 mg PK parameters are presented in **Table 2**. Overall, exposures were similar with no clinically relevant differences between groups
  - Mean macitentan C_{max} was ~35% higher in Chinese versus White participants, although total exposure (AUC_{inf}) was similar.
  - Interparticipant variability (coefficient of variation) was low in both groups, ranging from 22.4–30.9% in the White participants group and 12.2–20.7% in the Chinese participants group.
- Similarly, no clinically relevant differences were observed between White and Chinese participants across aprocitentan PK parameters (**Table 3**).
  - Median T_{max} was numerically higher in White participants versus Chinese participants (48.0 vs 24.0 h), while mean aprocitentan C_{max} and AUC_{inf} were ~24 and 11% higher in Chinese versus White participants.
  - Interparticipant variability was low in both groups, ranging from 24.0–32.6% in the White participants group and 8.5–26.1% in the Chinese participants group.
- Treatment-emergent adverse events (TEAEs) with macitentan were reported for 56% (n=5/9) of Chinese and 55% (n=12/22) of White participants; most common was headache (n=4/9 and 10/22, respectively) (**Table 4**).
  - 10 and 3 TEAEs in the White and Chinese groups, respectively, were reported as related to treatment by the investigator.
  - No serious TEAEs were reported.
- No new safety concerns with macitentan 75 mg were identified.

Table 1. Demographic and baseline characteristics of study participants

	Chinese participants (n=9)	White participants (n=23)[a]
Male, n (%)	9 (100.0)	3 (13.0)
Age, years	32.1 (9.2)	42.9 (10.8)
BMI, kg/m^2	21.8 (1.9)	24.6 (2.9)
Weight, kg	63.3 (6.7)	69.9 (9.8)

Values are arithmetic mean (SD) unless otherwise stated.
[a]PK parameters shown for n=22, as one randomized participant terminated the study prematurely.
BMI, body mass index.

Table 2. Summary of plasma macitentan PK parameters – in Chinese and White adults (PK analysis sets)

	Chinese participants (n=9)	White participants (n=22)
C_{max} (ng/mL)	2018 (371)	1,490 (443)
T_{max} (h)	7.0 (3.0–12.0)	5.0 (4.0–10.1)
AUC_{0-t} ng*h/mL	43,431 (8,970)	43,788 (14,137)
AUC_{0-inf} (ng*h/mL)	45,075 (8,162)	43,873 (14,150)
$t_{1/2}$ (h)	13.1 (1.7)	16.0 (2.8)
CL/F (L/h)	1.7 (0.29)	1.86 (0.5)
V_z/F (L)	31.8 (4.1)	41.7 (9.9)

Values are arithmetic mean (SD) except for T_{max} (median [min-max]).
AUC_{0-24h}, area under the plasma concentration–time curve from time 0 to 24 h; CL/F, apparent clearance; C_{max}, maximum plasma concentration; SD, standard deviation; $t_{1/2}$, terminal elimination half-life; T_{max}, time to reach the maximum plasma concentration; V_z/F, apparent volume of distribution.

Table 3. Summary of plasma aprocitentan PK parameters – in Chinese and White adults (PK analysis sets)

	Chinese participants (n=9)	White participants (n=22)
C_{max} (ng/mL)	1,774 (425)	1,427 (393)
T_{max} (h)	24.0 (24.0–48.0)	48.0 (16.0–72.0)
AUC_{0-t}, ng*h/mL	193,362 (50,069)	173,117 (53,112)
AUC_{0-inf} (ng*h/mL)	195,486 (51,045)	175,962 (54,659)
$t_{1/2}$ (h)	49.0 (4.2)	50.5 (5.8)

Values are arithmetic mean (SD) except for T_{max} (median [min-max]).
AUC_{0-24h}, area under the plasma concentration-time curve from time 0 to 24 h; C_{max}, maximum plasma concentration; SD, standard deviation; $t_{1/2}$, terminal elimination half-life; T_{max}, time to reach the maximum plasma concentration.

Table 4. Summary of patients with TEAEs by SOC and PT across both Chinese and White adults occurring in >1 participant (safety analysis set)

	Chinese adults (n=9)	White adults (n=22)
Participants with ≥1 TEAE, n (%)	5 (55.6)	12 (54.5)
Nervous system disorders		
Headache	4 (44.4)	10 (45.5)
Gastrointestinal disorders		
Nausea	-	5 (22.7)
General disorders and administration site conditions		
Fatigue	-	3 (13.6)
Malaise	-	2 (9.1)
Participants with TEAEs related to treatment, n (%)[a]	3 (33.3)	10 (45.5)

Patients are only counted once for any given event, regardless of the number of times they actually experienced the event. AEs are coded using MedDRA Version 23.0.
[a]Assessed as related by the investigator.
AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; SOC, system organ class; TEAE, treatment-emergent adverse event.

Key takeaway

- Macitentan 75 mg demonstrated similar pharmacokinetics and safety in Chinese and White participants, supporting no ethnicity-based dose adjustment and continued evaluation versus 10 mg in the Phase 3 UNISUS PAH trial.

Conclusion

- No clinically relevant differences in PK were observed between Chinese and White participants after a single dose of macitentan 75 mg, indicating that no dose adjustment based on these ethnic origins is required. Results are consistent with a recent study of food effect on macitentan 75 mg in Japanese participants.[11]
- The safety profile of macitentan 75 mg was similar between populations and was consistent with the known profile of macitentan 10 mg.[10]
- This results support the ongoing global Phase 3 UNISUS trial evaluating the efficacy and safety of macitentan 75 mg versus 10 mg in the treatment of PAH.[7]

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Disclosures

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