Pharmacokinetics, Safety, and Tolerability of Single-dose Obeldesivir in Healthy Japanese and White Participants

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Conclusions

- Following a single oral dose of obeldesivir, plasma pharmacokinetic exposures were higher in Japanese participants than in White participants, but within the range of pharmacokinetic exposures observed in previous Phase 1 studies
- The increase in exposures in Japanese participants is likely the result of differences in body weight between the 2 populations and will be further evaluated using population pharmacokinetic modelling
- Obeldesivir 350 mg was generally safe and well tolerated with no notable differences in adverse events or laboratory abnormalities between Japanese and White participants

Plain Language Summary

Obeldesivir is a broadly active, orally administered antiviral drug. In this study, we show that obeldesivir is tolerated similarly in Japanese and White participants. The levels of the obeldesivir metabolite GS-441524 observed in the blood were similar to those in other studies with obeldesivir.

Introduction

- Obeldesivir (ODV) is an oral nucleoside analogue prodrug with broad antiviral activity[1]
- There is a need for an effective oral treatment with a low pill burden, a high barrier to resistance, and minimal drug-drug interactions to combat COVID-19 across ethnically and racially diverse populations

Objective

- To assess the single-dose pharmacokinetics (PK), safety, and tolerability of ODV in healthy Japanese and White participants

Methods

- This was a single-centre, open-label, Phase 1 study
- The test group consisted of participants who were born in Japan, of first-generation descent, with parents and grandparents who had traceable maternal and paternal Japanese ancestry
- The reference group consisted of participants who were White and not of Japanese/Asian descent
- All participants were administered 1 tablet of ODV 350 mg orally on the morning of Day 1 in a fasted state
- Intensive PK sampling was performed at numerous time points from 0 to 72 hours post dose; plasma concentrations of the ODV metabolite GS-441524 were quantified via liquid chromatography-tandem mass spectrometry
- Statistical comparisons of GS-441524 exposures were conducted by comparing estimates for geometric least squares mean (GLSM) ratios and associated 90% CIs from the test group versus the reference group
- The primary endpoints were the plasma PK parameters (maximum observed concentration [C_{max}], area under the concentration-time curve from dosing to last measurable concentration, and area under the concentration-time curve extrapolated to infinite time [AUC_{inf}]) of GS-441524
- The secondary endpoints were the incidences of adverse events (AEs), serious AEs, and laboratory abnormalities

Results

Demographic and Baseline Characteristics

Table 1. Demographic and Baseline Characteristics

	Japanese (N = 20)	White (N = 20)	Total (N = 40)
Age, y, median (range)	45 (21-61)	33 (19-60)	41 (19-61)
Sex at birth, n (%)[a]			
Male	8 (40)	9 (45)	17 (43)
Female	12 (60)	11 (55)	23 (58)
Race, n (%)			
Asian	20 (100)	0	20 (50)
White	0	20 (100)	20 (50)
Ethnicity, n (%)			
Hispanic or Latino	0	17 (85)	17 (43)
Body weight, kg, median (range)	66.1 (50.0-93.3)	71.7 (59.2-92.3)	70.0 (50.0-93.3)
Body mass index, kg/m^2, median (range)	23.7 (20.5-29.1)	26.0 (22.0-29.2)	25.4 (20.5-29.2)

[a]Percentages may not sum to 100% due to rounding.

- Compared to White participants, Japanese participants were older (median age, 45 vs 33 years) and had a lower body weight (median, 66.1 vs 71.7 kg) and a lower body mass index (median, 23.7 vs 26.0 kg/m^2; **Table 1**)

PK Profile of ODV

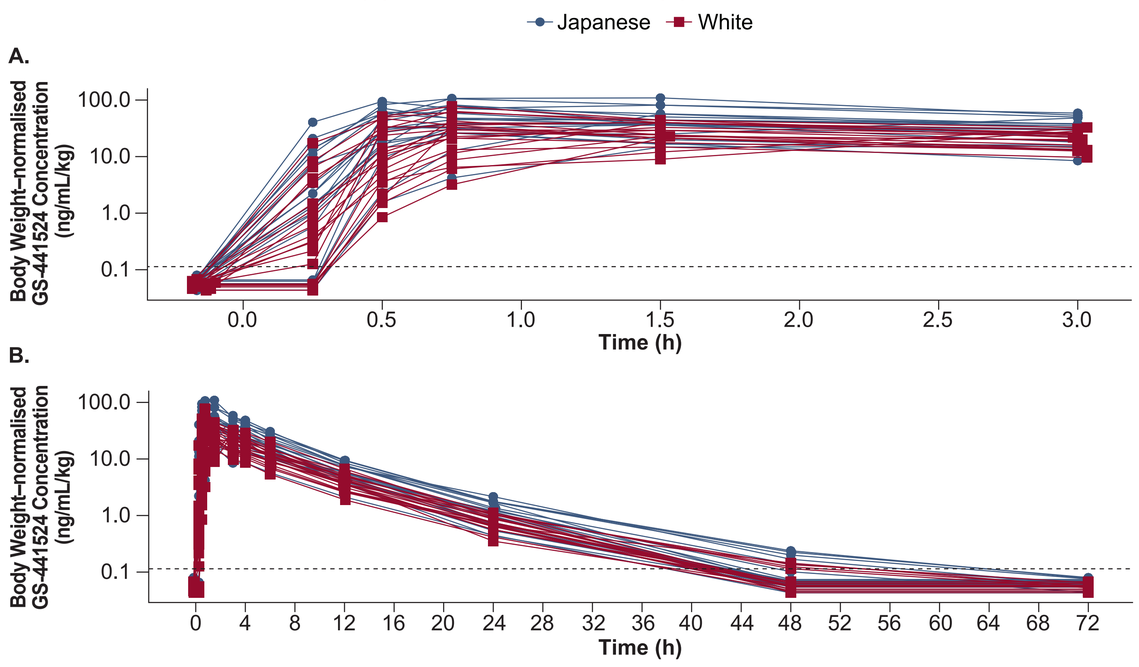
Table 2. GS-441524 PK Parameter Summary

	Japanese (N = 19)[a]	White (N = 20)	%GLSM Ratio (90% CI)[b]
C_{max}, ng/mL, mean (%CV)	3670 (37.0)	2600 (36.3)	139 (114-171)
AUC_{last}, h·ng/mL, mean (%CV)	18,000 (26.4)	12,900 (23.1)	138 (120-159)
AUC_{inf}, h·ng/mL, mean (%CV)	18,300 (25.5)	13,200 (22.7)	137 (120-157)
$t_{1/2}$, h, median (Q1, Q3)	5.0 (4.2, 6.5)	4.9 (4.3, 5.5)	ND

[a]One participant with all postdose samples <LLOQ was excluded from the PK analysis set.
[b]Statistical comparisons assumed that exposure differences between groups were solely due to race, as no other variables, such as body weight, were used to normalise the data above to calculate the presented %GLSM ratios.
AUC_{inf}, area under the concentration-time curve extrapolated to infinite time; AUC_{last}, area under the concentration-time curve from dosing to last measurable concentration; C_{max}, maximum observed concentration; CV, coefficient of variation; GLSM, geometric least squares mean; LLOQ, lower limit of quantification; ND, not determined; PK, pharmacokinetic; Q1, first quartile; Q3, third quartile; $t_{1/2}$, half-life.

- The %GLSM ratios suggest 37% to 39% increases in ODV PK exposures in Japanese versus White participants (**Table 2**)
  - This analysis did not account for differences in body weight, which may explain increased exposures in Japanese participants
  - Plasma PK exposures in Japanese participants were within the range of those observed in Phase 1 ODV studies[2]
- Half-lives ($t_{1/2}$) were estimated to be 5.0 hours and 4.9 hours for Japanese and White participants, respectively

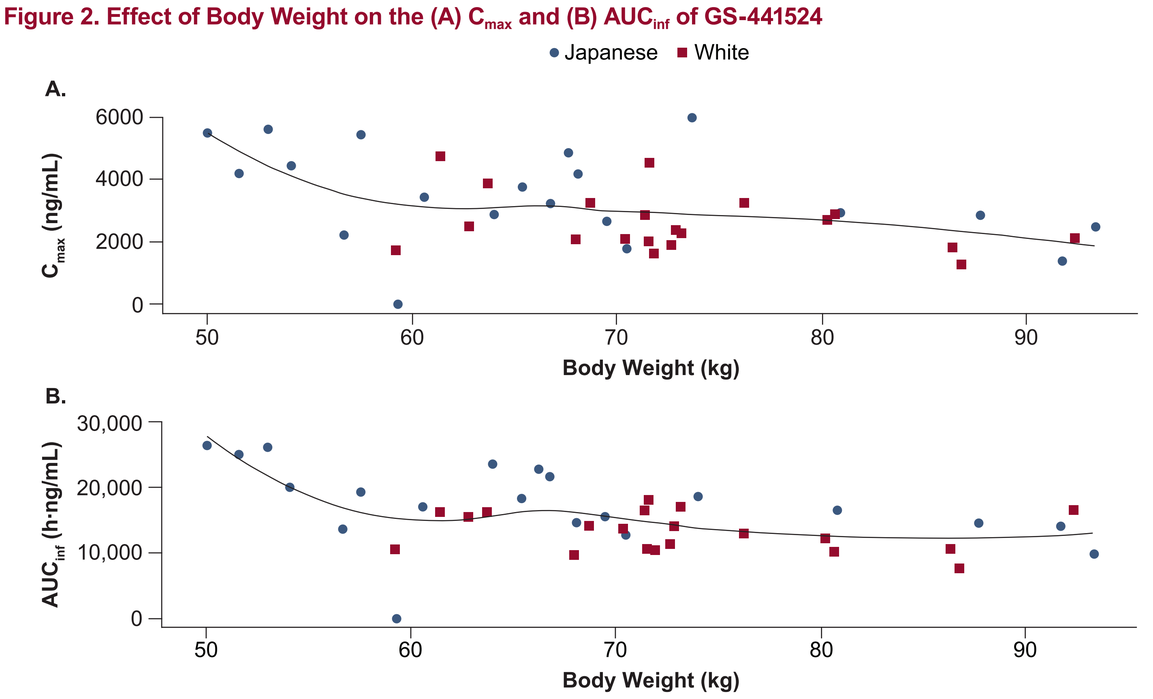
Figure 1. Body Weight–normalised Individual GS-441524 Plasma Concentration Versus Time in Japanese and White Participants (A) 3 Hours Post Dose and (B) 72 Hours Post Dose



Profiles shown in this figure were normalised to body weight by dividing participants' concentration-time profiles by their individual body weight.
Values below the limit of quantification were treated as 0 for baseline summaries and as one-half of the LLOQ for postbaseline summaries.
The LLOQ is defined as 8.0 ng/mL for GS-441524 in plasma.
One participant whose profile was <LLOQ throughout the entire PK sampling interval is not shown in the plot.
LLOQ, lower limit of quantification; PK, pharmacokinetic.

- After adjusting for body weight, mean plasma concentrations of GS-441524 peaked within the first hour and decreased at similar rates for both Japanese and White participants following a single oral dose of ODV 350 mg (**Figure 1**)

Figure 2. Effect of Body Weight on the (A) C_{max} and (B) AUC_{inf} of GS-441524



AUC_{inf}, area under the concentration-time curve extrapolated to infinite time; C_{max}, maximum observed concentration.

- **Figure 2** demonstrates that lower body weights (<60 kg; observed mostly in Japanese participants) correlated with higher C_{max} and AUC_{inf}, and higher body weights (≥60 kg; the weight group for most White participants) correlated with lower C_{max} and AUC_{inf}
- All PK exposures across both populations were within the range of PK exposures observed in previous Phase 1 studies[2]
- Ongoing population PK modelling will be able to quantify the potential differences in exposure due to race, after adjusting for body weight

Safety and Tolerability of ODV

- ODV 350 mg was generally safe and well tolerated (**Table 3**)
- All AEs were Grade 1 or 2 in severity

Table 3. AEs by Preferred Term

Preferred Term, n (%)	Japanese (N = 20)	White (N = 20)
Participants with any AE	2 (10)	3 (15)
Participants with any AE related to the study drug	2 (10)	2 (10)
Headache	0	2 (10)
Nausea	1 (5)	0
Vomiting	1 (5)	0

AE, adverse event.

References: 1. Cross RW, et al. *Science*. 2024;383(6688):eadk6176.
2. Anoshchenko O, et al. Presented at: 33rd European Congress of Clinical Microbiology and Infectious Diseases (ECCMID); 15-18 April 2023; Copenhagen, Denmark. Poster P2620.

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