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A Phase 1, Open-Label, Single Ascending (Two Levels) Dose Study to Evaluate the Pharmacokinetics of Vorasidenib in Healthy Japanese and Non-Asian Participants

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Abstract

Vorasidenib was first approved in 2024 for the treatment of Grade 2 gliomas with isocitrate dehydrogenase 1 and 2 mutations and is now approved in over 40 countries, including Japan. During early development, vorasidenib pharmacokinetics (PK) was estimated in populations without Japanese participants. In 2019, this Phase 1 single ascending (two levels) dose study (NCT04145128) was conducted to evaluate PK and safety of single oral 10- and 50-mg vorasidenib doses in healthy Japanese participants versus non-Asian participants to determine whether vorasidenib PK was ethnically sensitive. Thirty-two participants (16 Japanese, 16 non-Asian) were enrolled. After a single oral dose of 10 or 50 mg, vorasidenib was rapidly absorbed, distributed, and eliminated in a biexponential manner. Geometric mean maximum plasma concentration (C_{max}), area under the concentration–time curve (AUC) from time 0 to last measurable concentration, and AUC from time 0 extrapolated to infinity were generally comparable between race and dose groups (geometric mean ratios: 1.00–1.38). There were no new safety concerns, deaths, serious adverse events (AEs), study-drug-related AEs, or discontinuations due to AEs. In conclusion, vorasidenib was generally safe and well tolerated, and plasma exposures were generally similar between Japanese and non-Asian participants following single oral 10- and 50-mg vorasidenib doses. These results enabled vorasidenib clinical development in Japan and supported inclusion of Japanese sites in subsequent vorasidenib clinical trials without dose adjustments.

Keywords

bridging study, diffuse glioma, ethnicity-related differences, Japanese population, mIDH1/2 inhibitor, pharmacokinetics

Introduction

Gliomas with mutations in isocitrate dehydrogenase 1 or 2 (mIDH1/2) are the most common malignant primary brain tumors diagnosed in adult patients younger than 50 years and cause significant morbidity and premature death.[1–4] These tumors are graded 1 to 4 to indicate a low to high grade of malignancy based on histological, molecular, and clinical criteria defined by the World Health Organization.[5,6] Lower-grade gliomas initially grow at a slower rate and can be treated; however, current treatments are not curative, and, with time, these gliomas typically progress to a higher grade.[3,4] Adjuvant chemoradiotherapy after surgical resection can lead to long-lasting disease stabilization.[3,7] However, this therapy is associated with significant short- and long-term toxicities, leading to delays in receipt of adjuvant chemoradiotherapy immediately after surgery, with health professionals favoring an active monitoring approach in patients who are asymptomatic beyond epilepsy.[3,8] This watch-and-wait period represents an opportunity for the development and evaluation of additional therapies for mIDH1/2 gliomas with the potential to delay tumor progression and cause less treatment-associated toxicity.[9]

There are molecular differences between mIDH1/2 gliomas and IDH-wild-type glioblastomas.[5] Mutations in IDH1 and IDH2 disrupt the conversion of isocitrate to alpha-ketoglutarate, leading to an accumulation of the oncometabolite R-2-hydroxyglutarate (2-HG).[6,10] Vorasidenib is a first-in-class dual inhibitor of mIDH1/2 designed to suppress 2-HG production and achieve high levels of brain penetration.[11] An initial Phase 1 trial demonstrated that vorasidenib was well

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tolerated and exhibited preliminary antitumor activity in patients with non-enhancing mIDH1/2 glioma.[4] The objective response rate (complete response + partial response + minor response) with vorasidenib was 18%, stable disease as their best response was achieved in 73% of patients, and the median progression-free survival (PFS) was 36.8 months.[4] A subsequent perioperative Phase 1 trial in patients with recurrent mIDH1/2 glioma demonstrated a high brain penetrance and consistent short-term 2-HG suppression of over 90% in patients who were treated with vorasidenib before tumor resection.[12] Subsequently, a double-blind Phase 3 trial (INDIGO) was designed to determine whether vorasidenib could delay tumor progression in patients with residual or recurrent Grade 2 mIDH1/2 gliomas who had undergone surgery as their only previous treatment and who were suitable for a watch-and-wait approach.[9,13] Patients treated with vorasidenib had a significantly longer PFS (primary endpoint) and time to next intervention (TTNI; key secondary endpoint) than the placebo group (median PFS: 27.7 vs 11.1 months; hazard ratio for disease progression or death: 0.39; 95% confidence interval [CI]: 0.27–0.56; median TTNI: not reached vs 17.8 months; hazard ratio: 0.26; 95% CI: 0.15–0.43; $P < .001$).[9] Following these positive clinical outcomes, the trial was unblinded in March 2023.[9,13] Vorasidenib has subsequently been approved for the treatment of Grade 2 mIDH1/2 gliomas in over 40 countries, including Australia, Brazil, Canada, India, Israel, Japan, Saudi Arabia, Switzerland, the EU, the UAE, the United Kingdom, and the United States.[14–19]

Pharmacokinetic (PK) analyses of vorasidenib in patients with mIDH1/2 glioma and in healthy participants determined that, after a single oral dose of the highest approved recommended dose (40 mg), geometric mean maximum plasma concentration (C_{max}) was 75.4 ng/mL (coefficient of variation [CV%]: 44), median time to C_{max} (t_{max}) was 2.0 h, and the geometric mean area under the plasma concentration–time curve (AUC) was 2860 h·ng/mL (CV%: 56).[15] At steady state, geometric mean C_{max} was 133 ng/mL (CV%: 73), median t_{max} was 2.0 h (minimum 0.5 h, maximum 4 h), and geometric mean AUC was 1988 h·ng/mL (CV%: 95).[14,15] C_{max} and AUC increased approximately proportionally over the dose range of 10–200 mg following a single administration or once-daily administration of multiple doses.[14,15] Mean steady state volume of distribution was 3930 L (CV%: 40), mean terminal half-life ($t_{\frac{1}{2}}$) was 238 h (CV%: 57), and mean apparent clearance was 14.0 L/h (CV%: 56).[14,15] Vorasidenib is primarily metabolized by cytochrome P450 (CYP) 1A2 hepatic metabolism, with minor contributions from CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A, with non-CYP metabolism pathways potentially contributing up to 30% of metabolism.[14]

Vorasidenib PK was initially evaluated in populations without Japanese participants. Genetic and environmental factors could contribute to ethnic variability in drug metabolism, transport, and pharmacological response.[20] For example, published studies suggest that genetic and environmental factors may contribute to lower concentrations of CYP enzymes and lower enzymatic activity in Japanese and other Asian populations than in White populations.[21–23] Therefore, there was a need to evaluate whether vorasidenib PK in the Japanese population was different from vorasidenib PK in published studies in mostly non-Asian populations.

To support the clinical development of vorasidenib in Japan, and because of potential interethnic differences in drug PK,[20] this study was designed to evaluate the PK and safety of vorasidenib in a Japanese population and to compare results with those in a non-Asian population.

Methods

Ethics

The protocol and informed consent form were reviewed and approved by the Independent Ethics Committee of the study site before the start of the study (location: Alpha IRB, 1001 Avenida Pico, Suite C, #497, San Clemente, CA 92673; chairperson: Melissa Cortes, MEd, ET/P). All participants provided voluntary written informed consent. The study was designed and conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use E6 requirements for Good Clinical Practice and applicable national and local regulatory requirements.

Study Design

This was a Phase 1 single ascending (two levels) dose study (NCT04145128) designed to evaluate and compare the PK and safety of vorasidenib in healthy Japanese and non-Asian participants. The study was divided into two consecutive periods, with a washout period of 20 days between doses. At the start of both periods, participants received an oral dose of vorasidenib (Period 1, 10 mg on Day 1; Period 2, 50 mg on Day 22). Blood samples were collected throughout each period to determine plasma concentrations of vorasidenib for PK estimation. Participants were confined to the clinical unit from the day prior to dosing (Period 1, Day −1; Period 2, Day 21) until after the 72-h PK sample (Period 1, Day 4; Period 2, Day 25) and returned to the clinic throughout the study for additional PK blood

samplings. Clinical laboratory and safety parameters were collected throughout the study.

The primary objective of this study was to characterize and compare PK in healthy Japanese and non-Asian participants following single oral doses of 10 and 50 mg of vorasidenib. Endpoints included PK parameters such as AUC from time 0 to time of last measurable concentration (AUC_{0-last}), AUC from time 0 extrapolated to infinity ($AUC_{0-\infty}$), C_{max}, $t_{\frac{1}{2}}$, and t_{max}. The secondary objective was to characterize and compare the safety of single doses of vorasidenib in these populations, as measured by safety endpoints such as incidence and frequency of adverse events (AEs), clinical laboratory tests, physical examinations, vital signs, electrocardiograms (ECGs), and use of concomitant medication.

Participants

Participants were 18–55 years of age at screening, with a body mass index (BMI) between 18.0 and 32.0 kg/m^2, were continuous nonsmokers, were medically healthy with no clinically significant medical history, physical examination, laboratory profiles, vital signs, or ECG, and had liver function tests up to and including upper limit of normal. Female participants were required to be of non-childbearing potential by either having undergone a sterilization procedure at least 6 months prior to the first dosing or having medically confirmed postmenopausal status. Japanese participants had to be born in Japan, had to have two Japanese biological parents and four Japanese biological grandparents, had to have lived outside of Japan for under 5 years, and had to have made no significant lifestyle changes, including diet, since leaving Japan, while non-Asian participants had to have two biological parents and four biological grandparents not of Asian descent.

Drug Concentration and Safety Measurements

Blood samples for determination of plasma vorasidenib concentrations were collected prior to vorasidenib administration and at 0.5, 1, 2, 3, 4, 6, 8, 10, 24, 48, 72, 120, 168, 240, 336, and 504 h after each dosing.

The concentration of vorasidenib in plasma samples was analyzed using a validated high-performance liquid chromatography-tandem mass spectrometry detection method (PPD Laboratories, Middleton, WI) with a lower limit of quantitation (LLOQ) of 1 ng/mL and an upper limit of quantitation of 1000 ng/mL. The liquid chromatography system used was Agilent 1100 (Agilent Technologies, Santa Clara, CA), consisting of a binary solvent manager and an autosampler. The separation and analysis were performed using a Waters dC18 column (2.1 × 50 mm, 5 μm; Waters Corporation, Milford, MA) kept at ambient temperature whereas the autosampler was at 4°C. The analytical run time was 3 min. The mobile phases consisted of 0.1% formic acid in water (mobile phase A) and 0.1% formic acid in acetonitrile (mobile phase B), with a constant flow of 0.325 mL/min. The analyte and internal standard were eluted at isocratic of 65% mobile phase B. The mass spectrometry analysis was performed on a Sciex API 5500 mass spectrometer (AB Sciex, Framingham, MA) equipped with a turbo spray ionization source. The detection was conducted with positive ion multiple reaction monitoring mode. Mass transitions of m/z 415.0 > 260.1 and 421.0 > 266.1 were monitored for vorasidenib (also named AG-881 or AGI-23088; molecular weight = 414 Da) and internal standard AGI-28187 (stable isotope-labeled compound of vorasidenib, also named d6-AGI-23088; molecular weight = 420 Da [6 Da higher than that of vorasidenib]), respectively. In addition to study samples, each 96-well, plate-based analytical run contained calibration standards, quality controls (QCs), and blanks to determine its acceptability. An analytical run was considered acceptable when at least 67% of QCs and at least 50% of the QCs for each level met the acceptance criterion of having calculated concentrations within 15% of the theoretical value. A run was rejected if either the unfortified matrix blank or the matrix blank with internal standard had a response ratio greater than the mean response ratio of the LLOQ calibration standards.

Noncompartmental analyses (Phoenix WinNonlin version 6.3; Certara, Princeton, NJ) of plasma concentrations and the actual sampling times were used to estimate PK parameters. For analysis purposes, individual PK profiles were evaluated within each subpopulation and compared between the Japanese and non-Asian groups.

Safety assessments were conducted throughout the study and included clinical laboratory tests, physical examinations, vital sign measurements, ECGs, reporting of AEs, recording of concomitant medication, and the Columbia-Suicide Severity Rating Scale (C-SSRS) scoring. An end-of-study telephone call occurred 28 days after the last dose to follow up on any AEs and serious AEs (SAEs) reported.

Statistical Analysis

No formal sample size calculation was performed when designing this study. This sample size was chosen as a suitable number based on empirical considerations, literature, and past experience, and was considered adequate to meet the primary objective of the study. However, assuming a CV of 50% for PK parameters, a sample size of 16 participants per group would be expected to yield a 90% CI for the geometric mean ratio of approximately 0.75–1.33 if the true ratio was 1.0.

Plasma PK parameters and safety outcomes were summarized by dose and by subgroup using descriptive

Table 1. Summary of Demographics and Baseline Characteristics of Participants in the Safety Analysis Set

	Japanese Population (N = 16)	Non-Asian Population (N = 16)
Age, years		
Mean (SD)	34.8 (7.2)	38.3 (10.3)
Median (range)	35 (22–50)	35.5 (18–54)
Sex, n (%)		
Male	16 (100.0)	14 (87.5)
Female	0	2 (12.5)
Weight, kg		
Mean (SD)	70.1 (10.3)	82.8 (8.7)
Median (range)	69.0 (53.1–94.8)	82.2 (69.2–95.8)
Height, cm		
Mean (SD)	175.3 (6.1)	176.2 (6.2)
Median (range)	175.7 (163.1–183.7)	177.1 (167.0–189.8)
BMI, kg/m^2		
Mean (SD)	22.8 (2.8)	26.7 (2.6)
Median (range)	22.5 (19.4–29.4)	27.1 (22.3–30.2)

BMI, body mass index; SD, standard deviation.

statistics. The geometric mean ratios, presented as the ratio of geometric means of plasma exposure parameters in Japanese/non-Asian populations, were based on a mixed-effects model for log-transformed data with race, dose, and race-by-dose as fixed effects and participant as a random effect. The geometric mean ratios and corresponding CIs were calculated by exponentiating the model-based race differences and the corresponding CIs. The geometric mean ratios of the "overall" group were based on statistical analysis using a mixed-effects model with race, dose, and race-by-dose as fixed factors. Additional analyses of key plasma exposure parameters normalized to body weight were performed. Plasma PK parameters were analyzed in the PK analysis set, which included all participants who received at least one dose of vorasidenib and had an evaluable PK profile. Safety outcomes and demographics were described in the safety analysis set, which included all participants who received at least one dose of vorasidenib. Baseline was defined as the last non-missing measurement prior to receiving vorasidenib.

Results

Demographics and Clinical Characteristics

This study was conducted between October and December 2019. A total of 32 participants were enrolled; of these, 16 were Japanese and 16 were non-Asian. Age and height were generally similar across subpopulations, while weight and BMI were higher in the non-Asian group than in the Japanese group (Table 1). There were no female Japanese participants enrolled in this study.

All participants completed Period 1 and progressed to Period 2. During Period 2, one (6.3%) Japanese participant and one (6.3%) non-Asian participant withdrew from the study at their own request, and four (25.0%) non-Asian participants discontinued prematurely because of screen failure at Day 21; these participants did not receive the 50-mg vorasidenib dose. A total of 15 (93.8%) Japanese participants and 11 (68.8%) non-Asian participants completed Period 2 and the study.

The PK analysis set included 16 (100%) Japanese participants and 12 (75.0%) non-Asian participants. The safety analysis set included all 16 (100%) Japanese participants and all 16 (100%) non-Asian participants.

Pharmacokinetics

The mean plasma vorasidenib concentration–time profile following a single oral dose of 10 or 50 mg of vorasidenib in Japanese participants was generally similar to that in non-Asian participants (Figure 1).

Key PK parameters and statistical comparisons of these parameters between race subgroups and doses are summarized in Table 2. Vorasidenib absorption was rapid with a t_{max} ranging from 1.0 to 2.5 h and declined exponentially thereafter. Vorasidenib had a long terminal phase, with mean $t_{\frac{1}{2}}$ ranging from 76.0 to 212.1 h.

The geometric mean C_{max} was generally comparable between race and dose subgroups, as suggested by geometric mean ratios between 1.00 and 1.11. Median t_{max} was longer for Japanese participants than for non-Asian participants after the 10-mg vorasidenib dose (2.5 vs 1.0 h) although the respective ranges overlapped (0.8–6.0 vs 1.0–4.0). This difference was not seen after the 50-mg vorasidenib dose (2.0 vs 2.0 h). $AUC_{0-\infty}$ and AUC_{0-last} after the 10-mg vorasidenib dose were slightly greater in Japanese than in non-Asian participants (geometric mean ratios: 1.35 and 1.38, respectively); this difference was not observed after the 50-mg dose (geometric mean ratios: 1.00 and 1.13, respectively). Mean $t_{\frac{1}{2}}$ was longer for Japanese participants than for non-Asian participants after a 10-mg vorasidenib dose but slightly shorter after a 50-mg dose (103.5 vs 76.0 h and 185.0 vs 212.1 h, respectively); some samples in the terminal phase used to calculate $t_{\frac{1}{2}}$ after the 10-mg dose of vorasidenib were under the LLOQ. Of note, $AUC_{0-\infty}$, AUC_{0-last}, and C_{max} were generally comparable between race and dose groups, as suggested by geometric mean ratios between 1.00 and 1.38.

In addition, PK parameters normalized by dose and body weight are summarized in Figure 2. Normalized PK parameters were generally similar between the Japanese and non-Asian populations, as noted by geometric mean ratios around 1.

Table 2. Descriptive Statistics of Plasma Vorasidenib PK Parameters in the PK Analysis Set Following a Single Dose of 10 or 50 mg of Vorasidenib, Stratified by Race

Parameter	Vorasidenib 10 mg		Vorasidenib 50 mg		
	Japanese Participants (N = 16)	Non-Asian Participants (N = 12)	Japanese Participants (N = 15)	Non-Asian Participants (N = 11)	Overall
C_{max} (ng/mL)					
Geometric mean (CV%)	21.3 (39.8)	19.2 (47.5)	66.7 (48.8)	68.3 (54.9)	–
Geometric mean (95% CI)[a]	21.3 (17.0–26.9)	19.2 (14.7–25.0)	67.3 (53.2–85.1)	67.4 (51.3–88.5)	–
Japanese/non-Asian geometric mean ratio (90% CI)[a]	1.11 (0.83–1.49)		1.00 (0.74–1.34)		1.05 (0.81–1.38)
t_{max} (h)					
Median (range)	2.5 (0.8–6.0)	1.0 (1.0–4.0)	2.0 (1.0–6.0)	2.0 (0.5–3.0)	–
$AUC_{0\text{-last}}$ (h·ng/mL)					
Geometric mean (CV%)	435.0 (56.5)	315.6 (92.8)	2697.4 (57.9)	2402.5 (62.3)	–
Geometric mean (95% CI)[a]	435.0 (319.4–592.4)	315.6 (220.9–450.8)	2743.8 (2007.5–3750.1)	2424.6 (1687.7–3483.1)	–
Japanese/non-Asian geometric mean ratio (90% CI)[a]	1.38 (0.93–2.04)		1.13 (0.76–1.68)		1.25 (0.86–1.81)
$AUC_{0\text{-}\infty}$ (h·ng/mL)					
Geometric mean (CV%)	631.3 (60.1)	468.1 (113.7)	3311.7 (60.5)	3193.1 (78.8)	–
Geometric mean (95% CI)[a]	631.3 (445.9–893.9)	468.1 (313.3–699.5)	3355.3 (2361.7–4766.8)	3366.9 (2241.4–5057.4)	–
Japanese/non-Asian geometric mean ratio (90% CI)[a]	1.35 (0.87–2.09)		1.00 (0.64–1.56)		1.16 (0.76–1.77)
$t_{\frac{1}{2}}$ (h)					
Geometric mean (CV%)	103.5 (77.3)[b]	76.0 (207.8)[b]	185.0 (40.6)	212.1 (79.1)	–

A total of 952 original and 952 duplicate/replicate human plasma samples were analyzed.

$AUC_{0-\infty}$, area under the concentration–time curve from time 0 extrapolated to infinity; AUC_{0-last}, area under the concentration–time curve from time 0 to time of last measurable concentration; CI, confidence interval; C_{max}, maximum plasma concentration; CV, coefficient of variation; PK, pharmacokinetic; $t_{\frac{1}{2}}$, half-life; t_{max}, time to maximum plasma concentration.

[a]Results of mixed-effects model for log-transformed data with race, dose, and race-by-dose as fixed effects and participant as a random effect.

[b]Some samples in the terminal phase were under the LLOQ.

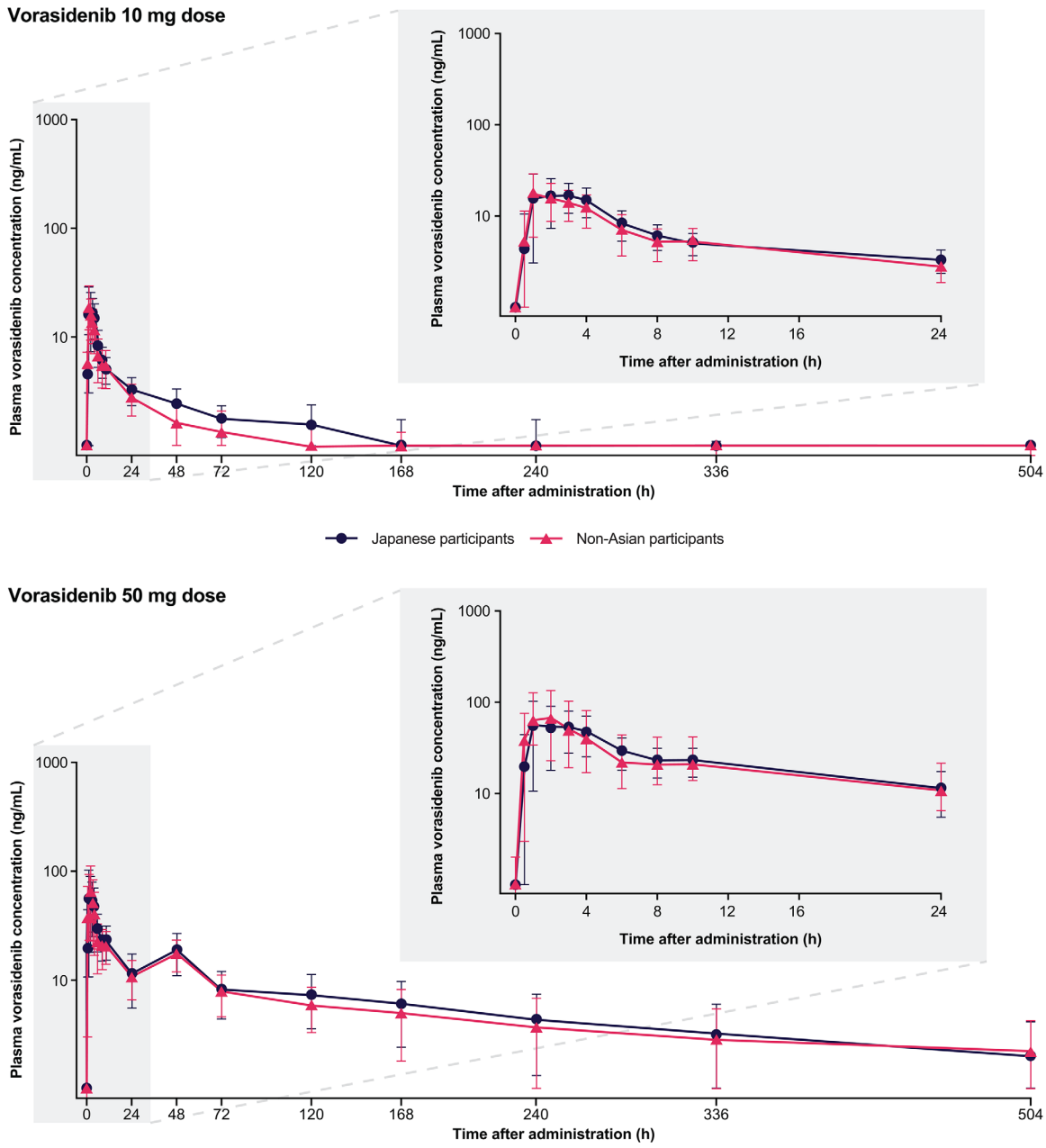

Figure 1. Mean (± standard deviation) plasma vorasidenib concentration over time after single oral doses of vorasidenib. Log plasma concentration is taken as 0 if the concentration value is below the limit of quantitation.

Safety

There were no deaths, SAEs, study-drug-related AEs, or study discontinuations due to AEs during the study. Following one single oral dose of 10 mg of vorasidenib, no Japanese participants experienced a treatment-emergent AE (TEAE). Three (18.75%) non-Asian participants experienced at least one TEAE: one experienced diarrhea, one experienced food poisoning, and one experienced vomiting and headache. These TEAEs were mild, considered by the Investigator not to be related to vorasidenib, and subsequently resolved.

After one single dose of 50 mg of vorasidenib, one (6.25%) Japanese participant reported TEAEs of cough and upper respiratory tract infection, which were mild, deemed not related to study drug by the Investigator, and resolved. Two (18.18%) non-Asian participants experienced at least one TEAE: one participant experienced upper respiratory tract infection, which was mild, deemed not related to study drug by the Investigator, and resolved, and one participant experienced mild increases in alanine aminotransferase and aspartate aminotransferase and a severe increase in blood crea-

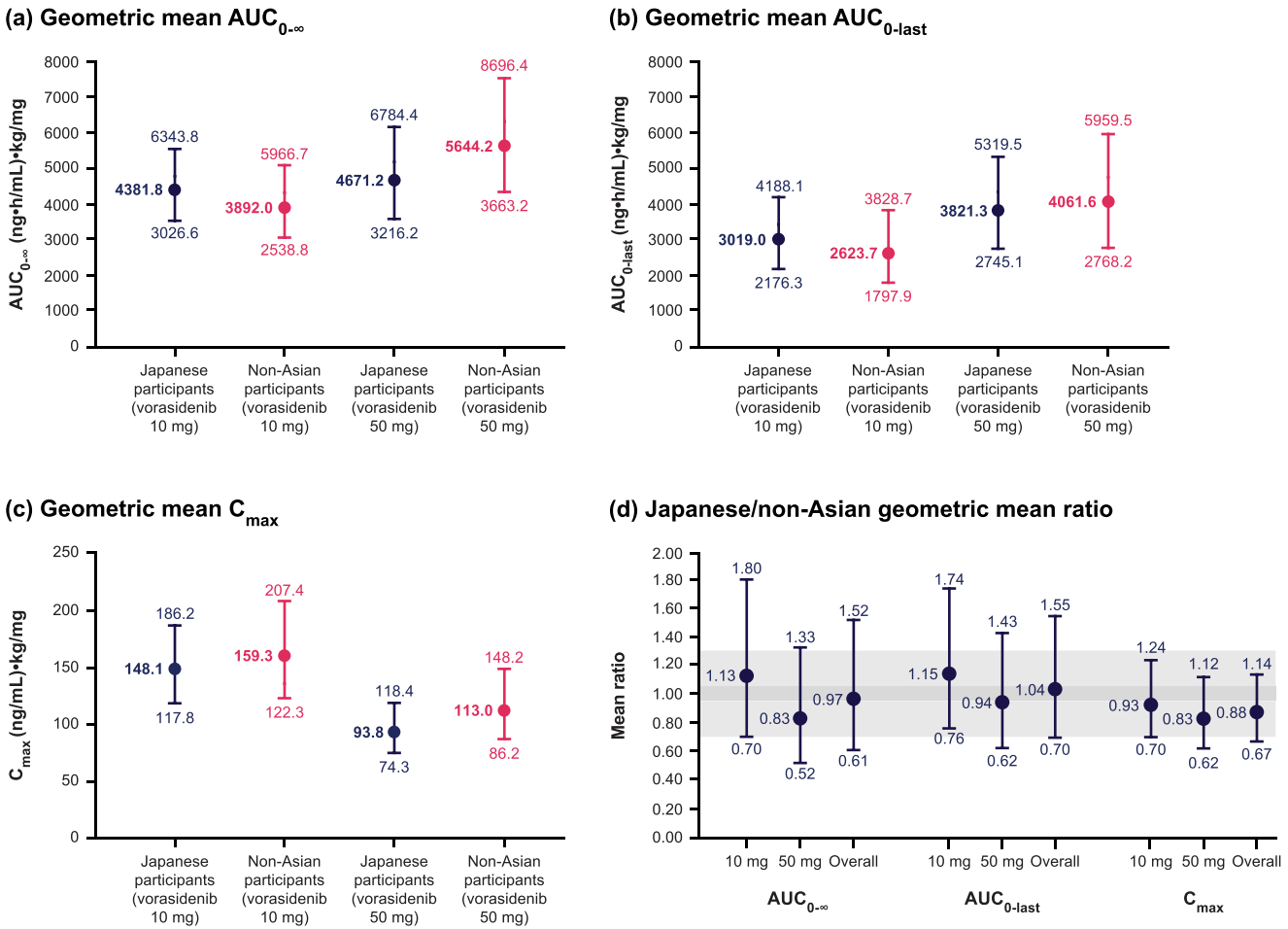

Figure 2. Plasma vorasidenib PK parameters in the PK analysis set following a single dose of 10 or 50 mg of vorasidenib normalized by dose and body weight and stratified by race. Error bars in panels (a), (b), and (c) indicate 95% CI. Error bars in panel (d) indicate 90% CI; the dark-gray area comprises mean ratio values from 0.95 to 1.05 while the light-gray area comprises values from 0.70 to 1.30. $AUC_{0-\infty}$, area under the concentration–time curve from time 0 extrapolated to infinity; AUC_{0-last}, area under the concentration–time curve from time 0 to time of last measurable concentration; CI, confidence interval; C_{max}, maximum plasma concentration; PK, pharmacokinetic.

tine phosphokinase, which were deemed not related to vorasidenib by the Investigator and the outcomes of which are unknown because the participant was lost to follow-up.

No clinically significant, abnormal findings were reported for vital signs, physical examinations, ECGs, or C-SSRS scoring. No Japanese participants reported taking concomitant therapy. Concomitant medication (paracetamol) was reported by one (3.1%) non-Asian participant.

Discussion

Regulatory agencies across the world require PK, safety, and efficacy data in different key populations for new drug approvals, as ethnic differences in the PK of a number of drugs have been previously reported.[20,24–26] Additionally, PK studies in different ethnic populations help to determine whether drug trials can be designed globally using the same dosing regimen or whether there may be a requirement for region-specific trials. Because of the lack of Japanese participants in previous vorasidenib PK studies, this study was designed to evaluate the PK and safety of 10- and 50-mg doses of vorasidenib in healthy Japanese participants and to compare results with those in healthy non-Asian participants.

Geometric mean C_{max} and mean plasma vorasidenib concentration–time profiles were generally similar between ethnic populations after a single oral dose of 10 or 50 mg of vorasidenib. Mean $t_{\frac{1}{2}}$ after a single oral dose of 10 mg of vorasidenib has to be interpreted with caution because of potential artifacts caused by samples for the terminal phase being below the LLOQ. These issues were not encountered when analyzing the samples obtained after a 50-mg dose of vorasidenib; mean $t_{\frac{1}{2}}$ (CV%) was slightly shorter (7.7 [40.6] days vs 8.8 [79.1] days) in Japanese than in non-Asian participants. Vorasidenib was rapidly absorbed. Median t_{max} for Japanese participants was longer than for non-Asian participants for the 10-mg dose, but given the overlap in the ranges of the two populations and the lack of difference observed for t_{max} for the 50-mg dose this difference was unlikely to be clinically significant. When body weight, reflective of body size, and dose were taken into account for normalization purposes, the PK parameters were comparable between Japanese and non-Asian populations, as demonstrated by overall geometric mean ratios close to 1. There were no deaths, SAEs, vorasidenib-related AEs, or study discontinuations due to AEs, and most AEs were mild, deemed not related to study drug by the Investigator, and resolved.

At the time the present study was conducted, the safety of vorasidenib had been investigated in clinical trials with mixed but mostly non-Asian populations.[4,12] Because of the potential for variability in PK and metabolism attributable to genetic factors,[20] there was a need to evaluate potential differences in vorasidenib PK in a Japanese population. The single ascending (two levels) dose study design was chosen as the appropriate approach for this study as a safeguard to ensure the safety of Japanese participants in the potential event of a high increase of exposure or ethnic-related SAE or severe AE. While there were some differences in PK parameters between Japanese and non-Asian patients in this study, plasma exposure to vorasidenib (AUC and C_{max}) was generally comparable between populations, as suggested by geometric mean ratios that ranged between 1 and 1.4, and therefore vorasidenib PK was demonstrated to not be ethnically sensitive in this study.

Body weight affects drug clearance.[27,28] To account for the differences in body weight between the Japanese and non-Asian populations in this study, key PK parameters were subsequently normalized to weight. After normalization, PK parameters were similar between groups, with geometric means ranging from 0.8 to 1.15, indicating that exposure to vorasidenib was similar between Japanese and non-Asian participants. Additionally, the geometric means of normalized and non-normalized PK parameters were relatively similar despite the differences in body weight between the two populations, further suggesting that no dose adjustments are needed for the Japanese population.

Overall, 10- and 50-mg doses of vorasidenib were well tolerated in both populations included in this study, as indicated by the low overall incidence of TEAEs. There were no unexpected safety findings, and reported AEs were similar to those observed in previous studies.[4,9] While the results of this study were generally positive, it is important to note some limitations. First, this was a single dose study; therefore, steady state was not achieved, and steady state PK parameters were not measured. Second, the sample size was not typically powered to demonstrate no differences in PK for this type of Phase 1 study. Additionally, there were a number of measurements below the LLOQ after a single dose of 10 mg of vorasidenib, which may have affected the reliability of parameters such as $t_{\frac{1}{2}}$ and $AUC_{0-\infty}$. Moreover, the length of sample collection may not have been long enough to allow for an accurate calculation of $AUC_{0-\infty}$, given that a considerable part of this is based on extrapolation. There were no female Japanese participants enrolled in this study; however, because of the small sample size, this could be considered an advantage as it limited the introduction of additional variabilities. Lastly, this study had an open-label design, which may have introduced an additional bias that must be taken into consideration when interpreting the safety outcomes reported here.

Conclusions

This study was designed to compare the PK of vorasidenib in healthy Japanese participants with that in healthy non-Asian participants and to assess the safety of vorasidenib in these populations. Vorasidenib was generally safe and well tolerated, and plasma exposures were generally similar and not ethnically sensitive between Japanese and non-Asian participants following a single oral dose of 10 or 50 mg of vorasidenib. The results from this study enabled the clinical development of vorasidenib in Japan and supported the inclusion of Japanese sites in subsequent global clinical trials of vorasidenib without any dose adjustments.

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Funding

The trial was designed by the former sponsor, Agios Pharmaceuticals, in collaboration with the investigators. After the start of the trial, Servier (the current sponsor) acquired the Agios Pharmaceuticals oncology business.

Conflicts of Interest

Tharin Limsakun is a former employee of Servier BioInnovation. Albert Man and Mohammad Hossain are employees of Servier BioInnovation. David Nguyen is an employee of Altasciences.

Data Availability Statement

Study-level clinical data from this study will be made available upon reasonable request from a qualified medical or scientific professional for the specific purpose laid out in that request and may include deidentified individual participant data. The data for this request will be available after a data access agreement has been signed. Please send your data sharing request to http://www.vivli.org

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