Pharmacokinetics and safety of cenobamate, a novel antiseizure medication, in healthy Japanese, and an ethnic comparison with healthy non-Japanese

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Abstract
Cenobamate (XCOPRI and ONTOZRY) is a novel antiseizure medication for the treatment of focal-onset seizures. Nonetheless, there is limited information on the pharmacokinetics (PKs), safety, and efficacy of cenobamate in Asian people, including Japanese people. This study aimed to evaluate the PKs and safety of cenobamate after a single oral dose in healthy Japanese subjects and to compare the PKs with that reported in non-Japanese subjects. A randomized, double-blind, placebo-controlled, single ascending dose study was conducted at four dose levels of 50, 100, 200, and 400 mg. Subjects were randomly assigned to cenobamate or placebo in a 6:2 ratio. Cenobamate was rapidly absorbed, reaching its maximum plasma concentration (Cmax) in 0.75 to 2.25 h, and was eliminated with a mean half-life of 37.0 to 57.7 h. The Cmax increased dose proportionally, whereas area under the concentration-time curve increased more than dose proportionally, which was consistent with the findings in non-Japanese subjects. The systemic exposure of cenobamate was comparable between Japanese and non-Japanese subjects at all dose levels evaluated. All adverse events were mild in severity, and their incidence did not show dose-dependent trends. Furthermore, there were no clinically significant issues in safety parameters, including sedation tests, neurologic examinations, and Columbia Suicide Severity Rating Scale interviews. In conclusion, the systemic exposure of cenobamate after a single dose in Japanese subjects increased by dose, which was similar to the pattern in non-Japanese subjects. In addition, a single dose of cenobamate was well-tolerated in the dose range of 50 to 400 mg in healthy Japanese subjects.

Study Highlights
WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
Cenobamate is a novel antiseizure medication newly approved for the treatment of focal-onset seizures in the United States and Europe. To date, properties of...
INTRODUCTION

Epilepsy, the most common neurological disease, accounts for more than 0.5% of the total disease burden worldwide. Among the seizures predisposed by epileptic status, focal-onset seizures compromise the highest portion.1,2 To manage focal-onset seizures, monotherapy with antiseizure medications (ASMs) such as carbamazepine, lamotrigine, levetiracetam, and valproate, is recommended.3 If monotherapy is ineffective or not tolerated, adjunctive therapy with other ASMs can be considered.3 Meanwhile, greater than 30% of patients with epilepsy remain refractory to treatment or experience intolerable side effects.4,5 It is especially noteworthy that patients with focal-onset seizures have a lower response rate to conventional ASMs than those with generalized seizures.6 Therefore, an effective treatment option for focal-onset seizures with an improved tolerability profile is needed.

Cenobamate (XCOPRI and ONTOZRY) is a novel ASM approved for the treatment of focal-onset seizures in the United States and Europe.7,8 The proposed mechanisms of the antiepileptic action of cenobamate are the reduction of repetitive neuronal firing by enhancing the inactivated state of voltage-gated sodium channels and the positive allosteric modulation of γ-aminobutyric acid type A (GABA_A) ion channels.9,10 In pivotal studies in patients with focal-onset seizures, cenobamate demonstrated a significant reduction in seizure frequency at doses of 100 to 400 mg/day compared with placebo and led to seizure freedom rates of up to 30%.11 Additionally, cenobamate was generally well-tolerated in all clinical studies to date. Common adverse events (AEs) are central nervous system disorders, including somnolence, dizziness, fatigue, and headache, which are the typical side effects of many ASMs.11,12 During clinical development, three cases of drug rash with eosinophilia and systemic symptoms (DRESS) were observed in subjects exposed to cenobamate, especially with relatively higher starting dose and rapid dose titration schemes.11 Thus, a start-low, go-slow titration approach for cenobamate has been proposed to mitigate the risk of DRESS.13 Currently, the recommended dosing regimen for cenobamate is 12.5 mg once daily as an initial dose, titrated every 2 weeks to 200 mg once daily as a maintenance dose, with a maximum dose of 400 mg once daily.7

To date, the pharmacokinetics (PKs), safety, and efficacy of cenobamate have been well characterized in non-Japanese subjects, including patients with focal-onset seizures.13–20 Following single oral doses, the terminal half-life (t1/2) of cenobamate ranged from 30 to 76 h at dose levels of 10 to 750 mg.14 In addition, in vitro studies showed extensive metabolism of cenobamate through glucuronidation and oxidation via various enzymes, including uridine 5'-diphospho-glucuronosyltransferase (UGT) 2B7, cytochrome P450 (CYP) 2E1, CYP2A6, and CYP2B6, which are known to have different allele frequencies among populations.21–23 Accordingly, the PKs of cenobamate might be slightly different among various ethnic groups.

The safety and efficacy of cenobamate have only been assessed in a relatively small population of Asian subjects thus far, and PK characteristics have not been extensively explored in any Asian population.13,15,16 Ethnic-specific data, including PKs, are also required for drug approval in many countries, including Japan.24,25 As such, there is a need to investigate the PKs, safety,
and efficacy of cenobamate in Asian subjects, including Japanese subjects.

In an effort to address the data/knowledge gap between ethnicities, this study aimed to evaluate the PKs and safety of cenobamate after a single oral dose in healthy Japanese subjects and to compare the PKs in healthy Japanese subjects with that reported in healthy non-Japanese subjects.14,17

METHODS

The protocol and informed consent form of this study were reviewed and approved by the Ministry of Food and Drug Safety of Korea and by the Institutional Review Board at Seoul National University Hospital. This study was registered in the public clinical trial registry of Korea (CRIS registration number: KCT0002880). This study was also performed in accordance with Korean Good Clinical Practice guidelines and the Declaration of Helsinki, and written consent was obtained from each subject prior to any study-related procedures.

Study population

Eligible subjects were healthy Japanese men or women who were born in Japan and had lived outside of Japan for less than 10 years and whose parents and grandparents were Japanese. Additionally, subjects between 19 and 50 years old with a body mass index (BMI) between 17.0 and 28.0 kg/m² were included. Major exclusion criteria were the following: any history of seizure disorder and/or severe head trauma; current evidence or history of suicidal tendencies, seizures, state of confusion, or any other clinically relevant psychiatric disease; any history of a serious cutaneous adverse reaction, such as DRESS, Steven Johnson, or toxic epidermal necrolysis syndrome; any hypersensitivity to drugs, such as cenobamate or its excipients. Use of any medication without the prior permission of the investigator as well as consumption of caffeine, alcohol, or other grapefruit products were prohibited throughout the study.

Study design

This study was designed as a randomized, double-blind, placebo-controlled, single ascending dose study with doses of 50, 100, 200, and 400 mg of cenobamate. In each cohort, eight subjects were randomly allocated to cenobamate film-coated tablet or placebo (manufactured by Patheon) in a 6:2 ratio. Subjects were orally administered their respective treatment with 200 ml of water following an overnight fast. Dose escalation was preceded by a review of all safety data up to day 7 postdose or day 14 postdose at each dose level.

Blood samples for PK analysis of cenobamate were collected at 0 (predose), 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 14, 18, 24, 48, 72, 96, 120, 144, 168, 192, 216, 240, 264, and 288 h postdose for all dose groups. For the 200 and 400 mg dose groups, additional PK blood samples were collected at 312, 336, and 360 h postdose. At each time point, ~5 ml of blood was collected in K2-ethylenediaminetetraacetic (EDTA) tubes, centrifuged at 5°C and 1,100 to 1,300 × g for 15 min, and stored at −20°C until analysis.

Determination of plasma cenobamate concentration

Plasma concentrations of cenobamate were measured by a validated bioanalytical method using liquid chromatography-tandem mass spectrometry (API 4000; SCIEX), as described in the previous study.14 The lower limit of quantification was 0.05 mg/L, and the accuracy and coefficient of variation (CV) were 93.4%–98.0% and less than or equal to 5.7%, respectively.

Pharmacokinetic evaluation

PK parameters were derived by noncompartmental methods using Phoenix WinNonlin (version 7.0; Certara USA). The maximum plasma concentration (Cmax) and time to reach Cmax (Tmax) were obtained from the observed plasma concentration-time profiles of cenobamate, and the area under the plasma concentration-time curve (AUC) from 0 to 24 h postdose (AUC0–24 h) and AUC from time 0 to last measurable time point (AUClast) were calculated by a linear-up and log-down trapezoidal rule. The AUC from time 0 to infinity (AUCinf) was calculated as AUClast + Clast/λz, where Clast is the last measurable concentration and λz is the terminal elimination rate constant. Apparent clearance (CL/F) was calculated as dose/AUCinf, and t1/2 was calculated as ln2/λz.

To investigate the dose-related PK properties of cenobamate over the dose range from 50 to 400 mg, dose-normalized Cmax (Cmax/D) and dose-normalized AUCinf (AUCinf/D) were compared among the dose groups by Kruskal-Wallis test. Additionally, a power model was used to assess dose-proportionality, and linear regression analyses between log-transformed dose and log-transformed Cmax or AUCinf were performed.
Ethnic comparison

To explore the ethnic sensitivity of cenobamate, PK data in healthy Japanese subjects from this study were compared with PK data in healthy non-Japanese subjects, which were pooled from three previous studies (Table 1). For PK parameters, such as C$_{\text{max}}$, AUC$_{0-24 \text{ h}}$, and AUC$_{\text{inf}}$, geometric mean ratios (GMRs) [90% confidence intervals (CIs)] of Japanese subjects to non-Japanese subjects were estimated for ethnic comparison.

Safety assessment

Safety was assessed by monitoring AEs and evaluating clinical laboratory tests, 12-lead electrocardiograms (ECGs), physical examinations, vital signs, neurologic examinations, sedation tests (modified Ramsay sedation test), and Columbia Suicide Severity Rating Scale (C-SSRS) interviews (version “since last visit”). Rash or related events, which could suggest drug-induced hypersensitivity reactions, such as DRESS, were carefully monitored in this study. Subjects who reported any potential drug-induced hypersensitivity reactions were intensively examined by hematology and chemistry blood tests and/or additional visits. Additionally, all enrolled subjects were asked if they experienced any of the following symptoms: rash; fever; swollen lymph nodes in the neck; abdominal or chest pain; puffy face or ankles; and yellowing of the skin or eyes.

Statistical analyses

All statistical analyses were performed via SAS (version 9.4, SAS Institute), and p values less than 0.05 were regarded as statistically significant.

RESULTS

Subjects

In total, 32 healthy Japanese male subjects were enrolled and randomized, and completed the study. Their baseline characteristics were not significantly different among the treatment groups. The mean (±SD) values for age, height, body weight, and BMI were 33.8 (±5.5) years, 172.6 (±5.4) cm, 65.8 (±7.6) kg, and 22.0 (±1.7) kg/m², respectively. PKs were analyzed in 24 subjects who had a complete PK profile of cenobamate. Safety was assessed in all 32 subjects who had received the treatment at least once.

Pharmacokinetics

Cenobamate was rapidly absorbed with median T$_{\text{max}}$ values of 0.75 to 2.25 h across the entire dose range. A single oral dose of cenobamate exhibited multiphase plasma concentration-time profiles up to 24 h postdose, followed by a monoeponential decline (Figure 1). The systemic exposure of cenobamate in terms of C$_{\text{max}}$ and AUC increased with increasing the dose. Mean CL/F values decreased from 0.79 to 0.44 L/h as the dose increased, and accordingly, mean t$_{1/2}$ values tended to be slightly prolonged at higher dose levels, ranging from 37.0 to 57.7 h (Table 2).

Following a single oral administration of cenobamate over the dose range of 50 to 400 mg, C$_{\text{max}}$ increased dose proportionally, whereas AUC$_{\text{inf}}$ increased more than dose proportionally. Unlike C$_{\text{max}}$/D, which showed similar values, AUC$_{\text{inf}}$/D values were significantly different among the dose groups (Figure 2). Similar results were acquired by the power model, where exponents [95% CI] were 0.96 [0.88–1.04] for C$_{\text{max}}$ and 1.30 [1.17–1.43] for AUC$_{\text{inf}}$. These findings were consistent with those in non-Japanese subjects from the previous study.

Ethnic comparison: Japanese versus non-Japanese

The plasma concentration-time profiles of cenobamate in healthy Japanese subjects were similar to those in healthy non-Japanese subjects previously reported. Likewise, a single oral dose of cenobamate resulted in comparable systemic exposure in Japanese and non-Japanese subjects across all dose levels (Figure 3). At each dose level, individual C$_{\text{max}}$, AUC$_{0-24 \text{ h}}$, and AUC$_{\text{inf}}$ values in Japanese subjects were mostly within the ranges of those reported in non-Japanese subjects. In the statistical comparison of PK parameters, 90% CIs of GMRs of Japanese to non-Japanese for C$_{\text{max}}$, AUC$_{0-24 \text{ h}}$, and AUC$_{\text{inf}}$ generally included the value of 1, suggesting similarity between ethnicities (Table 3). The C$_{\text{max}}$ values at the 50 mg level were ~20% higher in Japanese subjects than in non-Japanese subjects, but not statistically significant (p value = 0.06). The values for PK parameters at the other dose levels showed no significant difference between ethnicities.

Safety

A total of 45 treatment-emergent AEs (TEAEs) were reported in 15 subjects (46.9%): 34 cases in 11 subjects (45.8%) in the cenobamate groups and 11 cases in four subjects (50.0%) in the placebo group. By dose levels, TEAEs were observed in three subjects (50.0%, 19 cases) in the 50 mg
### TABLE 1  Overview of clinical studies analyzed for ethnic comparison

| Clinical studies | Current study | Laurent Vernillet et al.¹⁴ | YKP3089C027¹⁷ | YKP3089C030¹⁷ |
|------------------|---------------|-----------------------------|----------------|----------------|
| Description      | Single ascending dose study | Single ascending dose study | Hepatic impairment study | Healthy elderly study |
| Population used for analysis | Healthy Japanese | Healthy non-Japanese | Healthy non-Japanese with normal hepatic function | Healthy young non-Japanese |
| Treatment        | A single oral dose | A single oral dose | A single oral dose | A single oral dose |
| Analysis set     | • 50 mg (N = 6) | • 50 mg (N = 6) | • 200 mg (N = 8) | • 200 mg (N = 12) |
|                  | • 100 mg (N = 6) | • 100 mg (N = 6) |                  |                  |
|                  | • 200 mg (N = 6) | • 200 mg (N = 7) |                  |                  |
|                  | • 400 mg (N = 6) | • 400 mg (N = 7) |                  |                  |
| Age, yearsᵃ      | 19–50          | 19–55          | 36–65          | 20–42          |
| Gender, n (%)    |                |                |                |                |
| Male             | 24 (100.0)     | 26 (100.0)     | 6 (75.0)       | 6 (50.0)       |
| Female           | 0              | 0              | 2 (25.0)       | 6 (50.0)       |
| Ethnicity, n (%) |                |                |                |                |
| Asian            | 24 (100.0)     | 0              | 0              | 0              |
| Black            | 0              | 14 (53.9)      | 0              | 8 (66.7)       |
| White            | 0              | 5 (19.2)       | 8 (100.0)      | 0              |
| Hispanic         | 0              | 7 (26.9)       | 0              | 4 (33.3)       |

ᵃAge (years) is expressed as minimum–maximum.
group, five subjects (83.3%, 8 cases) in the 100 mg group, two subjects (33.3%, 6 cases) in the 200 mg group, and one subject (16.7%, 1 case) in the 400 mg group, and the incidence of TEAEs was not dose-related (Table 4). Of the TEAEs, 24 cases were evaluated as possibly related to the treatment: 20 cases in five subjects (20.8%) in the cenobamate groups and four cases in one subject (12.5%) in the placebo group. The frequent TEAEs possibly related to the treatment were headache (5 cases) and pyrexia (3 cases). All TEAEs were mild in intensity, and no serious AEs were reported. There were also no reported deaths or premature discontinuations throughout the study.

In this study, two subjects reported a total of four cases of rash. One subject in the 50 mg group experienced rash with urticaria and pruritis. Pyrexia was also reported, but it was well controlled by concomitant administration of acetaminophen tablets. Although absolute neutrophil count and high sensitivity C-reactive protein increased slightly, these values recovered to the normal range, and no other significant findings were observed. Consequently, all rash events in the first subject spontaneously resolved without any medication on day 11 postdose. The other subject in the placebo group experienced exfoliative rash in the perineal area accompanied by pruritis, papule, and skin irritation. The subject was afebrile, and there were no remarkable abnormalities in laboratory tests, such as eosinophilia or thrombocytopenia. The lesions for the second subject were assessed as eczema caused by shaving of pubic hair and resolved on day 21 postdose after concomitant medications of bepotastine tablets, mupirocin ointment, and hydrocortisone cream. Based on laboratory results and clinical manifestations, all rash events observed during the study were not classified as DRESS.

There were no clinically significant abnormalities in laboratory tests, vital signs, physical examinations, or 12-lead ECGs throughout the study. Furthermore, no suicidal ideation or behavior, or self-injurious action from the

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**TABLE 2** Summary of pharmacokinetic parameters following a single oral administration of cenobamate in healthy Japanese subjects

| PK parameter | 50 mg (N = 6) | 100 mg (N = 6) | 200 mg (N = 6) | 400 mg (N = 6) |
|--------------|--------------|--------------|--------------|--------------|
| Tmax, h      | 0.75 [0.50–2.00] | 2.00 [1.00–3.00] | 1.75 [1.00–3.50] | 2.25 [1.00–3.50] |
| Cmax, mg/L   | 1.48 ± 0.30  | 2.50 ± 0.28  | 5.23 ± 0.33  | 10.55 ± 1.37  |
| AUC_0–24 h, h*mg/L | 22.16 ± 2.91 | 42.52 ± 4.63 | 90.70 ± 7.27 | 198.24 ± 20.73 |
| AUC_last, h*mg/L | 64.93 ± 22.27 | 139.68 ± 31.18 | 404.44 ± 85.76 | 923.26 ± 139.52 |
| AUC_inf, h*mg/L | 68.16 ± 22.85 | 144.69 ± 33.54 | 415.52 ± 95.10 | 938.29 ± 147.53 |
| t1/2, h      | 37.03 ± 9.68 | 44.31 ± 13.27 | 57.74 ± 20.28 | 51.47 ± 15.17 |
| CL/F, L/h    | 0.79 ± 0.22  | 0.72 ± 0.15  | 0.50 ± 0.11  | 0.44 ± 0.07  |
| Vd/F, L      | 40.13 ± 5.76 | 44.04 ± 6.26 | 39.53 ± 6.94 | 31.23 ± 6.52 |

Note: Data are expressed as arithmetic mean ± SD, except for Tmax, which are expressed as median [minimum–maximum]. Abbreviations: AUC_0–24 h, area under the plasma concentration-time curve from 0 to 24 h postdose; AUC_inf, AUC from 0 to infinity; AUC_last, AUC from 0 to last measurable time point; CL/F, apparent clearance; Cmax, maximum plasma concentration; PK, pharmacokinetic; t1/2, terminal half-life; Tmax, time to reach maximum plasma concentration; Vd/F, apparent volume of distribution.

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**FIGURE 1** Mean plasma concentration-time profiles following a single oral administration of cenobamate in healthy Japanese subjects. Error bars represent SD. (a) linear scale and (b) semi-log scale.
C-SSRS interviews and no significant findings in sedation tests and neurologic examinations were reported. All subjects scored as fully awake in sedation tests, and no abnormalities were observed across all examination terms in neurologic examinations.

**DISCUSSION**

In this healthy Japanese study, PK blood samplings were performed for a longer duration than in the previous healthy non-Japanese study. Blood samples were collected up to 288 h postdose for 50 to 100 mg and 360 h postdose for 200 to 400 mg in Japanese subjects, whereas up to 72 h postdose for 50 mg and 144 h postdose for 100 to 750 mg dose in non-Japanese subjects. As a result, the mean AUC percent extrapolated in Japanese subjects from this study was estimated at 2% to 5%, indicating an almost complete elimination PK profile of cenobamate in healthy Japanese subjects. Regardless, the PK data from the different studies are still comparable.
Multipeak concentration-time profiles appeared at around 4 and 10 h after a single oral administration of cenobamate, which coincided with the timing of food intake in the study. The mechanism behind the multipeak phenomenon is not fully understood, but these findings suggest possible enterohepatic recycling of cenobamate given that food intake triggers bile acid secretion. It indicates that cenobamate is secreted into the gut with bile acid, followed by re-absorption from the gut back into systemic circulation. Especially, considering that cenobamate is extensively metabolized by UGTs, cenobamate glucuronides may be excreted to bile ducts via transporters such as multidrug resistant-association protein 2 (MRP2), be released to the gut along with bile acid secretion, and subsequently undergo deglucuronidation by intestinal microbiomes. The parent drug cenobamate may then be re-absorbed systemically. This recycling process can elicit multipeak PK profiles, as observed in this study. This phenomenon has also been reported in other cenobamate studies.

A single dose of cenobamate from 50 to 400 mg in Japanese subjects showed dose-proportionality in Cmax but supra-dose proportionality in AUC. Because this profile has also been identified in the previous study, the nonproportionality following single doses appears to be a property of cenobamate itself and is not limited to Japanese subjects. However, multiple doses of cenobamate from 50 to 500 mg/day across three multiple ascending dose studies indicated dose-proportionality in both Cmax and AUC. Hypotheses about mechanisms for the different PK profiles between single-dose and multiple-dose include a concentration-dependent inhibition of renal efflux transporters by cenobamate metabolites and/or a saturation of renal influx transporters at higher concentrations. In particular, because ~88% of the cenobamate dose recovered in urine consists of metabolites, the concentration-dependent inhibition of renal efflux transporters by metabolites in urine is regarded as one possible cause of the nonproportionality. Based on comparable AUCinf/D values across the dose range of 200 to 400 mg and the mean AUC0–24 h in the 200 mg dose group (90.70 h*mg/L) similar to the mean AUC in the 50 mg/day dose group (96.7 h*mg/L) in previous multiple ascending dose studies, renal efflux transporters might be maximally inhibited by accumulated metabolites in urine following single (≥200 mg) and multiple doses (50–500 mg/day). Given that cenobamate, an ASM, is administered chronically, nonproportional PK following single doses may not need to be considered when adjusting the dosing regimen in real clinical settings.

When assessing the compound’s relative sensitivity to ethnic factors according to International Conference on Harmonization (ICH) E5 guideline, comparison of cenobamate PK between Japanese and non-Japanese subjects appears to be similar and comparable. In addition, these observations suggest that ethnic factors do not appear to affect PK differences for cenobamate. Cenobamate has a flat dose-response curve, multiple metabolic pathways, and high bioavailability, which may minimize possible

| Dose | PK parameter | Geometric mean (CV%) | Geometric mean ratio [90% CI] (Japanese/Non-Japanese) |
|------|--------------|----------------------|---------------------------------------------------|
| 50 mg | Cmax, mg/L | 1.46 (20.49) | 1.20 (7.91) | 1.21 [1.03–1.42] |
| | AUC0–24 h, h*mg/L | 21.99 (14.08) | 21.67 (14.72) | 1.01 [0.87–1.18] |
| | AUCinf, h*mg/L | 65.45 (30.92) | 74.15 (29.58) | 0.88 [0.65–1.20] |
| 100 mg | Cmax, mg/L | 2.48 (11.58) | 2.37 (20.05) | 1.05 [0.88–1.24] |
| | AUC0–24 h, h*mg/L | 42.32 (10.68) | 43.16 (15.36) | 0.98 [0.85–1.13] |
| | AUCinf, h*mg/L | 141.74 (22.08) | 161.11 (17.08) | 0.88 [0.72–1.08] |
| 200 mg | Cmax, mg/L | 5.22 (6.39) | 4.91 (22.09) | 1.06 [0.91–1.24] |
| | AUC0–24 h, h*mg/L | 90.46 (8.05) | 81.43 (23.12) | 1.11 [0.94–1.31] |
| | AUCinf, h*mg/L | 406.68 (22.92) | 346.89 (36.69) | 1.17 [0.91–1.52] |
| 400 mg | Cmax, mg/L | 10.48 (12.98) | 10.30 (20.55) | 1.02 [0.86–1.21] |
| | AUC0–24 h, h*mg/L | 197.36 (10.32) | 205.77 (18.08) | 0.96 [0.83–1.11] |
| | AUCinf, h*mg/L | 928.17 (16.49) | 925.33 (27.42) | 1.00 [0.80–1.26] |

Abbreviations: AUC0–24 h, area under the plasma concentration-time curve from 0 to 24 h post-dose; AUCinf, AUC from 0 to infinity; CI, confidence interval; Cmax, maximum plasma concentration; CV, coefficient of variation; PK, pharmacokinetic.

aData set size is 6 (50, 100, 200, and 400 mg).

bData from three non-Japanese studies was used (N = 6 [50 and 100 mg], N = 27 [200 mg], N = 7 [400 mg]).
differences related to ethnicity. This study compared PK parameters in healthy Japanese subjects with those in non-Japanese subjects previously reported.\textsuperscript{14,17} This comparison demonstrated that despite the possibility of dissimilar metabolic rates due to potential genetic differences across ethnicities, the ethnic sensitivity of cenobamate is negligible. Because cenobamate has a dose-response relationship, cenobamate is expected to show a similar antiepileptic effect in Japanese patients compared with non-Japanese patients under the same dosing regimen, suggesting no necessity for dose adjustment according to ethnicity.

Given that up to 40\% of patients with epilepsy generally discontinue ASM treatment due to side effects, the safety profiles of any ASM are considered one of the most important factors in selecting appropriate ASM therapy.\textsuperscript{30} The most frequently observed AEs related to the treatment in healthy Japanese subjects were nervous system disorders, gastrointestinal disorders, and respiratory, thoracic, and mediastinal disorders. Notably, the occurrence of abdominal discomfort and diarrhea was higher in the placebo group compared to the cenobamate groups.

TABLE 4: TEAEs by system organ class occurred in healthy Japanese subjects

| SOC/TEAE                        | 50 mg (N = 6) | 100 mg (N = 6) | 200 mg (N = 6) | 400 mg (N = 6) | Placebo (N = 8) | Total (N = 32) |
|---------------------------------|---------------|---------------|---------------|---------------|----------------|---------------|
| Gastrointestinal disorders      | 1 [2]         | 1 [2]         | 1 [2]         | 0             | 1 [2]          | 5 [7]         |
| Abdominal discomfort            | 0             | 0             | 0             | 0             | 1 [1]          | 1 [1]         |
| Diarrhea                        | 1 [1]         | 0             | 0             | 0             | 1 [1]          | 2 [2]         |
| Infrequent bowel movement       | 0             | 0             | 1 [2]         | 0             | 0             | 1 [2]         |
| Lip blister                      | 0             | 1 [1]         | 0             | 0             | 0             | 1 [1]         |
| Nausea                          | 1 [1]         | 0             | 0             | 0             | 0             | 1 [1]         |
| General disorders and administration site conditions | 3 [4] | 0 | 1 [1] | 0 | 0 | 4 [5] |
| Chest discomfort                 | 0             | 0             | 1 [1]         | 0             | 0             | 1 [1]         |
| Chills                           | 1 [1]         | 0             | 0             | 0             | 0             | 1 [1]         |
| Pyrexia                          | 3 [3]         | 0             | 0             | 0             | 0             | 3 [3]         |
| Musculoskeletal and connective tissue disorders | 2 [2] | 0 | 0 | 0 | 1 [1] | 3 [3] |
| Musculoskeletal pain             | 0             | 0             | 0             | 0             | 1 [1]          | 1 [1]         |
| Myalgia                          | 2 [2]         | 0             | 0             | 0             | 0             | 2 [2]         |
| Nervous system disorders         | 3 [4]         | 0             | 1 [1]         | 1 [1]         | 1 [1]          | 6 [7]         |
| Dizziness                        | 1 [1]         | 0             | 0             | 0             | 0             | 1 [1]         |
| Headache                         | 3 [3]         | 0             | 1 [1]         | 1 [1]         | 1 [1]          | 6 [6]         |
| Psychiatric disorders            | 1 [1]         | 0             | 0             | 0             | 0             | 1 [1]         |
| Listless                         | 1 [1]         | 0             | 0             | 0             | 0             | 1 [1]         |
| Respiratory, thoracic and mediastinal disorders | 1 [1] | 4 [7] | 1 [2] | 0 | 2 [3] | 8 [13] |
| Cough                            | 0             | 1 [1]         | 0             | 0             | 0             | 1 [1]         |
| Epistaxis                        | 1 [1]         | 0             | 0             | 0             | 1 [1]          | 1 [1]         |
| Oropharyngeal pain               | 0             | 2 [2]         | 1 [1]         | 0             | 2 [2]          | 5 [5]         |
| Rhinorrhea                       | 0             | 4 [4]         | 1 [1]         | 0             | 1 [1]          | 6 [6]         |
| Skin and subcutaneous tissue disorders | 1 [5] | 0 | 0 | 0 | 1 [4] | 2 [9] |
| Exfoliative rash                 | 0             | 0             | 0             | 0             | 1 [1]          | 1 [1]         |
| Papule                           | 0             | 0             | 0             | 0             | 1 [1]          | 1 [1]         |
| Pruritus                         | 1 [1]         | 0             | 0             | 0             | 1 [1]          | 2 [2]         |
| Rash                             | 1 [3]         | 0             | 0             | 0             | 0             | 1 [3]         |
| Skin irritation                  | 0             | 0             | 0             | 0             | 1 [1]          | 1 [1]         |
| Urticaria                        | 1 [1]         | 0             | 0             | 0             | 0             | 1 [1]         |
| Total                            | 3 [19]        | 5 [8]         | 2 [6]         | 1 [1]         | 4 [11]        | 15 [45]       |

Note: Data are expressed as number of subjects [number of events].
Abbreviations: SOC, system organ class; TEAE, treatment emergent adverse event.
disorders, including headache and dizziness, which is in line with the AE profiles from other cenobamate studies in healthy non-Japanese subjects and patients with focal-onset seizures. Although four cases of rash were reported, there were no other events related to DRESS. There were also no significant findings from the C-SSRS interviews, sedation tests, or neurologic examinations, which were performed to assess the risk of the typical side effects of ASMs. Because this was a single dose study in healthy subjects, the safety results, especially the C-SSRS scores, should be translated carefully to patients in clinical settings. However, these results are thought to be meaningful in evaluating the drug-related effects for exploratory purposes, and it has recently been reported that there is no clear evidence of an increased risk of suicidality with cenobamate. The safety results from this study indicate that cenobamate may become an alternative ASM with reasonable exposure and tolerability profiles in Japanese.

In conclusion, after a single oral administration of cenobamate in healthy Japanese subjects, the systemic exposure of cenobamate increased according to the dose, and the PKs were consistent and similar to that in healthy non-Japanese subjects. In addition, a single dose of cenobamate was well-tolerated in the dose range of 50 to 400 mg. These results suggest that the PKs and safety of cenobamate in Japanese subjects are comparable to those from other studies and consistent with the clinical pharmacology data presented in the approved package insert in the United States and Europe.

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CONFLICT OF INTEREST
The authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS
E.S., S.H.L., and K.-S.Y. wrote the manuscript. Y.K.K., S.H.L., I.-J.J., and K.-S.Y. designed the research. All authors performed the research. E.Y. and K.-S.Y. analyzed the data.

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