A Randomized, Single-Center, Double-Blind, Placebo-Controlled Multiple-Dose Phase I Study to Evaluate the Safety, Pharmacokinetics, and Pharmacodynamics of Imarikiren in Healthy Adult Nonelderly and Elderly Male Subjects

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Abstract
Imarikiren hydrochloride (TAK-272/SCO-272) is a novel direct renin inhibitor. This randomized, double-blind, phase I study evaluated the safety and pharmacokinetics/pharmacodynamics of multiple oral administrations of imarikiren in healthy nonelderly (aged 20-45 years) and elderly (aged 65-85 years) Japanese male subjects. Subjects were randomized within 1 of 3 cohorts to receive imarikiren or placebo: Cohort 1 (imarikiren 80 mg; nonelderly), Cohort 2 (imarikiren 160 mg; nonelderly), or Cohort 3 (imarikiren 80 mg; elderly). Imarikiren or placebo was administered orally, once daily, for 7 days. Accumulation of imarikiren did not occur during the 7-day treatment period. Area under the plasma-concentration time curve and maximum plasma concentration of imarikiren were higher in elderly than in nonelderly subjects (52% and 39% higher, respectively). Inhibition of plasma renin activity was observed for 7 days and was maintained for at least 71 hours after the last imarikiren administration at the 80-mg (nonelderly and elderly) and 160-mg (nonelderly) doses. Plasma active renin concentration increased in nonelderly and elderly subjects; peak concentrations were higher on day 7 than on day 1. Increase from baseline in plasma active renin concentration was smaller in elderly than in nonelderly subjects during the 7-day treatment period and until 71 hours after last imarikiren administration. Treatment-emergent adverse events were reported in 33.3% (elderly) and 22.2% (nonelderly) of imarikiren subjects. Multiple oral administrations of imarikiren for 7 days were safe and well tolerated with no drug accumulation and strong and sustained suppression of plasma renin activity.

Keywords
clinical pharmacology, clinical trials, direct renin inhibitor, pharmacokinetics, renin-angiotensin system

Pharmacologic blockade of the renin-angiotensin (R-A) system through the use of angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers is a standard approach for the treatment of some cardiovascular/renal diseases, including hypertension, heart failure, and diabetic nephropathy.1,2 Renin is a rate-limiting enzyme which initiates the enzymatic cascade of the R-A system. As such, pharmacologic blockade of the R-A system through direct renin inhibition is expected to have systemic organ protection effects superior to those of angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, by virtue of the unique and potent mechanism of action.1 The successful development of the direct renin inhibitor aliskiren for hypertension validated direct renin inhibition as an effective therapeutic strategy for cardiovascular/renal disease. However, the bioavailability of aliskiren is low and the maximum dosage is limited by gastrointestinal toxicity.

Imarikiren hydrochloride (TAK-272/SCO-272) is a novel, potent, and orally active direct renin inhibitor that has demonstrated a better bioavailability profile and stronger in vivo renin inhibition compared with aliskiren in preclinical animal studies.3 In a single-dose study conducted in Japan (CPH-001), imarikiren at a dose of up to 200 mg demonstrated good tolerability in healthy, nonelderly, adult male subjects.4 Based on the results of study CPH-001, we evaluated the safety, pharmacokinetics (PK), and pharmacodynamics (PD)

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of multiple oral administrations of imarikiren once daily at doses of 80 mg and 160 mg in healthy adult nonelderly and elderly male subjects.

**Methods**

All patients provided written informed consent. The clinical study protocol was reviewed and approved by the institutional review board of the investigational site.

**Objectives**

The primary objective was to evaluate the safety and the PK of multiple oral administrations of imarikiren tablets in healthy Japanese adult nonelderly and elderly male subjects. The secondary objective was to evaluate the PD of multiple oral administrations of imarikiren tablets in healthy Japanese adult nonelderly and elderly male subjects.

**Inclusion and Exclusion Criteria**

This study was conducted in healthy Japanese adult nonelderly (aged 20-45 years) and elderly (aged 65-85 years) male volunteers. Key inclusion criteria included weight $\geq 50$ kg, with body mass index of $\geq 18.5$ kg/m$^2$ and $\leq 25.0$ kg/m$^2$, and agreement to employ adequate contraception up to 12 weeks after the last study drug administration. Key exclusion criteria included receipt of any study drug within 16 weeks of the first study drug administration, receipt of imarikiren in a clinical study in the past; history of hypersensitivity to drugs; history of cancer; and uncontrolled and clinically important neurologic, cardiovascular, pulmonary, hepatic, renal, metabolic, gastrointestinal, urologic, or endocrine diseases or other abnormalities. Subjects were also excluded if they had a clinically important abnormality in electrocardiogram (ECG) findings at screening, abnormal laboratory test results suggesting a clinically important underlying disease, alanine aminotransferase or aspartate aminotransferase $>1.5$ times the upper limit of normal, or systolic blood pressure $<80$ mm Hg at screening, day $-1$, and before the start of study drug administration along with 2 or more of the following suspected hypotensive symptoms and findings through physical examinations: lightheadedness, facial pallor, and cold sweat.

**Study Design**

This was a randomized, placebo-controlled, double-blind, multiple-dose study, comprising 3 cohorts evaluated consecutively. Subjects were randomized within 1 of 3 cohorts to receive imarikiren ($n = 9$) or placebo ($n = 3$): Cohort 1 (imarikiren 80 mg; nonelderly subjects), Cohort 2 (imarikiren 160 mg; nonelderly subjects), or Cohort 3 (imarikiren 80 mg; elderly subjects). Because of a possibility of increased exposure in elderly subjects compared with nonelderly subjects, the 160-mg dose was not assessed in elderly subjects.

The study started with the evaluation of Cohort 1. After comprehensive review of the safety results of Cohort 1 up to 168 hours after the last study drug administration and agreement between the investigator and the sponsor to move forward, evaluation of Cohort 2 was initiated. After a similar review of safety results from Cohorts 1 and 2, evaluation of Cohort 3 was initiated. The interval between the last study drug administration of one cohort and the first study drug administration of the subsequent cohort was $\geq 8$ days.

**Dosage, Regimen, and Diet**

Imarikiren or placebo tablets were administered orally, once daily, for 7 days. Subjects were hospitalized from day $-1$ to day 7 and received the study drug, once daily, 30 minutes after the start of taking breakfast with 200 mL of water. This timing was chosen because evaluation of the food effect after single-dose administration of imarikiren had showed minimal effect on the PK of imarikiren, and administration after a meal was expected to have a lower impact on subjects than alternative times. The 7-day treatment period was selected to allow evaluation of steady-state PK, which was estimated to be reached after around 4 days of once-daily administration based on the PK profile confirmed in a study of single-dose administration.

Subjects were prohibited from taking fluid from 2 hours prior to study drug administration until 4 hours after study drug administration except drinks at breakfast and 200 mL of water at administration. Medicines (including over-the-counter medications), vitamins, and supplements were prohibited from 4 weeks prior to the start of administration through the completion of follow-up examinations. Grapefruits (juice, pulp) and food and drinks containing caffeine and alcohol were prohibited from 72 hours prior to the start of administration through discharge. Subjects took only the prescribed meals during hospitalization and took no other foods. The same content of meals (regarding calorie intake and energy allocation, including sodium intake) was served for all subjects during hospitalization.

**Evaluations**

Blood sampling for PK assessment occurred on day 1 (1 hour before and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, and 12 hours after study drug administration), day 2 (16 hours after study drug administration on day 1 and immediately before study drug administration on day 2), days 3 through 6 (immediately before study drug administration on each day), and on day 7 and after (immediately before and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, 72, and 168 hours...
after study drug administration on day 7). Urine sampling for PK assessment was performed on day 1 (before administration and 0-4, 4-8, 8-12, and 12-24 hours after administration), day 2 (12-24 hours after study drug administration on day 1, 0-24 hours after study drug administration on day 2), days 3-6 (0-24 hours after study drug administration on day 2, 0-24 hours after study drug administration on each day), and on day 7 and after (0-24 hours after study drug administration on day 6, 0-4, 4-8, 8-12, 12-24, 24-48, and 48-72 hours after study drug administration on day 7). Plasma and urinary concentrations of imarikiren and its metabolite, M-I, were measured by high-performance liquid chromatography–tandem mass spectrometry.

R-A system examinations were performed on day 1 (1 hour before and 1, 2, 4, 6, and 12 hours after administration), days 2 through 6 (1 hour before administration), day 7 (1 hour before and 1, 2, 4, 6, and 12 hours after administration), and days 8 through 10 (23, 47, and 71 hours after the last administration). PD parameters evaluated included plasma renin activity (PRA), plasma active renin concentration (PRC), plasma angiotensin I concentration (AI), plasma angiotensin II concentration (AII), and plasma aldosterone concentration. PRA, AI, AII, and plasma aldosterone concentration were measured by radioimmunoassay. PRC was measured by immunoradiometric assay.

Safety evaluations included adverse events, vital signs, weight, ECG, and laboratory tests (hematology, serum chemistry, and urinalysis).

Statistical Considerations
PK parameters were estimated from plasma concentration-time profiles for each analyte using WinNonlin (Pharsight Corporation, Mountain View, California) by noncompartmental analysis. Actual sampling times were used for estimation of these PK parameters. To evaluate the age effect on the PK of imarikiren, the point estimate and two-sided confidence intervals (90% and 95%) of the difference between the groups (elderly-nonelderly) were calculated, based on the natural log-transformed area under the plasma concentration-time curve (AUC) from time zero to tau (AUC0-tau) and maximum serum concentration (Cmax) of imarikiren in Cohort 1 and Cohort 3 on day 7. Descriptive statistics, statistical analysis, and data plot were performed using SAS version 9.2 (SAS Institute Inc., Cary, North Carolina).

Results
Subject Disposition
A total of 78 subjects were screened and 46 were enrolled in the study (Figure 1). A total of 36 subjects were randomized and received the study drug, and 35 of 36 subjects completed the study. One subject was withdrawn from the study after using excluded concomitant medications. The safety, PK, and PD analysis sets each included all 36 subjects who received study drug.

Baseline Subject Characteristics
The baseline characteristics are shown in Table 1. The mean age of nonelderly subjects who received the study drug ranged from 24.8 years to 26.7 years; the mean age of elderly subjects ranged from 72.1 years to 72.7 years. The mean weight of nonelderly subjects ranged from 61.9 kg to 67.5 kg; the mean weight of elderly subjects ranged from 59.1 kg to 60.7 kg. The mean body mass index of nonelderly subjects ranged from 20.8 kg/m² to 22.9 kg/m²; the mean BMI of elderly subjects was 22.2 kg/m². The mean creatinine clearances of nonelderly groups ranged from 136.4 mL/min to 143.7 mL/min, and the mean creatinine clearances in elderly groups ranged from 74.2 mL/min to 77.3 mL/min. There were no obvious differences in demographic and baseline characteristics between the imarikiren and placebo groups within both nonelderly and elderly cohorts.

Pharmacokinetics

Nonelderly Subjects. Descriptive statistics for PK parameters of imarikiren are shown in Table 2. In nonelderly subjects, the median time to reach the maximum observed plasma concentration (Tmax) of imarikiren was between 1 and 2 hours for all groups on days 1 and 7. Tmax was similar regardless of the dose and was similar on day 1 and day 7. The mean terminal half-life (t1/2) of imarikiren was 10.3 hours in the imarikiren 80-mg group and 8.0 hours in the imarikiren 160-mg group on day 1, and was 11.0 hours in the imarikiren 80-mg group and 9.4 hours in the imarikiren 160-mg group on day 7. Based on the trough concentration of imarikiren, the plasma concentration of imarikiren reached the steady state by day 7 during multiple oral administration of 80 mg and 160 mg (Figure 2A).

The accumulation of imarikiren appeared not to occur during the 7 days of multiple administrations of imarikiren. The mean Cmax accumulation factor percentage (R [Cmax]; 100 × Cmax on day 7/Cmax on day 1) of imarikiren was 106.4% in the imarikiren 80-mg group and 101.0% in the imarikiren 160-mg group on day 1 of imarikiren was 104.7% in the imarikiren 80-mg group and 101.0% in the imarikiren 160-mg group. The mean AUC accumulation factor percentage (R [AUC]; 100 × AUC0-tau on day 7/AUC0-tau on day 1) of imarikiren was 106.4% in the imarikiren 80-mg group and 123.0% in the imarikiren 160-mg group. The mean accumulation index percentage (100 × AUC0-tau on day 7/AUC0-inf on day 1) of imarikiren was 94.4% in the imarikiren 80-mg group and 114.2% in the imarikiren 160-mg group, indicating that the PK of
imarikiren was independent of time following multiple daily doses for 7 days (Table 3).

At any dose, the AUC<sub>0-tau</sub> of M-I on day 7 was <3% that of imarikiren.

**Age Effect on Pharmacokinetics of Imarikiren.** Arithmetic mean time profiles of the plasma concentration of imarikiren following multiple oral administration of 80 mg imarikiren in nonelderly and elderly subjects are shown in Figure 2B. The mean t<sub>1/2</sub> of imarikiren or M-I was longer in elderly subjects than in nonelderly subjects on day 7. AUC<sub>0-tau</sub> and C<sub>max</sub> of imarikiren were higher in elderly than in nonelderly subjects (52% and 39% higher, respectively). The AUC and C<sub>max</sub> of M-I were greater in elderly subjects than in nonelderly subjects on day 1 and day 7.

**Pharmacodynamics**

**Nonelderly Subjects.** In nonelderly subjects, mean (standard deviation [SD]) baseline PRA values were 1.25 (1.060) ng/mL/hr in the placebo group, 3.08 (2.266) ng/mL/hr in the imarikiren 80-mg group, and 1.13 (1.034) ng/mL/hr in the imarikiren 160-mg group. The PRA was rapidly inhibited at any imarikiren dose in nonelderly subjects on day 1. The strong inhibition of PRA was observed for 7 days and maintained until 71 hours after the last administration of imarikiren (Figure 3A).

Mean (SD) baseline PRC values were 7.13 (4.804) pg/mL in the placebo group, 11.72 (7.113) pg/mL in the imarikiren 80-mg group, and 6.17 (3.481) pg/mL in the imarikiren 160-mg group. The PRC increased at any imarikiren dose, and the increase from baseline was observed for 7 days (Figure 3B). The peak concentrations of PRC were at similar levels across doses on day 1. However, the peak concentrations of PRC in the imarikiren 160-mg group were higher on day 7 than those in the imarikiren 80-mg group. In both dose groups, the peak concentrations of PRC were higher on day 7 than on day 1. Trough PRC continued to increase for at least 47 hours postdose.

**Age Effect on Pharmacodynamics.** The strong inhibition of PRA was also observed in elderly subjects for 7 days as with nonelderly subjects and maintained until 71 hours after the last administration of imarikiren (Figure 4A). The PRC increased in elderly subjects, and the increase from baseline was observed for 7 days. The peak concentrations of PRC were higher on day 7 than

**Figure 1.** Subject disposition.

**Table 1.** Baseline Characteristics

|                      | Nonelderly<sup>a</sup> | Elderly<sup>b</sup> | Total (N = 36) |
|----------------------|------------------------|--------------------|---------------|
| Placebo (n = 6)      | 26.7 (6.5)             | 72.7 (4.0)         | 72.1 (5.4)    |
| Imarikiren 80 mg (n = 9) | 26.4 (5.5)             | 165.7 (2.9)        | 163.0 (7.6)   |
| Imarikiren 160 mg (n = 9) | 24.8 (3.8)             | 63.2 (8.0)         | 60.7 (2.2)    |
| Placebo (n = 3)      | 171.7 (4.1)            | 22.2 (1.2)         | 22.2 (1.7)    |
| Imarikiren 80 mg (n = 9) | 169.0 (5.3)            | 22.0 (2.1)         | 22.2 (1.7)    |
| Total (N = 1)        | 22.9 (1.6)             | 58.2 (15.0)        | 41.1 (5.7)    |
| Mean (SD) BMI (kg/m²) | 174.3 (6.2)            | 59.6 (8.2)         | 62.2 (12.5)   |
| Mean (SD) PRA values | 143.7 (19.5)           | 55.0 (9.8)         | 57.3 (11.8)   |
| Mean (SD) PRC values | 136.4 (11.1)           | 140.8 (24.7)       | 118.3 (35.6)  |

AGP: alpha-1 acid glycoprotein; BMI, body mass index; SD, standard deviation.

<sup>a</sup>Subjects aged 20 to 45 years, inclusive.

<sup>b</sup>Subjects aged 65 to 85 years, inclusive.
Table 2. PK and PD Parameters of Imarikiren and M-I Following Multiple Oral Administrations of Imarikiren in Nonelderly and Elderly Subjects

| Parameters                  | Nonelderly     | Elderly       | Nonelderly     | Elderly       | Nonelderly     | Elderly       | Nonelderly     | Elderly       | Nonelderly     | Elderly       |
|-----------------------------|----------------|--------------|----------------|--------------|----------------|--------------|----------------|--------------|----------------|--------------|
| PK parameters of imarikiren |                |              |                |              |                |              |                |              |                |              |
| AUC_{0-tau} (ng · hr/mL), mean (SD) | 3732 (780.4) | 4938 (1793.5) | 8008 (2026.8) |              | 3937 (991.4) | 6017 (1701.9) | 9528 (2570.3) |
| AUC_{0-inf} (ng · hr/mL), mean (SD) | 4217 (863.8) | 5886 (2282.8) | 8599 (2108.0) |              |                |              |                |              |                |
| C_{max} (ng/mL), mean (SD) | 764.3 (275.4) | 958.9 (412.2) | 2021 (819.1)  |              | 754.2 (255.3) | 1071 (520.2)  | 1859 (417.1)  |
| T_{max} (hr), median (min-max) | 2.0 (1.0-3.0) | 1.5 (1.0-4.0) | 1.0 (1.0-2.5) |              | 2.0 (1.0-3.0) | 2.0 (1.0-4.0) | 1.5 (1.0-3.0) |
| CL/F (L/hr), mean (SD)    | 19.6 (3.6)    | 15.2 (4.6)   | 19.7 (5.1)    |              | 21.5 (5.6)    | 14.1 (3.4)    | 17.6 (3.3)    |

PK parameters of M-I

| Parameters                  | Nonelderly     | Elderly       | Nonelderly     | Elderly       | Nonelderly     | Elderly       | Nonelderly     | Elderly       | Nonelderly     | Elderly       |
|-----------------------------|----------------|--------------|----------------|--------------|----------------|--------------|----------------|--------------|----------------|--------------|
| AUC_{0-tau} (ng · hr/mL), mean (SD) | 58.2 (10.2)   | 70.8 (17.2)  | 138.4 (30.0)   |              | 84.4 (17.8)    | 117.3 (25.1)  | 206.7 (37.8)   |
| AUC_{0-inf} (ng · hr/mL), mean (SD) | 79.1 (12.0)   | 97.0 (22.1)  | 182.2 (44.8)   |              |                |              |                |              |                |
| C_{max} (ng/mL), mean (SD) | 113.4 (9.8)   | 159.3 (8.9)  | 35.1 (11.2)    |              | 11.8 (4.1)     | 19.0 (10.9)   | 32.9 (12.0)    |
| T_{max} (hr), median (min-max) | 2.0 (1.0-4.0) | 1.5 (1.0-4.0) | 1.0 (1.0-2.5)  |              | 2.0 (1.0-4.0)  | 2.0 (1.0-4.0) | 1.5 (1.0-3.0)  |
| CL/F (L/hr), mean (SD)    | 15.3 (4.8)    | 15.9 (7.3)   | 15.7 (6.6)     |              | 23.9 (9.7)     | 42.4 (26.0)   | 16.7 (12.0)    |

PD Parameters

| Parameters                  | Nonelderly     | Elderly       | Nonelderly     | Elderly       | Nonelderly     | Elderly       | Nonelderly     | Elderly       | Nonelderly     | Elderly       |
|-----------------------------|----------------|--------------|----------------|--------------|----------------|--------------|----------------|--------------|----------------|--------------|
| Inhibition rate of PRA (%) , mean (SD) | -286.2 (284.7) | 42.4 (19.8)  | 98.5 (2.4)     | 99.1 (1.9)   | 88.1 (17.2)   | -117.6 (154.6) | 4.0 (15.0)    | 98.0 (3.2)   | 98.3 (3.7)    | 89.9 (16.1)  |
| Change from baseline in PRC (pg/mL), mean (SD) | 6.8 (4.5)      | 1.9 (1.4)    | 169.3 (140.9)  | 78.3 (72.3)  | 129.5 (106.8) | 2.8 (3.9)     | 2.2 (3.3)     | 247.1 (130.1) | 154.4 (168.0) | 487.3 (264.9) |

AUC_{0-tau} indicates area under the plasma concentration-time curve from time 0 to time tau; AUC_{0-inf}, area under the plasma-concentration time curve from time 0 to infinity; CL/F, apparent total clearance; C_{max}, maximum observed plasma concentration; PRA, plasma renin activity; PRC, plasma active renin concentration; T_{max}, time to reach the maximum observed plasma concentration; t_{1/2}, apparent elimination half-life in the terminal elimination phase.
on day 1 as with nonelderly subjects. Increase from baseline in PRC was smaller in elderly subjects than in nonelderly subjects during the 7 days of treatment period and until 71 hours after the last administration of imarikiren (Figure 4B).

Table 3. Accumulation Factor (R) and Accumulation Index Percentages of Imarikiren Following Multiple Oral Administrations of Imarikiren in Nonelderly Subjects

| Parameters, Mean (SD) | Imarikiren 80 mg (n = 9) | Imarikiren 160 mg (n = 9) |
|-----------------------|--------------------------|--------------------------|
| R(AUC)                | 106.4 (22.4)             | 123.0 (32.6)             |
| R(Cmax)               | 104.7 (38.3)             | 101.0 (33.3)             |
| Accumulation index (AUC) | 94.4 (21.8)             | 114.2 (30.0)             |
| Accumulation index (t1/2) | 116.4 (39.1)             | 119.7 (34.3)             |

AUC indicates area under the plasma concentration-time curve; Cmax, maximum observed plasma concentration; SD, standard deviation; t1/2, apparent elimination half-life in the terminal elimination phase.

In nonelderly subjects, AII decreased from baseline on days 1 through 7 in the 160-mg dose group; in the 80-mg dose group, AII was decreased on day 1 but not on day 7. In elderly subjects, no changes from baseline in AII were observed at any time. No obvious changes in plasma aldosterone concentration from baseline were detected during the study except for decreases at 4 and 6 hours after imarikiren administration on day 7 in elderly subjects.

Safety

An overview of treatment-emergent adverse events (TEAEs) is presented in Table 4. In nonelderly subjects, TEAEs were reported in 16.7% of subjects (1 of 6 subjects) in the placebo group, 22.2% of subjects (2 of 9 subjects) in the imarikiren 80-mg group, and 22.2% of subjects (2 of 9 subjects) in the imarikiren 160-mg group. In elderly subjects, TEAEs were reported in 33.3% of subjects (1 of 3 subjects) in the placebo group and 33.3% of subjects (3 of 9 subjects) in the imarikiren 80-mg group. There was no
dose-dependent increase in the frequency of adverse events in non-elderly subjects. The frequency of TEAEs was higher in elderly than in non-elderly subjects who received imarikiren (33.3% vs 22.2%, respectively). The TEAEs that were reported in 2 or more subjects were alanine aminotransferase increased (4 subjects), diarrhea (2 subjects), aspartate aminotransferase increased (2 subjects), and headache (2 subjects). In nonelderly subjects, TEAEs related to the study drug were reported in 16.7% of subjects (1 of 6 subjects) in the placebo group, 22.2% of subjects (2 of 9 subjects) in the imarikiren 80-mg group, and 11.1% of subjects (1 of 9 subjects) in the imarikiren 160-mg group. In elderly subjects, TEAEs related to the study drug were reported in 33.3% of subjects (1 of 3 subjects) in the placebo group and 22.2% of subjects (2 of 9 subjects) in the imarikiren 80-mg group. In subjects who received imarikiren, TEAEs related to the study drug were reported in 16.7% of nonelderly subjects (3 of 18 subjects) and 22.2% of elderly subjects (2 of 9 subjects).

All TEAEs were mild in intensity, with the exception of moderate urticaria in 1 nonelderly subject in the imarikiren 80-mg group. The outcomes of all events were “recovered/resolved.” There were no serious TEAEs and no deaths during the study. No subject discontinued the study due to a TEAE.

No obvious changes were observed in the mean values of clinical laboratory tests. Of the TEAEs related to clinical laboratory tests, 5 were considered to be related to the study drug (alanine aminotransferase increased in 1 subject each in the placebo [nonelderly] group, imarikiren 160-mg [nonelderly] group, and imarikiren 80-mg [elderly] group, and aspartate aminotransferase increased in 1 subject each in the placebo [nonelderly] and imarikiren 80-mg [elderly] group). No obvious changes were observed in the mean values of vital signs and weight, except a decrease in mean blood pressure....
## Table 4. Treatment-Emergent Adverse Events (TEAEs; Safety Population)

| Preferred Term, n (%) | Placebo (n = 6) | Imarikiren 80 mg (n = 9) | Imarikiren 160 mg (n = 9) | Placebo (n = 3) | Imarikiren 80 mg (n = 9) |
|-----------------------|----------------|-------------------------|--------------------------|----------------|-------------------------|
| Subjects with any TEAEs | 1 (16.7) | 2 (22.2) | 2 (22.2) | 1 (33.3) | 3 (33.3) |
| Eye disorders | 0 | 0 | 0 | 1 (33.3) | 0 |
| Vision blurred | 0 | 0 | 0 | 1 (33.3) | 0 |
| Gastrointestinal disorders | 0 | 0 | 0 | 1 (33.3) | 1 (11.1) |
| Diarrhea | 0 | 0 | 0 | 1 (33.3) | 1 (11.1) |
| General disorders and administration site conditions | 0 | 1 (11.1) | 0 | 0 | 0 |
| Feeling hot | 0 | 1 (11.1) | 0 | 0 | 0 |
| Investigations | 1 (16.7) | 1 (11.1) | 2 (22.2) | 0 | 2 (22.2) |
| Alanine aminotransferase increased | 1 (16.7) | 0 | 2 (22.2) | 0 | 1 (11.1) |
| Aspartate aminotransferase increased | 1 (16.7) | 0 | 0 | 0 | 1 (11.1) |
| Blood creatinine phosphokinase increased | 1 (16.7) | 0 | 0 | 0 | 0 |
| Blood triglycerides increased | 1 (16.7) | 0 | 0 | 0 | 0 |
| White blood cell count decreased | 0 | 0 | 0 | 0 | 1 (11.1) |
| White blood cell count increased | 0 | 1 (11.1) | 0 | 0 | 0 |
| Nervous system disorders | 0 | 0 | 0 | 1 (33.3) | 1 (11.1) |
| Headache | 0 | 0 | 0 | 1 (33.3) | 1 (11.1) |
| Skin and subcutaneous tissue disorders | 0 | 2 (22.2) | 0 | 0 | 0 |
| Pruritus | 0 | 1 (11.1) | 0 | 0 | 0 |
| Urticaria | 0 | 1 (11.1) | 0 | 0 | 0 |

*Subjects aged 20 to 45 years, inclusive.

bSubjects aged 65 to 85 years, inclusive.

in the imarikiren groups at day 7 compared with baseline. No obvious changes were observed in ECG parameters, and no clinically significant abnormalities were observed at any time.

### Discussion

This is the first study to evaluate the safety and PK/PD of multiple oral administrations of imarikiren in human subjects. The plasma concentration of imarikiren during a period of multiple oral administrations of imarikiren (80 or 160 mg) reached steady state by day 7. Accumulation of imarikiren did not occur during the 7 days of multiple administrations of imarikiren at the 80- and 160-mg doses. The AUC and C<sub>max</sub> of imarikiren increased with a dose increase of 80 to 160 mg on day 1 and day 7 in nonelderly subjects. The AUC and C<sub>max</sub> of imarikiren were greater in elderly than in nonelderly subjects.

In terms of PD, PRA was rapidly inhibited at either dose; strong inhibition of PRA was observed for 7 days and maintained for at least 71 hours after the last administration of imarikiren. There was no effect of age on the inhibition rate of PRA activity despite the higher exposure observed in elderly subjects, possibly because the PRA inhibition effect reached plateau at the exposure of 80 mg in nonelderly and elderly subjects. The CPH-001 study of single oral administration of imarikiren showed that a ≥5 mg dose of imarikiren completely inhibited PRA, suggesting that an >80 mg dose of imarikiren should inhibit PRA completely in nonelderly and elderly populations.4

Increase from baseline in PRC was smaller in elderly subjects than in nonelderly subjects during the 7 days of the treatment period and until 71 hours after the last administration of imarikiren. The peak concentrations of PRC were similar for the 80- and 160-mg doses on day 1. In the CPH-001 study, peak PRC levels were also similar among dosing cohorts for imarikiren doses of >50 mg.4 Furthermore, in nonelderly subjects, the peak PRC levels for the 80- and 160-mg doses in the current study were similar to those for the >50-mg doses in the CPH-001 study.4 This suggests that there is a saturation in the initial activation effect of renin secretion at baseline without any R-A-related treatment due to renin inhibition. A >50-mg dose of imarikiren may reach the saturable level of initial activation. However, we observed that the difference between peak and trough PRC was greater on day 7 than on day 1, and the peak concentrations of PRC in the imarikiren 160-mg...
group were higher on day 7 than those in the imarikiren 80-mg group in nonelderly subjects, suggesting that the capacity of initial renin secretion may be induced by continuous renin inhibition and that the saturable level of this activation may increase due to this induction. Thus, it remains unknown if the maximum inhibition of renin at the site of renin secretion has been reached with once-daily imarikiren 160 mg.

Interestingly, even in elderly subjects, the peak trough difference on day 7 was larger than that on day 1. However, on both day 1 and day 7, these differences were lower in elderly than in nonelderly subjects. This may be caused by a baseline difference in the capacity of initial renin secretion between nonelderly and elderly populations. In elderly subjects, the capacity of initial renin secretion and/or the induction effect of renin secretion may be lower than those in nonelderly subjects.

Multiple oral administrations of imarikiren (80 or 160 mg) for 7 days were safe and well tolerated in nonelderly subjects; the 80-mg dose was also safe and well tolerated in elderly subjects. There was no dose-dependent increase in the incidence of TEAEs. The incidence of TEAEs in the subjects who received imarikiren was higher in elderly subjects than in nonelderly subjects. No obvious changes were observed for mean values of clinical laboratory tests, vital signs and weight (except for a decrease in blood pressure in the imarikiren groups), and ECG parameters.

The results from this study build upon those from the CPH-001 study evaluating the safety and PK/PD following administration of a single dose of imarikiren in healthy Japanese male subjects and provide important information regarding the chronic use of imarikiren. In both studies, imarikiren showed strong and prolonged PRA inhibition. In a study of aliskiren in Japanese and white subjects, administration of aliskiren (300 mg on day 1 and days 4-10) resulted in incomplete PRA inhibition at steady state, whereas multiple dosing of imarikiren in the current study resulted in complete inhibition for 7 days, which was sustained for nearly 3 days after the last administration.

A limitation of this study is that efficacy was not evaluated. Furthermore, imarikiren was given for only 7 days. Despite these limitations, multiple oral administrations of imarikiren were found to be safe and well tolerated in nonelderly and elderly subjects, with no PK accumulation and strong and sustained suppression of PRA. Our results support future studies evaluating longer periods of imarikiren administration and also studies evaluating the efficacy of imarikiren in subjects with cardiovascular and/or renal disease.

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Declaration of Conflicting Interests
K.M., S.T., T.H., H.N., and E.K. are employees and stockholders of Takeda Pharmaceutical Company Ltd. T.K. is an employee of SCOHIA PHARMA, Inc.

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