Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Single Doses of Empagliflozin, a Sodium Glucose Cotransporter 2 (SGLT2) Inhibitor, in Healthy Japanese Subjects

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Summary: This randomized, placebo-controlled within dose groups, double-blind, single rising dose study investigated the safety, tolerability, pharmacokinetics and pharmacodynamics of 1 mg to 100 mg doses of empagliflozin in 48 healthy Japanese male subjects. Empagliflozin was rapidly absorbed, reaching peak levels in 1.25 to 2.50 h; thereafter, plasma concentrations declined in a biphasic fashion, with mean terminal elimination half-life ranging from 7.76 to 11.7 h. Increase in empagliflozin exposure was proportional to dose. Oral clearance was dose independent and ranged from 140 to 172 mL/min. In the 24 h following 100 mg empagliflozin administration, the mean (%CV) amount of glucose excreted in urine was 74.3 (17.1) g. The amount and the maximum rate of glucose excreted via urine increased with dose of empagliflozin. Nine adverse events, all of mild intensity, were reported by 8 subjects (7 with empagliflozin and 1 with the placebo). No hypoglycemia was reported. In conclusion, 1 mg to 100 mg doses of empagliflozin had a good safety and tolerability profile in healthy Japanese male subjects. Exposure to empagliflozin was dose proportional. The amount and rate of urinary glucose excretion were higher with empagliflozin than with the placebo, and increased with empagliflozin dose.

Keywords: diabetes; empagliflozin; SGLT2 inhibitor; pharmacokinetics; pharmacodynamics

Introduction
The global prevalence of type 2 diabetes is high, with estimates of 366 million in 2011.1) However, there is considerable variability in prevalence across ethnic groups. In a 2009 survey of 187,439 individuals from 5 ethnic groups, prevalence of self-reported diabetes was higher in ethnic Japanese compared with Caucasians (10.2% versus 6.3%).2) In a global study in 2010, Japan numbered among the top 10 countries in terms of the number of people with diabetes aged between 20 and 79 years.3)

Several classes of glucose-lowering medications have been developed, a number of which act partly or wholly through insulin-independent mechanisms.4) However, gradual deterioration of β-cell function that epitomizes the progressive nature of type 2 diabetes compromises the effectiveness of anti-diabetic agents, necessitating the use of higher doses and combinations of agents.5,6) Despite the multitude of therapies available, maintenance of glycemic control in patients with type 2 diabetes remains challenging.7) In addition, existing anti-diabetic medications are associated with side effects, such as weight gain, hypoglycemia, and gastrointestinal effects.8) Thus efficacious and well tolerated treatments with novel insulin-independent modes of action are warranted, particularly for use as combination therapy with existing therapeutic agents.

Sodium glucose cotransporter 2 (SGLT2) inhibitors are a new class of therapeutic agents in development for the treatment of type 2 diabetes.9) The kidney performs a key role in glucose homeostasis, whereby the glomeruli filter blood glucose, which,
in healthy subjects, is almost completely reabsorbed in the proximal tubules via sodium-coupled transporters. SGLT2 is predominantly expressed in the S1 segment of the renal proximal tubules, and is responsible for ~90% of renal glucose reabsorption in healthy individuals. Once blood glucose levels reach the threshold for renal reabsorption (defined as the maximal reabsorptive transport capacity of the tubules $T_m$, occurring at an average filtered glucose load of 375 mg/min), excess glucose is excreted via the urine. Thus, selective SGLT2 inhibition has the potential to improve glycemic control in type 2 diabetes by increasing urinary glucose excretion (UGE) independently of insulin-reliant mechanisms, with additional benefits of a low risk of hypoglycemia and potential for weight loss.

Empagliflozin is a potent inhibitor of SGLT2 (IC$_{50}$ 3.1 nM [pIC$_{50}$ (SE) 8.5 (0.02) nM]) with ~2,500 greater selectivity versus SGLT1 that has been shown to be an effective inhibitor of renal glucose reabsorption and promoter of UGE. Based on the selectivity of empagliflozin for SGLT2 versus SGLT1, the contribution of SGLT1 inhibition to the effects of empagliflozin on UGE are likely to be negligible. In rodent models, administration of empagliflozin was found to promote UGE and attenuate plasma glucose levels following a glucose challenge, while in patients with type 2 diabetes, an increase in UGE and a reduction in fasting plasma glucose versus placebo was observed after multiple oral doses of empagliflozin up to 100 mg once daily for 4 weeks.

Empagliflozin has been shown to be well tolerated in healthy adults and patients with type 2 diabetes in Phase I and Phase II studies performed in mostly Caucasian populations.

This Phase I study was the first to investigate empagliflozin in Japanese subjects and evaluated the safety, tolerability, pharmacokinetics and pharmacodynamics of single rising doses of empagliflozin (1 mg to 100 mg) in healthy Japanese volunteers.

Methods

This was a Phase I, randomized, placebo-controlled within dose groups, double-blind, single rising dose trial of empagliflozin in 48 healthy Japanese male subjects. The study was undertaken at a single center in Japan. The study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Guidelines for Good Clinical Practice (ICH-GCP), and was approved by the local Institutional Review Board (Maruyama Hospital Institutional Review Board). Written informed consent was provided by all subjects prior to study participation.

Subjects: Eligible subjects were male, aged from 20 to 35 years inclusive, with a body mass index (BMI) of 18.0 to 25.0 kg/m² inclusive. All study participants were required to be in good general health, as determined by physical examination, vital signs (blood pressure, pulse, and body temperature), 12-lead electrocardiogram (ECG), and clinical laboratory tests.

Subjects were excluded from the study if they had evidence of a clinically relevant disease, known allergy/hypersensitivity, or somatic or central nervous system disorders, as were those with evidence of alcohol or drug abuse, a history of renal disease, renal glucosuria or urinary glucose levels exceeding 15 mg/dL at screening. Exclusion criteria also included participation in another trial with an investigational drug within the previous 4 months, or use of drugs within 10 days before administration of study treatment.

Study design: Participants were randomized equally across 6 empagliflozin dose groups: 1 mg, 5 mg, 10 mg, 25 mg, 100 mg, and 10 mg with an oral glucose tolerance test (OGTT). Within each group, subjects were randomly assigned to 6 active treatments and 2 placebo treatments. The dose level was known to subjects and investigators, but the drug type (i.e., active drug or placebo) was blinded to both.

The decision to proceed to the next dose was based on safety and tolerability in the preceding dose group. Prior to escalation to the 100 mg dose, pharmacokinetic data from the preceding groups were also evaluated.

Empagliflozin was administered orally with approximately 150 mL of water after an overnight fast of at least 10 h. Subjects were kept under close medical surveillance at the trial center for 3 days following drug administration.

In the 10 mg dose group with an OGTT, the glucose test (intake of 75 g of glucose in solution) was performed 1 h following administration of empagliflozin. A baseline glucose profile was collected by conducting a glucose test under similar conditions 1 day before without empagliflozin administration.

Endpoints: The primary endpoint was an evaluation of safety and tolerability, as measured by the incidence of adverse events (AEs; classified by MedDRA, version 11.0; http://www.medramosso.com), vital signs, physical examination, clinical laboratory tests, and 12-lead ECG. Vital signs, ECG assessments and clinical laboratory tests were performed at baseline, on days 2, 3, 4, and at the end of the study. Vital signs and ECGs were assessed at regular intervals throughout day 1. AEs were monitored throughout the study.

Secondary endpoints encompassed the pharmacokinetics of empagliflozin after single oral administration, which were the maximum measured concentration of empagliflozin in the plasma ($C_{max}$), time from dosing to maximum concentration ($t_{max}$), area under the concentration-time curve of empagliflozin in plasma over the time interval from 0 extrapolated to infinity ($AUC_{0-\infty}$) or last quantifiable data point ($AUC_{0-t}$), total clearance of empagliflozin in plasma (CL/F), terminal half-life ($t_{1/2}$), fraction of dose eliminated in urine over 72 h ($fe_{0-72}$), and renal clearance of analyte over 72 h ($CL_{R,0-72}$).

Pharmacodynamic endpoints were UGE (Ae), maximum urinary glucose excretion rate ($U_{max}$), area under the effect-time curve of glucose in plasma (AUEC), maximum glucose concentration in plasma ($F_{max}$), and time from dosing to the maximum excretion rate of glucose in urine ($U_{max}$).

Pharmacokinetic and pharmacodynamic sampling and analysis: For the purposes of pharmacokinetic measurements, blood samples (6 mL) were drawn from the forearm of each subject at 5 min before and 0.167, 0.333, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 14, 24, 34, 48, and 72 h after empagliflozin administration. An additional 2 mL of blood was collected at these time points for determination of plasma glucose concentrations. All urine voided during time intervals $–2–0$, 0–2, 2–4, 4–6, 6–8, 8–12, 12–24, 24–34, 34–48, and 48–72 h relative to study drug administration was collected. In addition, urine samples were collected at 2-h intervals from 26 to 18 h before administration of empagliflozin in the 10 mg dose group with an OGTT.

Empagliflozin concentrations in plasma and urine were analyzed using a validated high performance liquid chromatography coupled to tandem mass spectrometry (HPLC-MS/MS) assay with a lower limit of quantification of 1.11 nmol/L for plasma, or 4.44 nmol/L for urine. The mean precision and accuracy of the quality control samples in plasma and urine at each concentration level were...
descending concentrations. The AUC0
subject. AUC was calculated using the linear trapezoidal method
derived directly from plasma concentration-time pro

\[
\text{AUC} = \int_{0}^{\infty} C(t) \, dt
\]

where \( C(t) \) is the plasma concentration at time \( t \). The terminal elimination rate constant (\( k_{\text{el}} \)) was determined as the negative of the slope of the terminal phase of the concentration-time profile from observations made after the last measurable concentration.

The area under the first moment curve (AUMC) was calculated as the sum of AUC to the last measured concentration, with the latter calculated as the difference between the final measured concentration and the extrapolated baseline concentration.

\[
\text{AUMC} = \int_{0}^{\infty} t \cdot C(t) \, dt
\]

The terminal elimination half-life (\( t_{\text{1/2}} \)) was calculated as the quotient of the terminal rate constant \( k_{\text{el}} \) and 2.303.

The renal clearance (CLR) was determined as the quotient of the amount of drug excreted unchanged in urine (Ae) over AUC.

\[
\text{CLR} = \frac{\text{Ae}}{\text{AUC}}
\]

The renal clearance of unchanged drug (CLR\text{u}) was calculated as

\[
\text{CLR}_{\text{u}} = \text{CL}_{\text{u}} \cdot \text{F}
\]

where \( \text{CL}_{\text{u}} \) is the renal clearance of the unchanged fraction of the drug and \( F \) is the fraction of the dose (\( \text{fe} \)) that was filtered.

The glomerular filtration rate (GFR; estimated based on age and serum creatinine levels using the Modification of Diet in Renal Disease [MDRD] equation) and plasma mean daily glucose (MDG). Mean values for UGE and plasma MDG from the placebo group were used as baseline TG for calculation of inhibition of glucose reabsorption.

**Statistical analysis:** The planned sample size of 48 subjects, comprising 8 individuals per dose group, was considered sufficient for exploratory evaluation of the safety, tolerability, and pharmacokinetics of empagliflozin.

Safety and pharmacodynamic analyses were carried out in the treated set and pharmacodynamic set, respectively. These populations were identical, and included all subjects who received at least one dose of empagliflozin or the placebo. Pharmacokinetic analyses were carried out in the pharmacokinetic set, which included all subjects who received empagliflozin. Results from analyses of primary and secondary endpoints are presented descriptively as arithmetic mean and SD or arithmetic coefficient of variation (CV).

Dose proportionality (functional relationship between empagliflozin dose [excluding data from the 10 mg dose group with an OGTT] and the pharmacokinetic endpoints: \( C_{\text{max}} \) and AUC) was described using the power model. Two-sided 95% confidence intervals (CIs) were derived from estimates of the slope parameter (\( \beta \)), for which a value of 1 was indicative of 100% dose-proportionality.

**Results**

**Subject disposition and demographics:** Forty-eight healthy Japanese male subjects were randomly assigned to receive a placebo (\( n = 12 \)) or single doses of 1 mg, 5 mg, 10 mg, 25 mg or 100 mg empagliflozin (\( n = 36; \ n = 6 \) to each dose group, plus an additional 6 subjects to 10 mg empagliflozin with OGTT). Baseline characteristics were similar in all groups (Table 1). All subjects completed the trial; thus all 48 subjects were included in the treated set and pharmacodynamic set and all 36 empagliflozin-treated subjects were included in the pharmacokinetic set.

**Safety and tolerability results:** Overall, 8 (16.7%) of the 48 subjects experienced an AE: 7 with empagliflozin (1 subject each on 1 mg and 5 mg, 2 on 10 mg and 3 on 100 mg) and 1 with the placebo (Table 2). A total of 9 AEs were reported among these subjects, all of which were mild and resolved without treatment prior to study end. There were no discontinuations due to AEs, no serious AEs, and no deaths. Three of the 9 AEs were regarded as drug-related by the investigator. These were 2 cases of headache (1 mg and 100 mg empagliflozin groups) and 1 case of somnolence (100 mg empagliflozin group). Hypoglycemia was not reported in any group. There were no clinically relevant changes in laboratory tests, vital signs or ECG recordings.

**Pharmacokinetic results:** Empagliflozin was rapidly absorbed, with median \( t_{\text{max}} \) values ranging between 1.25 h (1 mg dose)
Empagliolizin exposure were dose proportional from 0.943 (95% CI 0.884; 1.00), 0.973 (0.929; 1.02), and 0.988 (0.942; 1.03) for Cmax, AUC0–∞, and AUC0–α, respectively, where a slope of 1 indicates perfect dose proportionality. Exposure was higher under OGTT conditions: AUC0–∞ was increased by 16% compared with the same dose of empagliolizin (10 mg) without OGTT.

Empagliolizin was detected in the urine in all dose groups and remained measurable in all fractions up to 72 h, with the exception of the 48–72 h time interval for 1 subject in the 1 mg group. Rates of renal clearance (CLR0–72) and cumulative fractions of empagliolizin excreted in the urine (FE0–72) over 72 h were generally similar between dose groups (Table 3).

Pharmacodynamic results: Mean (SD) percent inhibition of glucose reabsorption was 13.1 (5.27), 27.2 (5.52), 36.0 (6.35), 41.7 (9.05) and 49.6 (7.60) % with single doses of empagliolizin 1, 5, 10, 25 and 100 mg, respectively, and −0.612 (8.94) % with the placebo. In accordance, UGE was higher with empagliolizin than with the placebo, and increased with rising dose (Fig. 2A). Mean (%CV) cumulative amount of glucose excreted in urine within the first 24 h after drug administration (AE0–24) was 19.6 (26.6) g for the 1 mg dose, increasing to a maximum of 74.3 (17.1)

Table 3. Summary of pharmacokinetic parameters of empagliolizin after oral administration of single doses

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Empagliolizin dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 mg (n = 6)</td>
</tr>
<tr>
<td>AUC0–∞, nmol·h/L</td>
<td>266</td>
</tr>
<tr>
<td>(23.1)</td>
<td>(10.2)</td>
</tr>
<tr>
<td>AUC0–α, nmol·h/L</td>
<td>247</td>
</tr>
<tr>
<td>(24.5)</td>
<td>(10.7)</td>
</tr>
<tr>
<td>Cmax, nmol/L</td>
<td>36.6</td>
</tr>
<tr>
<td>(23.9)</td>
<td>(26.6)</td>
</tr>
<tr>
<td>tmax, h</td>
<td>1.25</td>
</tr>
<tr>
<td>(1.00–2.00)</td>
<td>(0.75–2.00)</td>
</tr>
<tr>
<td>t1/2, h</td>
<td>7.76</td>
</tr>
<tr>
<td>(13.9)</td>
<td>(19.9)</td>
</tr>
<tr>
<td>CL/F, mL/min</td>
<td>145</td>
</tr>
<tr>
<td>(21.6)</td>
<td>(10.2)</td>
</tr>
<tr>
<td>fE0–72, %</td>
<td>23.3%</td>
</tr>
<tr>
<td>(13.0)</td>
<td>(9.97)</td>
</tr>
<tr>
<td>CLR0–72, mL/min</td>
<td>32.4%</td>
</tr>
<tr>
<td>(20.2)</td>
<td>(9.57)</td>
</tr>
</tbody>
</table>

Data are means (% coefficient of variation) unless otherwise indicated.

\( n = 6 \)

AUC0–∞, area under concentration-time curve of analyte in plasma over time interval from 0 extrapolated to infinity; AUC0–α, area under concentration-time curve of analyte in plasma over time interval from 0 to last quantifiable data point; Cmax, maximum measured concentration of analyte in plasma; tmax, time from dosing to maximum concentration; t1/2, terminal half-life of analyte in plasma; CL/F, total clearance of analyte in plasma after extravascular administration; fE0–72, fraction of dose eliminated in urine over 72 h; CLR0–72, renal clearance of analyte over 72 h.

and 2.50 h (100 mg dose) (Table 3). Thereafter, empagliolizin plasma levels declined in a biphasic manner indicative of a rapid distribution phase and a slower elimination phase (Fig. 1). Plasma empagliolizin levels were generally detectable 72 h after administration of the 25 mg and 100 mg doses, but were below the limit of quantification by this time-point for the 5 mg and 10 mg groups, and by 48 h for the 1 mg group. Across the dose range, the t1/2 of empagliolizin ranged between 7.76 and 11.7 h. Total clearance of empagliolizin in plasma was dose independent and ranged from 140 to 172 mL/min (Table 3).

Fig. 1. Mean (±SD) plasma concentration-time profiles of empagliolizin after single oral dose of empagliolizin

A: Linear scale (mean ±SD). B: Semi-logarithmic scale (mean ±SD). Empagliolizin was rapidly absorbed, reaching peak levels in 1.25–2.50 h, and had a biphasic decline, with a rapid distribution phase and slower elimination phase. Increases in empagliolizin exposure were dose proportional from 1 mg to 100 mg. © 1 mg empagliolizin; ■ 5 mg empagliolizin; □ 10 mg empagliolizin; ▲ 25 mg empagliolizin; ▼ 100 mg empagliolizin; ◆ 10 mg empagliolizin + OGTT.
Table 4. Summary of pharmacodynamic parameters of single doses of empagliflozin and placebo

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Placebo (n = 10)</th>
<th>1 mg (n = 6)</th>
<th>5 mg (n = 6)</th>
<th>10 mg (n = 6)</th>
<th>25 mg (n = 6)</th>
<th>100 mg (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{AUEC}_{0-24} ), mg·h/dL</td>
<td>2,480 (8.53)</td>
<td>2,510 (7.31)</td>
<td>2,480 (4.23)</td>
<td>2,490 (7.17)</td>
<td>2,480 (6.22)</td>
<td>2,480 (5.69)</td>
</tr>
<tr>
<td>( \text{E}_{\text{max,0-24}} ), mg/dL</td>
<td>130 (14.5)</td>
<td>132 (13.3)</td>
<td>130 (11.8)</td>
<td>126 (11.9)</td>
<td>125 (9.86)</td>
<td>135</td>
</tr>
<tr>
<td>( \text{Ae}_{0-24} ), g</td>
<td>0.0443 (34.2)</td>
<td>19.6 (26.6)</td>
<td>43.2 (13.1)</td>
<td>50.6 (8.50)</td>
<td>62.0 (23.1)</td>
<td>74.3</td>
</tr>
<tr>
<td>( \text{Ae}_{0-72} ), g</td>
<td>0.174 (23.3)</td>
<td>23.5 (33.7)</td>
<td>53.6 (19.7)</td>
<td>75.0 (16.2)</td>
<td>110.0 (41.7)</td>
<td>184.0</td>
</tr>
<tr>
<td>( \text{U}_{\text{max}} ), mg/h</td>
<td>4.77 (66.5)</td>
<td>2.650 (17.2)</td>
<td>3.690 (16.4)</td>
<td>3.670 (12.8)</td>
<td>4.540 (15.1)</td>
<td>5.100</td>
</tr>
<tr>
<td>( \text{U}_{\text{etmax}}^\text{a} ), h</td>
<td>8.50 (5.00)</td>
<td>5.00 (5.00)</td>
<td>7.00 (5.00)</td>
<td>5.00 (5.00)</td>
<td>5.00 (5.00)</td>
<td>6.00</td>
</tr>
</tbody>
</table>

Data are means (% coefficient of variation) unless otherwise indicated.

\( ^a \text{Median (range)}. \)

\( ^b n = 9. \)

\( ^c n = 8. \)

\( ^d n = 5. \)

\( \text{AUEC}_{0-24}, \) area under effect-time curve of glucose in plasma from 0 to 24 h; \( \text{E}_{\text{max,0-24}}, \) maximum glucose concentration in plasma from 0 to 24 h; \( \text{Ae}_{0-24}, \) amount of glucose eliminated in urine from 0 to 24 h; \( \text{Ae}_{0-72}, \) amount of glucose eliminated in urine from 0 to 72 h; \( \text{U}_{\text{max}}, \) maximum excretion rate of glucose in urine; \( \text{U}_{\text{etmax}}, \) time from dosing to the maximum excretion rate of glucose in urine.

Fig. 2. Mean (±SD) urinary glucose excretion after single oral dose of empagliflozin
A: Mean (±SD) cumulative urinary glucose excretion. B: Mean (±SD) rate of urinary glucose excretion. Urinary glucose excretion was higher with all doses of empagliflozin versus the placebo. The amount (A) and rate (B) of urinary glucose excretion increased with empagliflozin dose. ●, placebo; ○, 1 mg empagliflozin; ■, 5 mg empagliflozin; □, 10 mg empagliflozin; ▲, 25 mg empagliflozin; △, 100 mg empagliflozin.
g with the 100 mg dose, compared with only 0.0443 (34.2) g with the placebo (Table 4). AUC0–24 increased more steeply at lower doses (10 mg empagliflozin or less), with a 2.6-fold increase over the 10-fold dose range from 1 mg to 10 mg, compared with only a 1.5-fold increase over the 10-fold dose range from 10 mg to 100 mg. On the other hand, the duration of the effect on UGE lengthened with increasing empagliflozin dose; at doses of 5 mg or less, the majority of glucose was excreted within the first 24 h, but at the highest dose of 100 mg, UGE continued for up to 72 h (Fig. 2A).

Glucose challenge as part of the OGTT had no significant effect on mean (CV) AUC0–24 after treatment with 10 mg empagliflozin [54.8 (17.0) g with OGTT versus 50.6 (8.50) g without OGTT].

The rate of UGE was markedly higher with empagliflozin compared with the placebo (with maximum rates of UGE [Umax] of 2,650–5,100 mg/h versus 4.77 mg/h, respectively), and increased with dose (Fig. 2B, Table 4). There was a relationship between empagliflozin exposure (AUC0–∞ and Cmax) and UGE; as AUC0–∞ and Cmax increased, there were increases in both the cumulative amount of UGE (Figs. 3A and 3B) and the maximum rate of UGE (Umax) (Figs. 3C and 3D). However, the time to reach maximum rate of UGE (Umax) was similar in all empagliflozin groups (5 to 7 h; Table 4). A second sharp increase in the rate of UGE was apparent at around 30 h (fraction of 24–34 h) with the 100 mg dose, with smaller increases at this time point with the 10 mg and 25 mg doses (Fig. 2B).

Under the controlled fluid intake conditions used in this study, no significant differences in mean cumulative urine volume in the first 24 h were observed between subjects treated with empagliflozin (3.11–3.98 L) and with the placebo (3.17 L). Similarly, there were no significant differences in mean cumulative urine volumes over 72 h (7.12–8.71 L in empagliflozin groups versus 7.30 L with the placebo).

As expected, plasma glucose levels were not significantly altered by single doses of empagliflozin versus the placebo (Table 4). Over 24 h, observed mean values for AUEC0–24 and Emax,0–24 were similar across treatment groups (AUEC0–24: 2,480–2,510 mg/h/dL [empagliflozin]; 2,480 mg/h/dL [placebo] and Emax,0–24: 125–135 mg/dL [empagliflozin]; 130 mg/dL [placebo]). Elevations in plasma glucose levels following OGTT were slightly reduced by pretreatment with 10 mg empagliflozin compared with when OGTT was administered without empagliflozin (mean AUC1–5 [%CV]: 438 [6.78] mg/h/dL on day 1 versus 487 [6.86] mg/h/dL on day −1; Emax,1–5 [%CV]: 150 [15.1] mg/dL on day 1 versus 171 [7.04] mg/dL on day −1).

Discussion

This Phase I single rising dose study was conducted to evaluate the safety, tolerability and pharmacokinetic and pharmacodynamic profile of the SGLT2 inhibitor empagliflozin in healthy Japanese male subjects. The results showed that, at single doses between 1 mg and 100 mg, empagliflozin exhibited a good safety profile and was well tolerated. These results are consistent with studies in Caucasian healthy volunteers and patients with type 2 diabetes.10,11,14

Single rising doses of empagliflozin up to 100 mg were rapidly absorbed, with dose-proportional exposure to empagliflozin. The dose-proportional increase in empagliflozin exposure demonstrated in this study is in line with the findings of a similar study involving healthy Caucasian male subjects.13 However, empagliflozin exposure was approximately 1.5-fold higher in this Japanese study...
than in the study in Caucasians, which can be partly attributed to differences in body weights between the two populations. The median body weight of the Japanese volunteers was approximately 20% lower than that of their Caucasian counterparts (62.6 kg versus 79.0 kg, respectively).

With an increase in empagliflozin dose, there was a marked increase in the cumulative amount of glucose excreted in the urine. The duration of effects on UGE also increased with dose: the majority of UGE occurred within 24 h for empagliflozin doses of <10 mg, but the effect on UGE was extended beyond this period with higher doses. Analysis of relationships between pharmacokinetic and pharmacodynamic data showed that both the amount and rate of UGE increased with empagliflozin exposure. Incremental changes in the amount and rate of UGE were greater at lower levels of empagliflozin exposure than at high exposure. The second peak in the rate of UGE (24–36 h after dosing) was more prominent at higher empagliflozin doses (≥10 mg). Two factors could have accounted for this second peak. Firstly, food intake varied during this time interval: a light snack was given 12–24 h after dosing (night time), 3 meals were given during the 24–34 h after dosing (day time) and no food was given 34–48 h after dosing (night time). Diurnal variability in renal blood flow is another possible reason for the second peak, as renal filtration rates have been shown to be lower at night than during the day. Higher empagliflozin doses would have continued to have an effect on UGE on Day 2 after dosing, which may explain the more prominent second peak at doses ≥10 mg.

The amount of UGE in 24 h after empagliflozin administration was similar between Japanese subjects and Caucasian subjects (1) at doses tested in both trials (10, 25 and 100 mg). These data from healthy subjects suggest that the difference in empagliflozin exposure between Caucasian and Japanese subjects may not affect the expected therapeutic dose of empagliflozin to be tested in future clinical trials in patients with type 2 diabetes. Exposure was slightly higher under OGTT conditions; however, this was not considered to be clinically significant.

In the current study, the inhibition of filtered glucose reabsorption increased with increasing doses of empagliflozin, with no significant reductions in plasma glucose after a single dose. No significant effect on plasma glucose was expected in healthy subjects in whom counter-regulatory mechanisms are maintained and compensate for increased UGE. Following glucose challenge (OGTT), pre-treatment with 10 mg empagliflozin was associated with a slight reduction in plasma glucose levels, which was not considered clinically significant.

In conclusion, this study shows that empagliflozin is well tolerated in healthy Japanese subjects, with dose-proportional exposure to empagliflozin, and increased UGE with increasing dose of empagliflozin. These findings support continued evaluation of empagliflozin as a treatment option for Japanese patients with type 2 diabetes.

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