ORIGINAL RESEARCH

Evaluation of Age-Related Changes in Teneligliptin Pharmacokinetics in Japanese and European Descent Subjects Using a Physiologically Based Pharmacokinetic Model

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ABSTRACT

Introduction: Drugs often show differing pharmacokinetic (PK) profiles, such as higher plasma concentrations, in older people than in younger people owing to age-related decreases in physiological functions. However, it is difficult to evaluate the PK in older populations. Therefore, we simulated the plasma age-related changes in the PK of teneligliptin, a dipeptidyl peptidase-4 inhibitor, using physiologically based PK (PBPK) models.
Methods: The previously developed PBPK model was revalidated by comparison between simulated data and clinical study data that included older subjects (up to 75 years old). We then simulated the plasma concentration–time profiles for teneligliptin at a dose of 20 mg (single and multiple doses) in virtual Japanese (20–70 years old) and European descent (20–98 years old) subjects. PK parameters were calculated by race and age group.
Results: We confirmed the validity of the previous PBPK model by comparison between

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simulated data and clinical study data. In the evaluation of age-related changes in PK after single and multiple doses using the PBPK model, the area under the plasma concentration–time curve (AUC) of teneligliptin tended to increase slightly with age in both populations up to 70 years old. However, no clear age-related change in the maximum plasma concentration (C_{max}) of teneligliptin was observed. In the European descent subjects aged $\geq$ 70 years, the AUC tended to increase but the ratio of the change in C_{max} was smaller than that in AUC. In both populations, there were positive correlations between AUC and age, but not between C_{max} and age.

Conclusion: The simulation using a PBPK model showed a tendency for the AUC of teneligliptin to increase with age, whereas C_{max} was less affected by age than AUC.

Key Summary Points

Why carry out this study?

Drugs often show differing pharmacokinetic (PK) profiles, such as higher plasma concentrations, in older people than in younger people owing to age-related decreases in physiological functions. Because changes in PK, especially increased exposure, may increase the risk of adverse events, the PK profiles of drugs in older people should be carefully considered.

There is limited information on PK profiles in older people because of the difficulty of performing clinical studies in this population.

The aim of this study was to evaluate the age-related changes in the PK of teneligliptin, a dipeptidyl peptidase-4 inhibitor, in Japanese and European descent subjects using a physiologically based PK (PBPK) model.

What was learned from the study?

The simulation using the PBPK model showed a tendency for the area under the plasma concentration–time curve (AUC) of teneligliptin to increase with age, whereas the maximum plasma concentration was less affected by age than AUC.

Older patients are highly diverse and individualized treatment is important. Since an increased plasma concentration of a drug may lead to adverse events, careful administration is necessary for patients with characteristics in which drug exposure is likely to increase.

INTRODUCTION

The prevalence of type 2 diabetes (T2D) is increasing worldwide, and the number of older people with T2D is also increasing with population aging [1–4]. The principles of managing older people with T2D do not differ from those in younger people with T2D, consisting of a stepwise approach to dietary and exercise therapy, followed by pharmacotherapy. However, in older people, dietary restriction is likely to increase the risk of sarcopenia and frailty [5–10], making it difficult to implement. Furthermore, exercise is not always beneficial because many older people have cardiopulmonary disorders or joint problems [8–11]. Thus, older people with T2D are often more reliant on pharmacotherapy than on dietary and exercise therapy.

In pharmacotherapy, drugs often show different pharmacokinetic (PK) profiles in older people, such as higher plasma concentrations, than in younger people owing to age-related decreases in physiological functions, particularly renal and hepatic functions, both of which are involved in the metabolism and excretion of drugs. Changes in PK, especially increased drug exposure, may increase the risk of adverse events [12–14]. Therefore, the PK profiles of drugs in older people should be carefully

considered. However, there is limited information on the PK of drugs in older people due to the difficulty of performing clinical studies in this population.

Dipeptidyl peptidase-4 (DPP-4) inhibitors are widely used glucose-lowering drugs. In Japan, DPP-4 inhibitors are prescribed as a first-line drug to > 60% of people with T2D, and are frequently used in older patients with T2D [15] even though the PK properties of DPP-4 inhibitors in older populations are still not well established. Previous studies demonstrated that PK parameters, including the area under the plasma concentration–time curve (AUC) and the maximum plasma concentration (C_{max}), for several DPP-4 inhibitors tend to show mild increases in older populations (≥ 65 years old) compared to younger populations [16–20]. However, those studies comprised small numbers of subjects, and the authors did not report any PK data on DPP-4 inhibitors for subjects aged ≥ 85 years [16–20].

Teneligliptin is a DPP-4 inhibitor launched in several Asian countries (Japan, South Korea, Thailand and China). This drug is eliminated through multiple pathways involving hepatic cytochrome P450 3A4 (CYP3A4), flavin-containing monooxygenase 3 (FMO3) and renal excretion, with approximately equal contributions of these pathways [21, 22]. Therefore, the increase in exposure to teneligliptin due to renal or hepatic impairment is considered to be limited and dose adjustment is not required for these patients [22]. One clinical trial (the MP-513-E05 study) also showed similar PK profiles of teneligliptin between older (≥ 65 to ≤ 75 years old) and younger (≥ 45 to < 65 years old) subjects [22–24]; however, only 24 subjects were included in that trial, and all of them were of European descent. Thus, current PK data for teneligliptin in older people is very limited.

Physiologically based PK (PBPK) modeling and simulation has been applied to predict the plasma drug concentrations in special populations and to evaluate drug–drug interactions, and such data have been used in regulatory submissions as part of new drug applications [25–28]. Because the changes in physiological functions that occur with age are considered in the virtual populations used in PBPK simulations [29], this approach has also been used to predict the PK profiles of drugs in older populations [30–32].

We previously developed a PBPK model to predict the plasma concentration of teneligliptin in healthy Japanese subjects and various sets of subjects of European descent (healthy, renal impairment and hepatic impairment) using Simcyp Simulator software (Certara UK Ltd., Sheffield, UK). This PBPK model has also been validated in subjects of European descent aged ≥ 45 to < 65 years and in those aged ≥ 65 to ≤ 75 years [33]. However, in Japanese subjects, this PBPK model has only been validated in a young population (twenties and thirties); it has yet to be validated in subjects aged ≥ 40 years.

The aim of this study was to evaluate the age-related change of teneligliptin PK in Japanese and European descent subjects using the PBPK model. First, the published teneligliptin PBPK model was revalidated in the Japanese population by comparison to clinical study data, which include subjects aged ≥ 40 years. In the next step, we utilized this PBPK model to evaluate the age-related changes in the PK of teneligliptin in virtual Japanese (≥ 20 to ≤ 70 years old) and European descent (≥ 20 to ≤ 98 years old) populations derived from the upper age limits of the Simcyp subject library.

METHODS

Ethical Approval

This study was a pharmacokinetic simulation using virtual subjects. The clinical studies cited in this article were conducted in compliance with the Declaration of Helsinki and were previously published. This article does not include any new studies involving human participants or animals performed by any of the authors.

Generation and Revalidation of the PBPK Model

A PBPK model for teneligliptin was developed in the population-based Simcyp Simulator and

validated against clinical PK studies in healthy subjects and in subjects with hepatic or renal impairment, as well as in older populations (65–75 years old) [33]. The model includes teneligliptin's physicochemical parameters (molecular weight, LogP, pKa, polar surface area and hydrogen bond donor) and PK parameters, such as absorption (solubility and membrane permeability), distribution (blood-to-plasma partition ratio, fraction unbound in plasma and partition coefficient to tissues), metabolism and elimination (recombinant system, enzyme kinetics and renal clearance) parameters. The model was previously used to simulate plasma teneligliptin concentrations in healthy subjects, subjects with renal or hepatic impairment and older subjects (65–75 years old), in drug–drug interaction scenarios and for comparisons among virtual Japanese, European descent, and Chinese subjects [33]. Population libraries developed based on data gathered from epidemiological studies and implemented in Simcyp software were used to generate the virtual subjects for the PK simulations. The population libraries in this simulator have an age limit. In the present study, the PK simulation in virtual Japanese and European descent populations was performed using the PBPK model for teneligliptin in the population-based Simcyp Simulator ver. 18.2.

The PK characteristics of teneligliptin in the Japanese population, including in older subjects ($\leq$ 75 years old), were only evaluated in the clinical pharmacology study in people with T2D (3000-A12 study) [34]. Since there were no differences in the PK profiles of teneligliptin between people with and without diabetes [22, 23], and a PBPK model for people with diabetes has not been developed in the Simcyp software, the teneligliptin PBPK model was revalidated in the Japanese general population including older subjects, with comparison to the data from the 3000-A12 study. A virtual Japanese general population library (Sim-Japanese) was used to generate virtual subjects with similar background data (age, male/female ratio) to those of the 3000-A12 study. Each virtual subject was administered 20 mg teneligliptin orally before a meal for 28 days, and PK parameters such as C_{max} and AUC from 0 to

24 h (AUC_{0-24h}) were calculated within the Simcyp Simulator. In order to confirm whether the accuracy of this model is comparable between the Japanese and European descent populations, the simulations were performed using a similar population to that included in the MP-513-E05 study [24], a PK study in European descent subjects. Two virtual general population libraries of European descent subjects were used to generate the virtual subjects: (1) the Sim-NEurCaucasian library comprised population data on subjects aged $\geq$ 20 to < 65 years and (2) the Sim-GeriatricNEC library comprised population data on subjects aged $\geq$ 65 to $\leq$ 98 years. After a single dose of 20 mg teneligliptin, PK parameters, such as C_{max} and AUC from 0 h to infinity ($AUC_{0-\infty}$), were calculated within the Simcyp Simulator.

Simulation of Age-Related Changes of PK in Japanese and European Descent Subjects

A virtual Japanese general population library (Sim-Japanese) was used to generate virtual subjects aged $\geq$ 20 to $\leq$ 70 years in 5-year steps yielding ten groups (N = 100/group, male:female ratio = 1:1). Two virtual European descent general population libraries were used to generate virtual subjects; the Sim-NEurCaucasian library comprised population data for subjects aged $\geq$ 20 to < 65 years and the Sim-GeriatricNEC library comprised population data for subjects aged $\geq$ 65 to $\leq$ 98 years. Virtual subjects were generated from both population libraries with 5-year steps through to < 90 years old, and in 4-year steps from 90 to 98 years old, yielding 16 groups (N = 100/group, male:female ratio = 1:1). Because a virtual population library for people with T2D has not been established for PK simulations, this study was conducted using a general population library.

Each virtual subject was administered 20 mg teneligliptin orally before a meal for 7 days. After repeated doses of 20 mg teneligliptin, the plasma concentration of teneligliptin reached steady state by day 7 [23, 24]. The plasma concentrations up to 72 h after the first dose (single dosing) and up to 24 h after the last dose

(multiple dosing) were simulated, and the following PK parameters were calculated within the Simcyp Simulator: C_{max}, $AUC_{0-\infty}$, AUC_{0-24h}, time to C_{max} (t_{max}) and half-life ($t_{1/2}$). For the AUCs, C_{max} and $t_{1/2}$, we calculated the mean ratio for each age group relative to the youngest group. The characteristics and PK parameters of the subjects calculated by race and age group are summarized in Electronic Supplementary Material (ESM) Table S1.

Exploration of Factors Associated with Teneligliptin PK Parameters

Pearson's correlation coefficients between physiological factors (age, body weight, height, body surface area [BSA], brain weight, kidney weight, liver weight, body mass index [BMI], cardiac output, hematocrit, human serum albumin, α1-acid glycoprotein, serum creatinine, glomerular filtration rate [GFR], hepatic CYP3A4 content) and single-dose PK parameters ($AUC_{0-\infty}$ and C_{max}) were calculated using individual subject data, by race, to characterize the PK profiles of teneligliptin in the Japanese and European descent populations. According to Guilford's Rule of Thumb [35], we considered absolute correlation coefficients of < 0.20 as an "almost negligible relationship," 0.20–0.40 as a "low correlation," 0.40–0.70 as a "moderate correlation," 0.70–0.90 as a "high correlation" and > 0.90 as a "very high correlation."

Data Analysis

Microsoft Excel 2010 (Microsoft Corp., Redmond, WA, USA) was used to calculate the summary statistics and Pearson's correlation coefficients.

RESULTS

Revalidation of the PBPK Model in Japanese Subjects

The PK simulations of teneligliptin in virtual Japanese subjects, which included older subjects, were performed using the previously developed PBPK model, and the PK parameters (AUC_{0-24h}, C_{max}) were compared to those obtained in a Japanese clinical study (3000-A12 study). As shown in Table 1, the models replicated the clinical data acceptably. In the European descent population, the simulated PK parameters were also similar to the observed parameters (ESM Table S2). Additionally, the $AUC_{0-\infty}$ and C_{max} ratios between older subjects ($\geq$ 65 to < 75 years old) and subjects aged $\geq$ 45 to < 65 years were generally comparable between the observed and simulated data in the European descent population.

Age-Related Changes in the PK Profiles of Teneligliptin

The PK simulations of teneligliptin in virtual Japanese and European descent populations were performed using the previously reported PBPK model [33], and the PK parameters were calculated for each age group in 5-year steps (4-year steps from $\geq$ 90 to $\leq$ 98 years old).

As shown in Fig. 1, the mean $AUC_{0-\infty}$ tended to increase with age whereas no clear change was apparent for the mean C_{max} after a single dose of 20 mg teneligliptin in both the Japanese and European descent populations. In Japanese subjects aged $\geq$ 65 to $\leq$ 70 years, the mean

Table 1 Observed and simulated pharmacokinetic parameters in Japanese subjects

PK parameters	Observed [34][a]	Simulated[b]	Ratio (simulated/observed)
AUC_{0-24h} (ng·h/mL)	1625.1 (352.8)	2183.9 (1068.5)	1.34
C_{max} (ng/mL)	274.5 (57.4)	202.9 (137.9)	0.74

Data are mean (SD) unless otherwise stated

AUC_{0-24h} Area under the plasma concentration–time curve from 0 to 24 h, C_{max} maximum plasma concentration, *PK* pharmacokinetic, *SD* standard deviation

[a] Mean (SD) age: 57.1 (8.7) years [n = 33]

[b] Mean (SD) age: 56.2 (8.6) years [n = 320]

$AUC_{0-\infty}$ and C_{max} of teneligliptin were 1.35- and 1.04-fold the respective mean values in the youngest age group (≥ 20 to < 25 years old) as a reference (Table 2). In European descent subjects aged ≥ 65 to < 70 years, the mean $AUC_{0-\infty}$ and C_{max} were 1.30- and 0.95-fold the respective mean values in the youngest age group, similar to those in the Japanese population (Table 2). The mean $AUC_{0-\infty}$ and C_{max} in European descent subjects aged ≥ 70 years were 1.77- to 2.28-fold and 0.97- to 1.16-fold the respective mean values in the youngest age group (Table 2). The mean elimination half-life ($t_{1/2}$) in subjects aged ≥ 65 years tended to be longer than that in the youngest age group (Table 2; ESM Fig. S1a; ESM Table S1), and the mean t_{max} did not increase with age in the Japanese and European descent populations (ESM Fig. S1b; ESM Table S1).

After multiple doses of 20 mg teneligliptin per day for 7 days, the age-related change in mean AUC_{0-24h} was similar to that after a single dose of teneligliptin in both populations (ESM Fig. S2a; ESM Tables S1, S3). Although the mean C_{max} after multiple doses increased to a greater extent than the C_{max} after a single dose (ESM Fig. S2b; ESM Tables S1, S3), the age-related change in C_{max} was smaller than that in AUC_{0-24h} after multiple doses.

Correlation Between Physiological Factors and PK Parameters of Teneligliptin

We investigated which physiological factors were correlated with the PK parameters ($AUC_{0-\infty}$ and C_{max}) of teneligliptin in the Japanese and European descent populations in single-dose simulations. As shown in Fig. 2, there was a positive correlation between $AUC_{0-\infty}$ and age in both populations. The Pearson's correlation coefficient was 0.22 and 0.55 for Japanese subjects aged ≥ 20 to ≤ 70 years and European descent subjects aged ≥ 20 to ≤ 98 years, respectively (Fig. 2a). GFR, hepatic CYP3A4 content, liver weight,
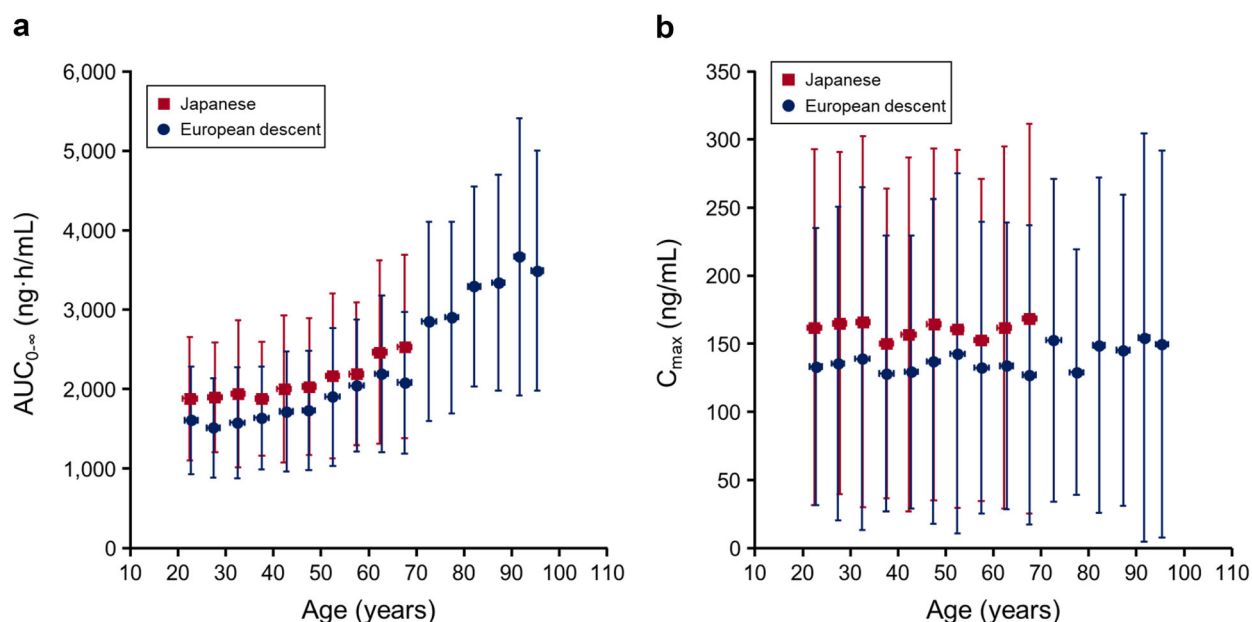

Fig. 1 Simulated pharmacokinetic (*PK*) parameters after a single dose of 20 mg teneligliptin in virtual Japanese and European descent populations. Age versus $AUC_{0-\infty}$ (**a**) and C_{max} (**b**). Values are shown as the mean $\pm$ standard deviation for age and both PK parameters in the Japanese (20–70 years; red-filled squares) and European descent (20–98 years; blue-filled circles) populations. Age was divided into 5-year categories (4-year categories for those aged ≥ 90 years). $AUC_{0-\infty}$ Area under the plasma concentration–time curve from 0 h to infinity, C_{max} maximum plasma concentration

Table 2 Ratio of pharmacokinetic parameters for each age group versus the youngest age group (≥ 20 to < 25 years) for a single dose of 20 mg teneligliptin in the virtual Japanese and European descent populations

Age group (years)	Single dose					
	Japanese			European descent		
	$AUC_{0-\infty}$	C_{max}	$t_{1/2}$	$AUC_{0-\infty}$	C_{max}	$t_{1/2}$
≥ 20 to < 25 (reference)	1.00	1.00	1.00	1.00	1.00	1.00
≥ 25 to < 30	1.01	1.02	0.98	0.94	1.02	1.04
≥ 30 to < 35	1.03	1.02	1.03	0.98	1.04	1.02
≥ 35 to < 40	1.00	0.93	1.03	1.02	0.96	1.07
≥ 40 to < 45	1.06	0.97	1.09	1.07	0.97	1.08
≥ 45 to < 50	1.08	1.01	1.06	1.08	1.03	1.16
≥ 50 to < 55	1.15	0.99	1.18	1.18	1.07	1.18
≥ 55 to < 60	1.16	0.94	1.16	1.27	0.99	1.27
≥ 60 to < 65	1.31	1.00	1.29	1.36	1.00	1.31
≥ 65 to < 70[a]	1.35	1.04	1.27	1.30	0.95	1.39
≥ 70 to < 75	N.A.	N.A.	N.A.	1.77	1.15	1.58
≥ 75 to < 80	N.A.	N.A.	N.A.	1.80	0.97	1.73
≥ 80 to < 85	N.A.	N.A.	N.A.	2.04	1.12	1.82
≥ 85 to < 90	N.A.	N.A.	N.A.	2.07	1.09	1.89
≥ 90 to < 94	N.A.	N.A.	N.A.	2.28	1.16	2.04
≥ 94 to ≤ 98	N.A.	N.A.	N.A.	2.17	1.12	1.97

$AUC_{0-\infty}$ Area under the plasma concentration–time curve from 0 h to infinity, C_{max} maximum plasma concentration, *N.A.* not available, $t_{1/2}$ elimination half-life

[a] ≥ 65 to ≤ 70 in Japanese subjects

cardiac output, BSA and body weight showed low to moderate negative correlations with $AUC_{0-\infty}$ in both populations (Fig. 2b–g). There was an almost negligible relationship between C_{max} and age in Japanese (correlation coefficient: 0.003) and European descent (correlation coefficient: 0.04) subjects.

Age-Related Changes in Physiological Factors

We also investigated the age-related changes in the four physiological factors (GFR, hepatic CYP3A4 content, liver weight and cardiac output) that showed moderate correlations with

$AUC_{0-\infty}$ in European descent subjects up to 98 years old. We found that GFR and cardiac output decreased with age in both populations (Fig. 3a, d; ESM Table S1). Hepatic CYP3A4 content and liver weight tended to decrease in subjects aged ≥ 40 years and ≥ 60 years, respectively (Fig. 3b, c; ESM Table S1).

DISCUSSION

Owing to the limited PK data for teneligliptin in older people, due to the difficulty of conducting clinical studies in this population, we simulated these data in the present study. The PBPK model
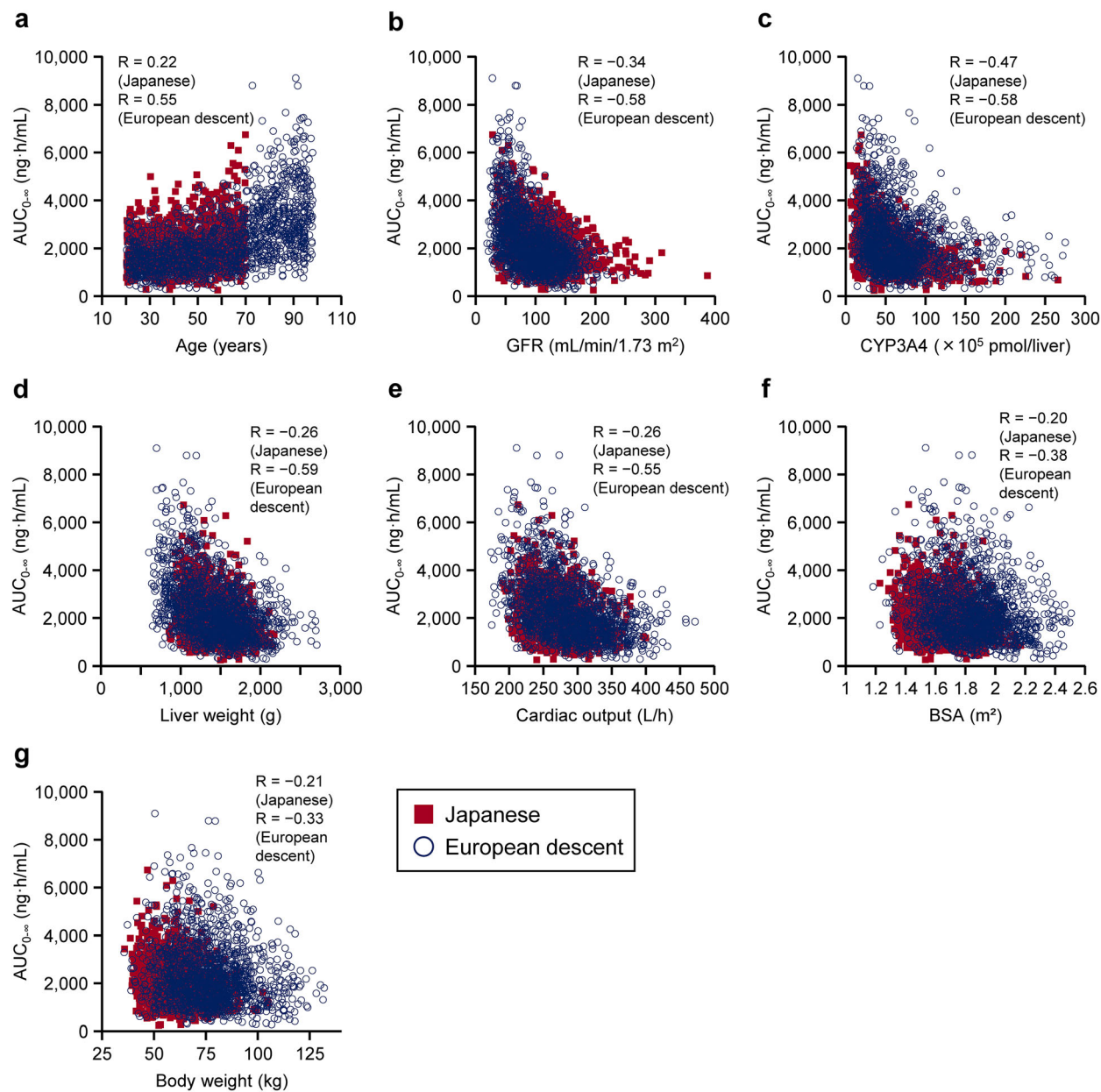
Fig. 2 Correlations between $AUC_{0-\infty}$ and physiological factors in virtual Japanese and European descent populations after a single dose of 20 mg teneligliptin. $AUC_{0-\infty}$ was plotted against age (**a**), GFR (**b**), hepatic CYP3A4 content (**c**), liver weight (**d**), cardiac output (**e**), BSA (**f**) and body weight (**g**) for individual virtual subjects aged 20–70 years (Japanese; red-filled squares) or 20–98 years (European descent; blue open circles). The Pearson's correlation coefficients (R) are provided on each graph. $AUC_{0-\infty}$ Area under the plasma concentration–time curve from 0 h to infinity, *BSA* body surface area, *CYP3A4* cytochrome P450 3A4, *GFR* glomerular filtration rate

for teneligliptin was revalidated using data from a clinical study in a Japanese population, including older subjects. We found that the AUC of teneligliptin after single or multiple doses tended to increase with age in the Japanese (aged ≥ 20 to ≤ 70 years) and European descent (aged ≥ 20 to ≤ 98 years) populations,

whereas C_{max} showed a relatively smaller change with age.

The AUC of teneligliptin increased to some extent with age. Teneligliptin is eliminated via renal excretion and hepatic metabolism by CYP3A4 and FMO3 [21, 22]. Four physiological factors (GFR, hepatic CYP3A4 content, liver weight and cardiac output) showed negative correlations with $AUC_{0-\infty}$ in our study, but all of the other factors investigated showed weaker correlations with $AUC_{0-\infty}$. As might be expected, these four physiological factors tended to decrease with age. Additionally, a decrease in cardiac output may affect hepatic metabolism and renal excretion through decreased blood flow. These age-related changes may contribute to a delayed metabolism and elimination of teneligliptin, contributing to the tendency for the AUC to increase with age.

In the present simulation, the $AUC_{0-\infty}$ for a single dose of 20 mg teneligliptin was 1.30- to 2.28-fold greater in subjects aged ≥ 65 years compared with the youngest age group (≥ 20 to < 25 years). By comparison, in a clinical trial of older European descent subjects (MP-513-E05 study), the $AUC_{0-\infty}$ of teneligliptin in older people (aged 65–75 years; mean age: 68.1 years) was 1.08-fold that of subjects aged 45–64 years (mean age: 59.4 years) (ESM Table S2). When we used simulated data for subjects aged ≥ 55 to < 60 years as a reference group (mean age 57.5 years, similar to the mean age of the 45–64 years old group in the MP-513-E05 study), the $AUC_{0-\infty}$ in subjects aged ≥ 65 years was 1.02- to 1.79-fold that of the reference group, and the ratio for the increase in $AUC_{0-\infty}$ in the MP-513-E05 study was within this range. The maximum ratio for the increase in $AUC_{0-\infty}$ in the current simulation is not numerically much different from that reported in clinical studies of people with renal or hepatic impairment that provided evidence that a dose adjustment was not required, in which $AUC_{0-\infty}$ increased by up to 1.7-fold [23, 24].

The ratio of the age-related change in C_{max} in the Japanese and European descent populations was smaller than that of the change in AUC. Teneligliptin is highly water soluble and is rapidly absorbed into the systemic circulation with a t_{max} of 1–2 h [21, 22, 36]. The elimination of teneligliptin is much slower than its absorption, with a $t_{1/2}$ of about 24 h, and its bioavailability is considered to be good [21, 22, 36]. The C_{max} of compounds with these physicochemical properties, such as teneligliptin, is susceptible to the process of absorption, but absorption is less affected by factors like aging. For these reasons, C_{max} may have shown smaller changes with age compared to AUC. The slightly greater C_{max} at steady state in older subjects than in younger subjects after multiple doses for 7 days may be due to the prolonged $t_{1/2}$ associated with aging.

No racial differences in the PK profiles of teneligliptin have been reported [22]. The age-related changes in the $AUC_{0-\infty}$ of teneligliptin and those in the physiological factors correlated with $AUC_{0-\infty}$ were similar between virtual Japanese and European descent subjects aged ≤ 70 years (see Figs. 1, 3). Epidemiological studies have reported that these physiological factors decline with age in both races, including those aged > 70 years [37–47]. Assuming that the rates of decline in these factors are similar in both races aged > 70 years, the age-related increase in AUC in Japanese subjects aged > 70 years could be similar to that in European descent subjects aged > 70 years.

DPP-4 inhibitors are commonly used in older people with diabetes in clinical practice. In a 3-year follow-up post-marketing surveillance of teneligliptin in Japan [48, 49], 43.0% ($n = 4596$) of patients were < 65 years old, 31.5% ($n = 3371$) were aged ≥ 65 to < 75 years and 25.5% ($n = 2729$) were aged ≥ 75 years [49]. In that real-world surveillance, the incidence of adverse drug reactions (ADRs) was not dependent on age, with a frequency of 3.4%, 4.4% and 4.0% in patients aged < 65, ≥ 65 to < 75 and ≥ 75 years, respectively. Furthermore, there were no additional safety concerns among older patients that had not been described in the package insert. However, the incidence of serious ADRs in that surveillance tended to increase with age (0.7%, 1.2% and 1.7% in patients aged < 65, ≥ 65 to < 75 and ≥ 75 years, respectively) [49]. The mean age of those age groups was 53.9, 69.3 and 80.2 years, respectively, which corresponded to the age groups of ≥ 50 to < 55, ≥ 65 to < 70 and ≥ 80
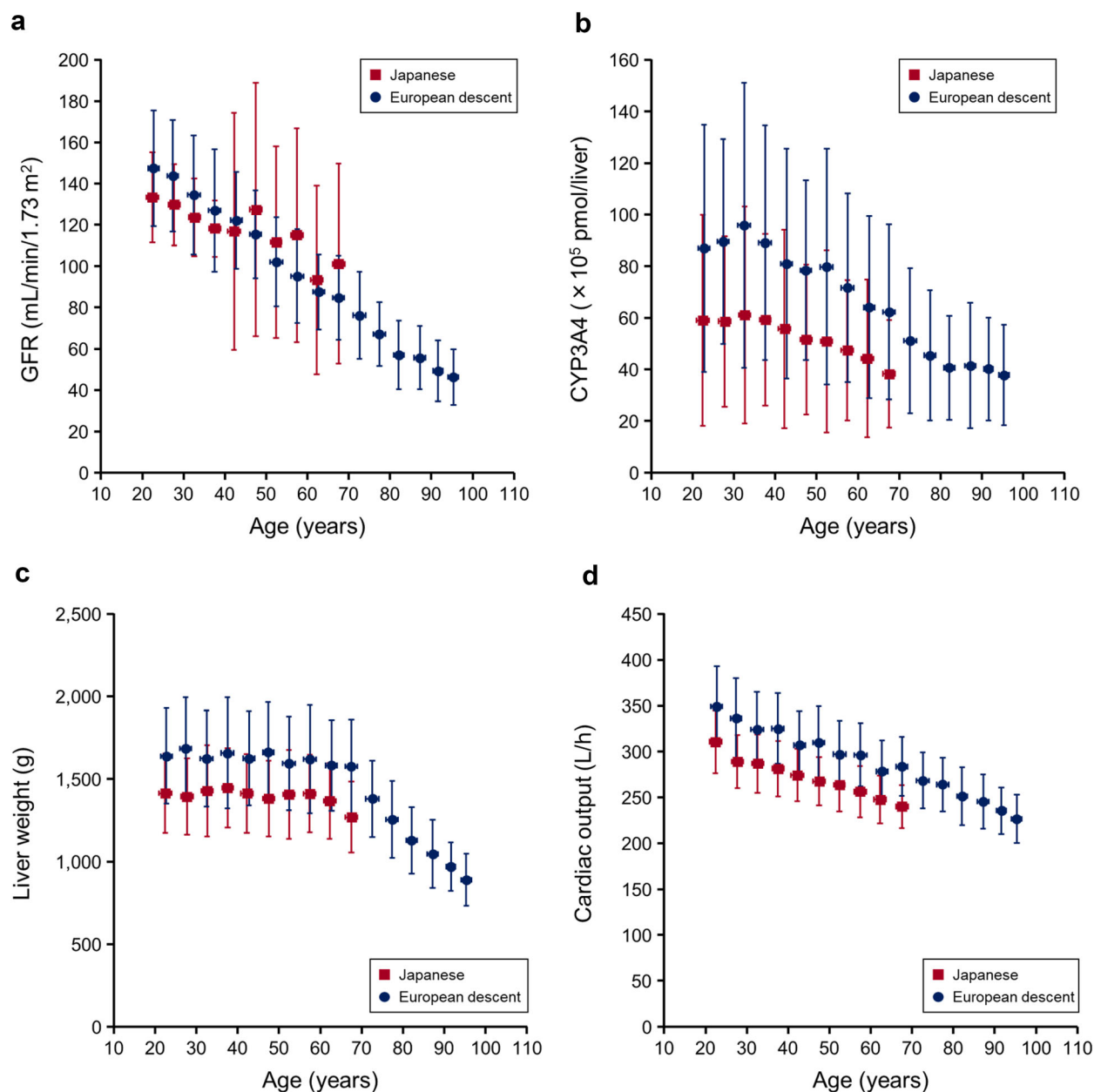
Fig. 3 Age-related changes in the physiological factors correlated with AUC in the virtual populations. Age versus GFR (**a**), hepatic CYP3A4 content (**b**), liver weight (**c**) and cardiac output (**d**). Values are shown as the mean ± standard deviation for age and each physiological factor in Japanese (20–70 years old; red-filled squares) and European descent populations (20–98 years old; blue-filled circles). Age was divided into 5-year categories (4-year categories for subjects aged ≥ 90 years). *AUC* Area under the plasma concentration-time curve, *CYP3A4* cytochrome P450 3A4, *GFR* glomerular filtration rate

to < 85 years, respectively, in this simulation. Using the $AUC_{0-\infty}$ of teneligliptin for patients aged ≥ 50 to < 55 years as the reference, the AUC was 1.09- and 1.73-fold greater in patients aged ≥ 65 to < 70 years and patients aged ≥ 80 to < 85 years, respectively, although these were simulated using the virtual European descent population. However, the relationship between

the increase in AUC and the incidence of serious ADRs remains unclear because older patients are generally at increased risk of serious ADRs due to renal/hepatic impairment or the presence of comorbidities and the need for polypharmacy [50].

The present study has some limitations. First, this study was conducted using general populations because a virtual population with diabetes has not been established for use in PK simulations. Because the PK profiles of teneligliptin in people with T2D have been found to be similar to those in healthy individuals in clinical studies [22, 23], we believe that this limitation is relatively minor. Second, this simulation does not consider enzyme-specific information regarding FMO3, such as enzyme abundance, variability and age-related changes. In this teneligliptin model, we included human liver microsomal clearance, which reflects age-related changes in liver microsomes, as a clearance by FMO3 [33]. It has been reported that FMO activity peaks in subjects in their twenties, but it does not change significantly in subjects in their thirties to seventies [51], which differs from human liver microsomal activity. Accordingly, the increase in the AUC of teneligliptin in older subjects may be overestimated by including liver microsomal clearance in the simulation. Finally, the PK profiles of teneligliptin in the Japanese population were simulated only up to the age of 70 years. Because there is insufficient comparative information on the age-related changes in physiological functions between the Japanese and European descent populations, we cannot confirm that the age-related changes in PK in Japanese subjects aged $\geq$ 70 years are similar to those in European descent subjects.

In conclusion, this simulation using a PBPK model showed a tendency for the AUC of teneligliptin to increase with age, whereas the C_{max} is less affected by age than AUC. The factors investigated in this study, other than the physiological factors related to the elimination of teneligliptin, such as renal and hepatic factors, seem unlikely to be associated with the increase in AUC in virtual Japanese and European descent populations. Older patients are highly diverse and individualized treatment is

important. Since an increased plasma concentration of a drug may lead to adverse events, careful administration is necessary when treating patients with characteristics in which drug exposure is likely to increase.

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Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflicts of Interest. Hiroaki Iijima, Hidetoshi Shimizu, Kazumi Mori-Anai, Atsuhiro Kawaguchi, and Yoji Mochida are employees of Mitsubishi Tanabe Pharma Corporation. Toshimasa Yamauchi has received research grants from AstraZeneca K.K., Kowa Company Ltd.,

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