Application of Physiologically Based Pharmacokinetic Modeling to Predict Pharmacokinetics in Healthy Japanese Subjects

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Pharmacokinetics (PKs) in Japanese healthy subjects were simulated for nine compounds using physiologically based PK (PBPK) models parameterized with physicochemical properties, preclinical absorption, distribution, metabolism, and excretion (ADME) data, and clinical PK data from non-Japanese subjects. For each dosing regimen, 100 virtual trials were simulated and predicted/observed ratios for peak plasma concentration (C_{max}) and area under the curve (AUC) were calculated. As qualification criteria, it was prespecified that >80% of simulated trials should demonstrate ratios to observed data ranging from 0.5–2.0. Across all compounds and dose regimens studied, 93% of simulated C_{max} values in Japanese subjects fulfilled the criteria. Similarly, for AUC, 77% of single-dosing regimens and 100% of multiple-dosing regimens fulfilled the criteria. In summary, mechanistically incorporating the appropriate ADME properties into PBPK models, followed by qualification using non-Japanese clinical data, can predict PKs in the Japanese population and lead to efficient trial design and conduct of Japanese phase I studies.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ It has been widely recognized in the field of drug development that qualified physiologically based pharmacokinetic (PBPK) models can help predict PKs for unknown scenarios (e.g., drug–drug interactions, hepatic or renal impairment, and targeted ethnic populations) with accuracy.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ This study evaluated the ability of qualified PBPK models, on the basis of non-Japanese PKs, for predicting PKs in the Japanese population.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ PBPK models incorporating key absorption, distribution, metabolism, and excretion data along with renal and metabolic elimination pathways and PKs in non-Japanese subjects can accurately predict PKs in the Japanese population.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ This study suggests that PBPK modeling can provide reliable PK data in different populations and races, and this can enable streamlining and accelerating drug development and help mitigating risks of enrolling Japanese subjects in global phase II or III trials.

The pharmaceutical industry is continually striving to optimize and accelerate drug development to improve productivity in a competitive environment. Regulatory agencies, such as the Pharmaceutical and Medical Devices Agency, are also making an active effort to shorten the "drug lag."[1–3] Physiologically based pharmacokinetic (PBPK) modeling and simulation approaches can offer PK profiles in untested populations, such as children, pregnant women, and patients with renal and hepatic impairment.[4] PBPK models are also frequently used to predict unstudied drug–drug interactions (DDIs). The results of such simulations have recently been included in drug labels.[5,6] PBPK approaches are thus being recognized as important tools, allowing the integration

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of clinical and nonclinical knowledge and data; and they can offer robust prediction of PKs of drugs, thus providing more efficient and effective drug development and review processes for both industry and regulatory authorities.[6–13]

The safety profile of new molecular entities in a Japanese population is a major concern during the early phase of drug development.[14–17] In 2014, the Ministry of Health, Labor and Welfare (MHLW) in Japan issued a guideline requiring sponsors to conduct phase I clinical trials in Japanese subjects before participation in the global clinical development if, at the point of initiating the global phase II or III trial, tolerability in humans has not been sufficiently confirmed or the safety risk is thought to be high in the Japanese population.[14,15] If the safety risk of a compound is poorly evaluated, it can lead to a delay in the ability of Japanese patients to enter global clinical trials, which may limit the number of Japanese subjects in pivotal trials, leading to a less robust ethnic sensitivity analysis (e.g., Japanese vs. non-Japanese comparison).

In phase I trials, the primary objective of a study is generally to assess the safety profile, which is often driven by the exposure to the compound of interest. Because exposure in the Japanese population is generally unknown before initiation of a Japanese phase I study, PBPK models can provide an opportunity to predict PKs in the unstudied Japanese population by simulating various clinical scenarios.[16–18] In fact, PBPK simulation results for the anti–hepatitis C viral agents, elbasvir and grazoprevir, were included in the Common Technical Documents for these products to demonstrate bridging of the PK profile from non-Japanese to Japanese subjects and from healthy subjects to patients.[19,20] Physiological models for various populations, such as European white, Chinese, and Japanese, are commercially available in PBPK platforms (e.g., SimCYP and Gastroplus). In these population models, known interethnic physiological differences in height and weight distribution, liver volume, enzyme abundances (in particular for cytochrome P450s (CYPs) 3A4, 2C19, 2D6, and 2J2, and uridine diphosphate–glucuronosyltransferases (UGTs) 1A1, 1A9, and 2B7), and phenotypes have been incorporated on the basis of literature data.[20–23] In addition, differences in other physiological parameters, such as gastrointestinal transit times and plasma protein composition, are also considered.[24,25] By using these population characteristics as an integral part of a PBPK model, the model can predict the PKs of drugs in various populations.

Thus, the authors believe that PBPK modeling can inform appropriate study design for a Japanese phase I study. Furthermore, in situations in which there are no major safety concerns in the populations studied, PBPK analyses can streamline drug development by predicting PKs and confirming exposure in Japanese subjects. In such situations, the prediction results can be evaluated with the plasma concentration data through sparse sampling in Japanese subjects in a phase II study.

In the current study, nine compounds from the MSD Research Laboratories (MRL) development pipeline were retrospectively evaluated for predictability of exposure (area under the concentration-time curve from time 0 to infinity (AUC0-inf), area under the concentration-time curve from time 0 to the last time point, and peak plasma concentration (C_{max})) in Japanese subjects using PBPK models built with physicochemical, *in vitro*, and preclinical absorption, distribution, metabolism, and excretion (ADME) data and PK data from non-Japanese phase I trials.

RESULTS

PBPK modeling using non-Japanese data

For eight of the nine compounds, the mean simulated concentration–time profiles in the non-Japanese population closely followed the observed profiles after single- and multiple-dose administration. In addition, the 95% confidence intervals generally contained most of the observed data points (**Figure 1**, **Figure S1**).

The predicted PK parameters at the clinically therapeutic doses for each compound were, in most cases, comparable with the observed values (**Table 1**). Of 64 dosing regimens included in this analysis (41 single-dose and 23 multiple-dose regimens; **Table S1**) in the non-Japanese populations, only three regimens from two compounds (compounds A and F) demonstrated >20% prediction errors for C_{max} outside the 2.0-fold range and were, therefore, grouped into category 3, where the prediction error was <0.5 or >2.0. For AUC_{0-t}, one regimen of one compound (compound I) gave >20% prediction error outside the 2.0-fold range, resulting in a category 3 designation.

Table 1 C_{max} and AUC ratios after single oral and intravenous administration to non-Japanese and Japanese healthy subjects at the clinical dose

		Non-Japanese subjects		Japanese subjects	
Compound	Dose	C_{max} ratio[a]	AUC ratio[a]	C_{max} ratio[a]	AUC ratio[a]
A	10 mg	0.846	0.933	0.930	1.09
B	2 mg	1.37	1.26	1.63	1.50
C	160 mg	1.05	1.14	1.08	1.00
D	400 mg	1.01	0.957	0.722	0.926
E	100 mg	0.699	1.10	0.808	1.41
F	100 mg	1.02	0.805	0.955	0.835
G	8 mg/kg	Not applicable[b]	1.07	Not applicable[b]	1.03
H	20 mg	0.698	1.02	1.12	2.71
I	150 mg	0.703	1.43	0.582	1.47

AUC, area under the curve; C_{max}, peak plasma concentration.
[a]C_{max} or AUC ratios are the ratios of predicted values/observed values. [b]C_{max} ratio for compound G is not applicable because this compound is intravenously administered.

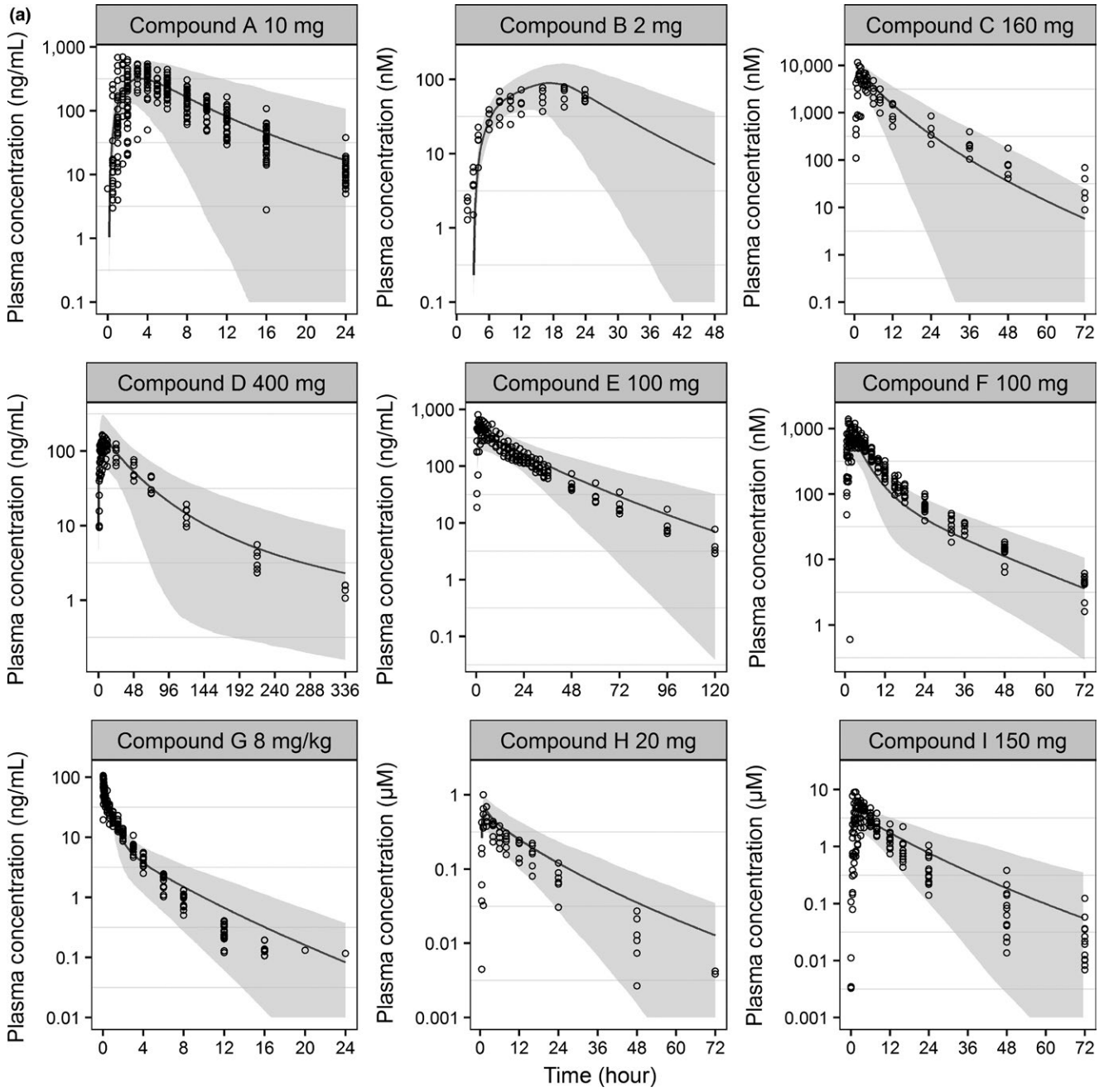

Figure 1 Simulated concentration–time curves overlaid with actual observed plasma concentrations of each compound at clinical dosage or expected clinical dosage in non-Japanese subjects. (**a**) After single-dose administration. (**b**) After repeated-dose administration. The solid line and shaded area represent predicted mean plasma concentration and its 95% confidence intervals, respectively. The open symbols represent the observed plasma concentration in each individual subject from actual clinical trials.

For compound I, the model was not fully qualified because it was unable to describe the kinetics in the non-Japanese population at lower dose levels in phase I. The model had predictive value for doses from 150–800 mg; thus, the simulations in Japanese populations were run only within this dose range.

Japanese PK simulation

After model qualification, simulations were conducted for a total of 49 dosing regimens (34 single-dose and 15 multiple-dose regimens) in the Japanese population. For all compounds except compound H, the 95% confidence intervals of the simulated concentration–time curves in Japanese subjects contained the observed concentration data after single and repeated dosing (**Figure 2**, **Figure S2**, **Table S2**). On the basis of the terminal slopes in the concentration–time profile of compounds H and I, the simulations appeared to project a lower rate of elimination compared with the observed data. This resulted in overestimating the predicted mean AUC_{0-inf} values for compounds H and I by 2.7- and 1.5-fold, respectively

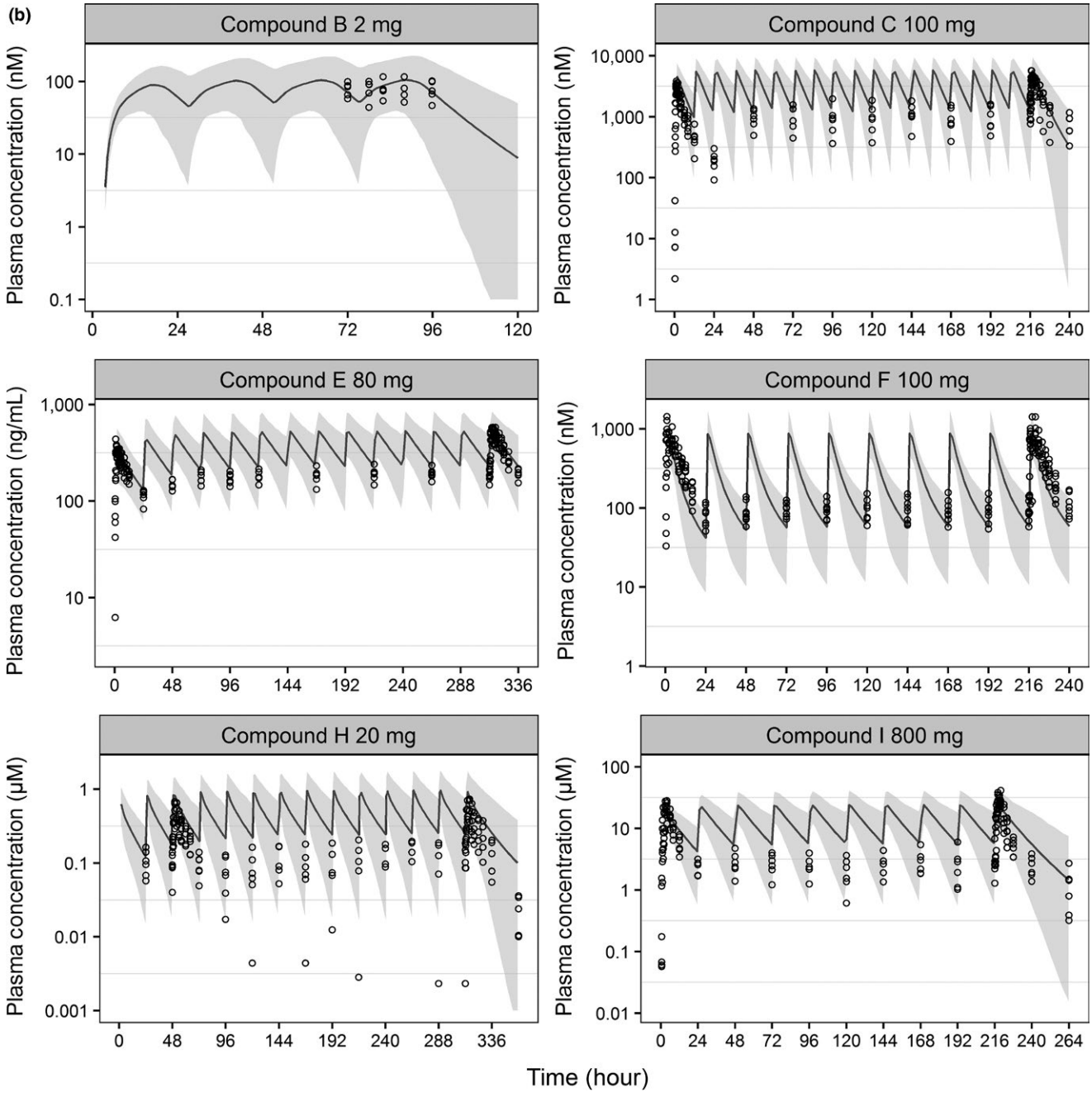

Figure 1 continued

(**Table 1**). Interestingly, a trend of overestimating the half-lives was not apparent in the non-Japanese population, because the predicted mean half-lives for compounds H and I in this population were 1.1- and 0.7-fold of the observed half-lives, respectively. For the other seven compounds, mean concentration–time curves were generally consistent with observed profiles, and the predicted PK parameters at the clinical dosage were similar to those observed in the clinical studies (**Table 1**).

With respect to predicting C_{max} (**Figure 3a**), in the case of compound A, the prediction errors in the single-dose regimens were evenly distributed around a value of 1.0, whereas in the multiple-dosing regimen, they were distributed around 0.8 (**Figure 3**). For compound B, >97% of prediction errors were distributed between 1.25 and 2.0 across the dose range, and fell into category 1 (prediction error, 0.8–1.25) or 2 (prediction error, 0.5–2.0), with a slight trend of overprediction. The prediction errors for compounds D and F tended to be larger at a lower dose and decreased in a dose-dependent manner, whereas the prediction errors for compounds C and H appeared to increase with a higher dose. For compound E, the prediction errors were distributed around 0.8 (or below) in four of five single-dose regimens, and >1.0 in the multiple-dose regimens. For compound I, C_{max} appeared to be underpredicted across the dose range, with the prediction error ranging between 0.5 and 0.8 for 150-mg single dose and 800-mg

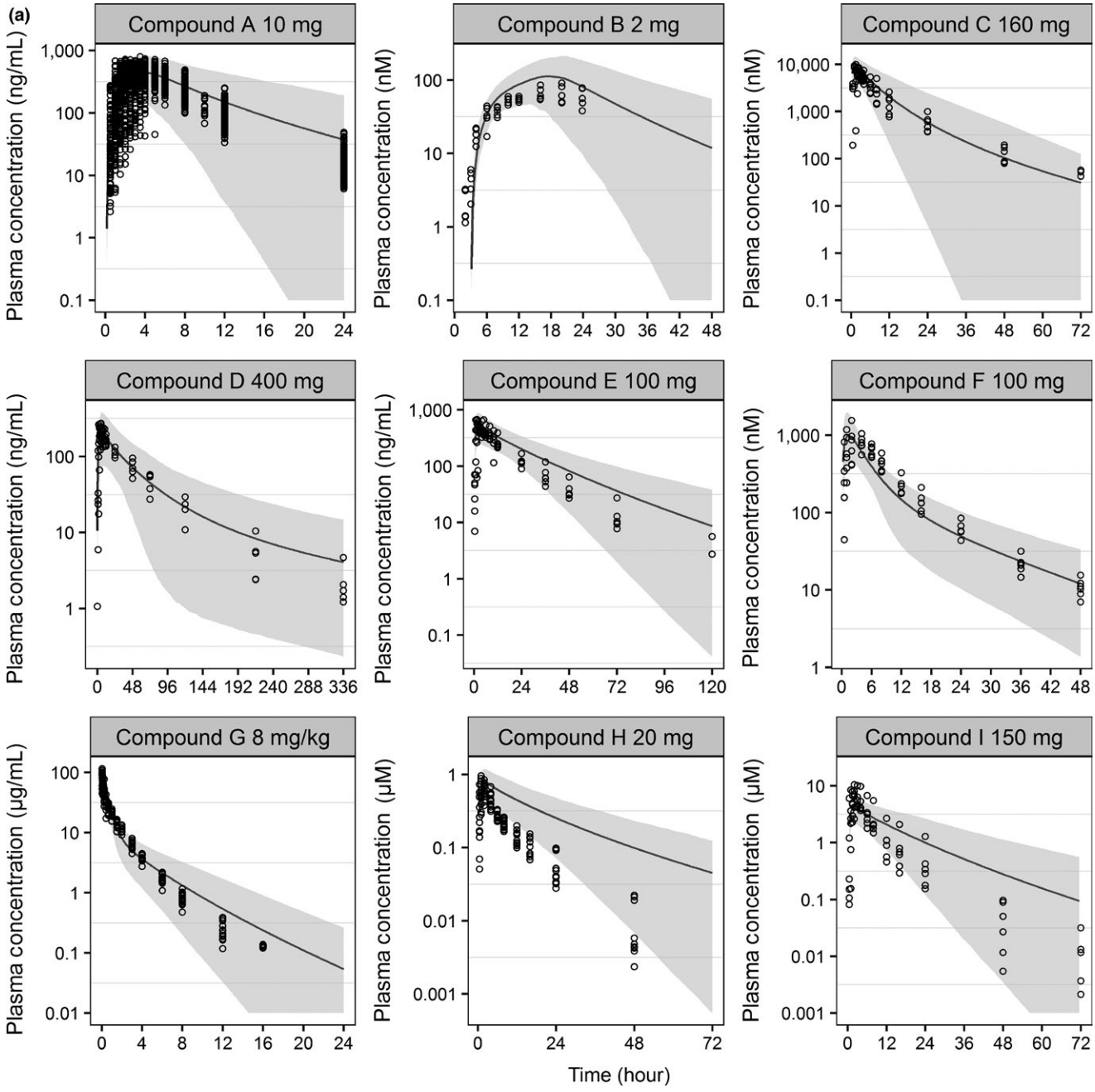

Figure 2 Simulated concentration–time curves overlaid with actual observed plasma concentrations of each compound at clinical dosage or expected clinical dosage in Japanese subjects. (**a**) After single-dose administration. (**b**) After repeated-dose administration. The solid line and shaded area represent predicted mean plasma concentration and its 95% confidence intervals, respectively. The open symbols represent the observed plasma concentration in each individual subject from actual clinical trials.

multiple dose and <0.5 for 800-mg single dose. C_{max} for compound G was not applicable because this compound is intravenously administered.

For the parameters AUC_{0-inf} and AUC_{0-t} (**Figure 3b,c**), an even distribution of prediction errors around 1.0 was observed for all compounds, except compounds E, H, and I. For compound E, the prediction errors were distributed between 1.0 and 2.0 across the dose range. Most (50–100%) of prediction errors for compound H were >2.0 across the entire dose range. For compound I, only two dosing regimens were simulated (150-mg single dose and 800-mg multiple dose). At these dose levels, the prediction errors were distributed between 0.8 and 2.0.

On the basis of these findings, the prediction errors for C_{max} and AUC_{0-inf} for compounds C, H, and I in some dosing regimens were grouped into category 3 (**Figure 3a,c**). For compound C, in two of seven dosing regimens, >95% of prediction errors for C_{max} were classified into category 3. However, for the same compound, >90% of AUC_{0-inf} and AUC_{0-t} predictions were successful, and were grouped into either category 1 or 2. For compound H, in six dosing regimens, >90% of prediction errors for C_{max} were within

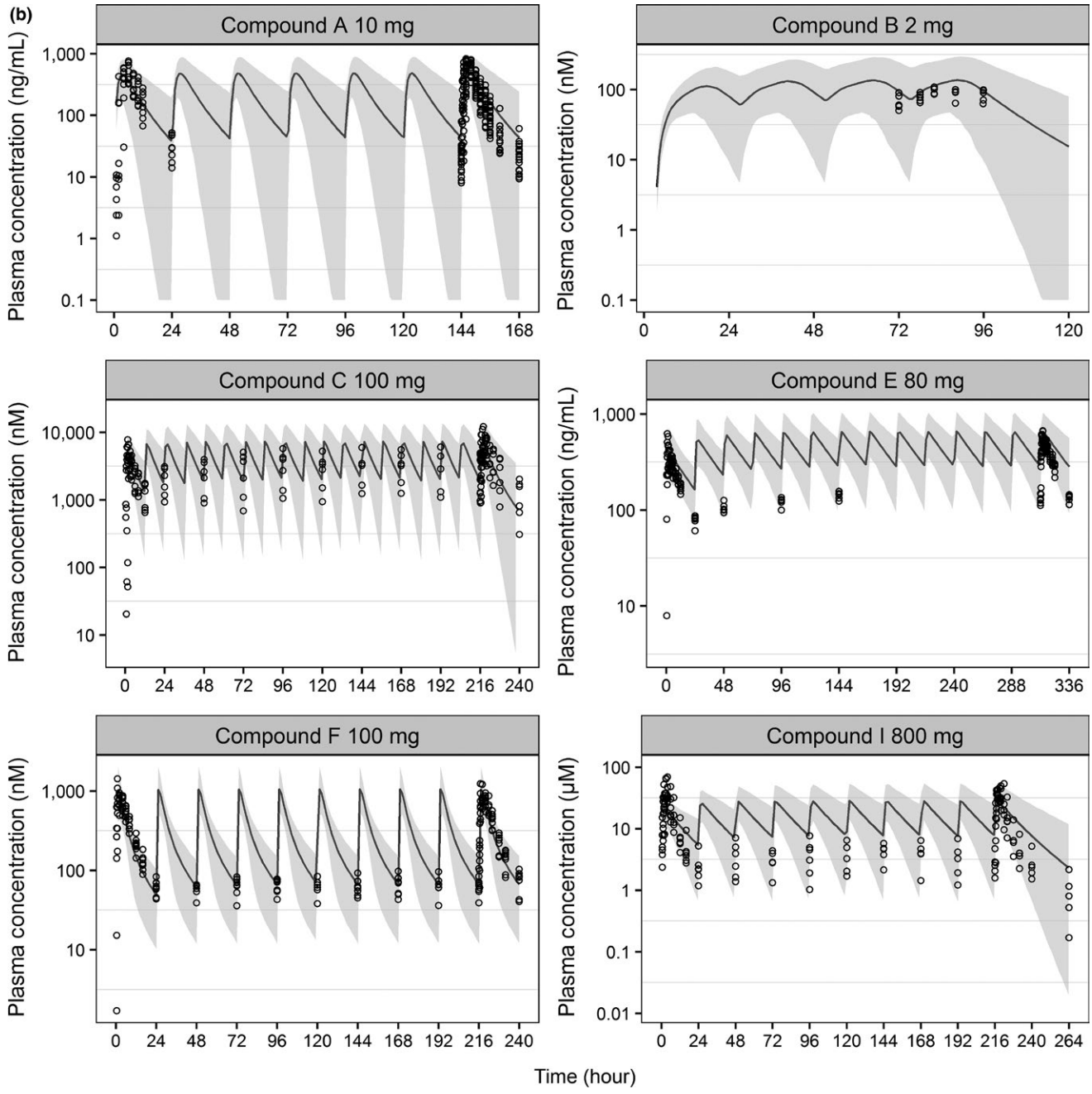

Figure 2 continued

0.5- to 2.0-fold, whereas the prediction errors for AUC_{0-inf} were outside the 2.0-fold range. For compound I, in three dosing regimens (two single-dose and one multiple-dose regimen), C_{max} at the highest dose was in category 3.

For compounds other than the three aforementioned, >80% of predictions for both C_{max} and AUC were deemed successful.

DISCUSSION

In this study, PBPK models were built using nonclinical ADME and phase I PKs in non-Japanese subjects for nine compounds. The models were qualified using clinical PK data from non-Japanese subjects, and then used to simulate PK profiles in the Japanese population. The predictive performance was then assessed for each model.

Biotransformation by CYP or UGT enzymes was the major elimination pathway for seven of these compounds. The PBPK models were parameterized with the fraction of metabolism (f_m) via each enzyme, using *in vitro* and *in vivo* preclinical ADME and clinical data (**Table 2**). Integrating the preclinical ADME data, both *in vitro* and *in vivo*, allows the models to be parameterized in a mechanistic manner, quantitatively incorporating the appropriate elimination pathways. The models for compounds F and G incorporated elimination via the kidney, using total and renal clearance data obtained from non-Japanese studies (**Table 2**). Each model was built

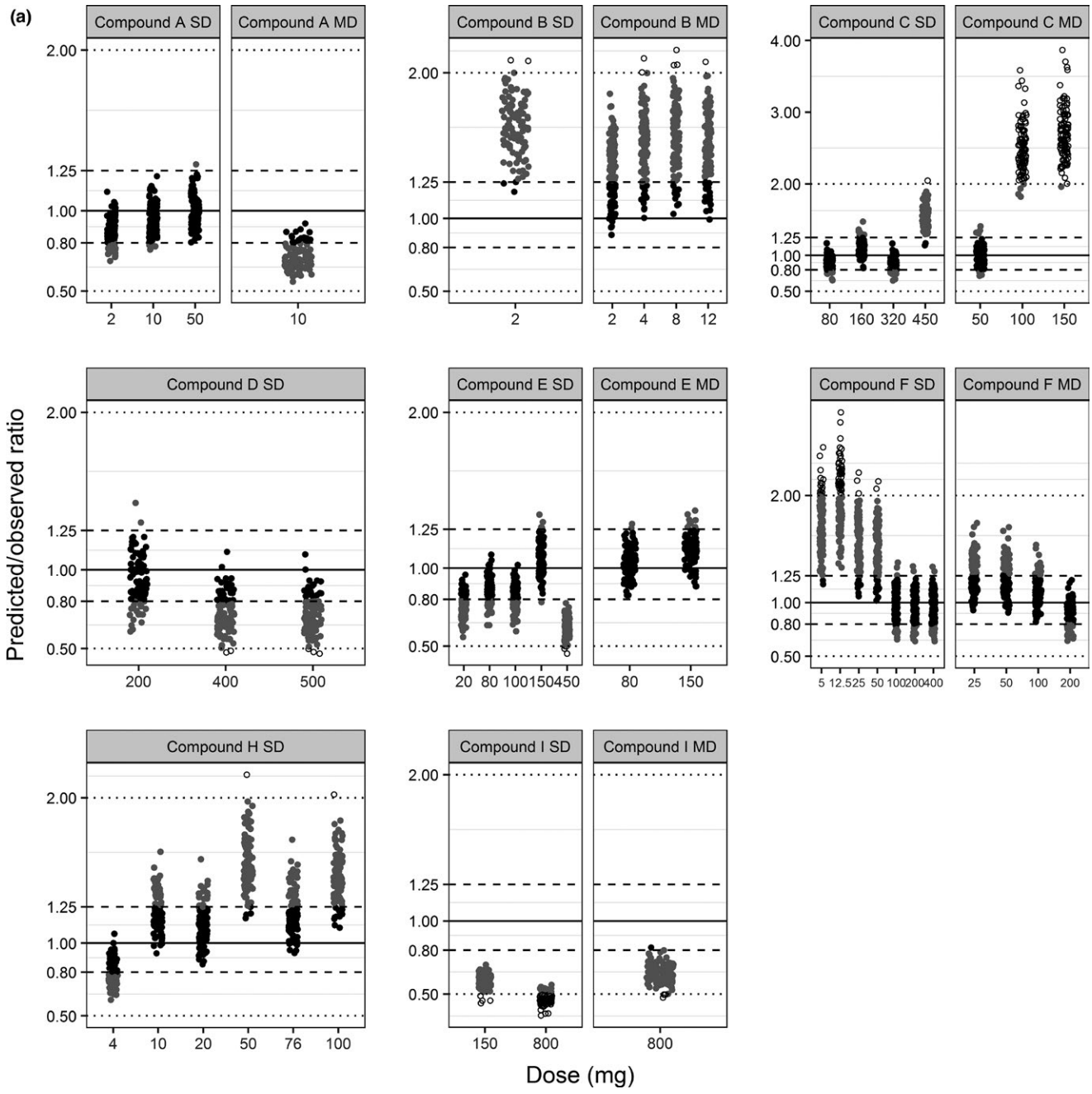

Figure 3 Distribution of prediction errors for C_{max}, AUC_{0-inf}, and AUC_{0-t} for each compound in each dosing regimen in a Japanese population. (**a**) C_{max} after SD and MD administration. (**b**) AUC_{0-inf} after SD administration. (**c**) AUC_{0-t} after MD administration. Solid line and dotted lines represent prediction errors of 1.0, and 0.5, 0.8, 1.25, and 2.0, respectively. Prediction errors = $X_{predicted}/X_{observed}$, where $X_{predicted}$ and $X_{observed}$ are the simulated and observed geometric mean C_{max} or AUC values for each clinical trial. Black, gray, and white symbols demonstrate prediction errors categorized as category 1 (prediction error, 0.8–1.25), category 2 (prediction error, 0.5–2.0), and category 3 (prediction error, <0.5 or >2.0), respectively. AUC_{0-inf} area under the concentration-time curve from time 0 to infinity, AUC_{0-t} area under the concentration-time curve from time 0 to the last time point, C_{max}, peak plasma concentration; MD, multiple dose; SD, single dose.

and qualified in the non-Japanese population (Healthy Volunteer's Population in SimCYP) and then used to predict PKs in the Japanese population. SimCYP's Japanese population incorporates known physiological ethnic differences in enzyme abundance, liver size, glomerular filtration rate, and allele frequency for poor metabolizers vs. extensive metabolizers (EMs) for CYP enzymes.

Visually, the predicted mean concentration–time curves were able to describe the central tendency of the observed concentrations. The 95% confidence intervals of the simulated concentration–time curves generally contained the actual observed drug concentrations (**Figures 1 and 2**). In the non-Japanese population, 93.8%, 98.0%, and 96.6% of simulated C_{max}, AUC_{0-inf}, and AUC_{0-last} values,

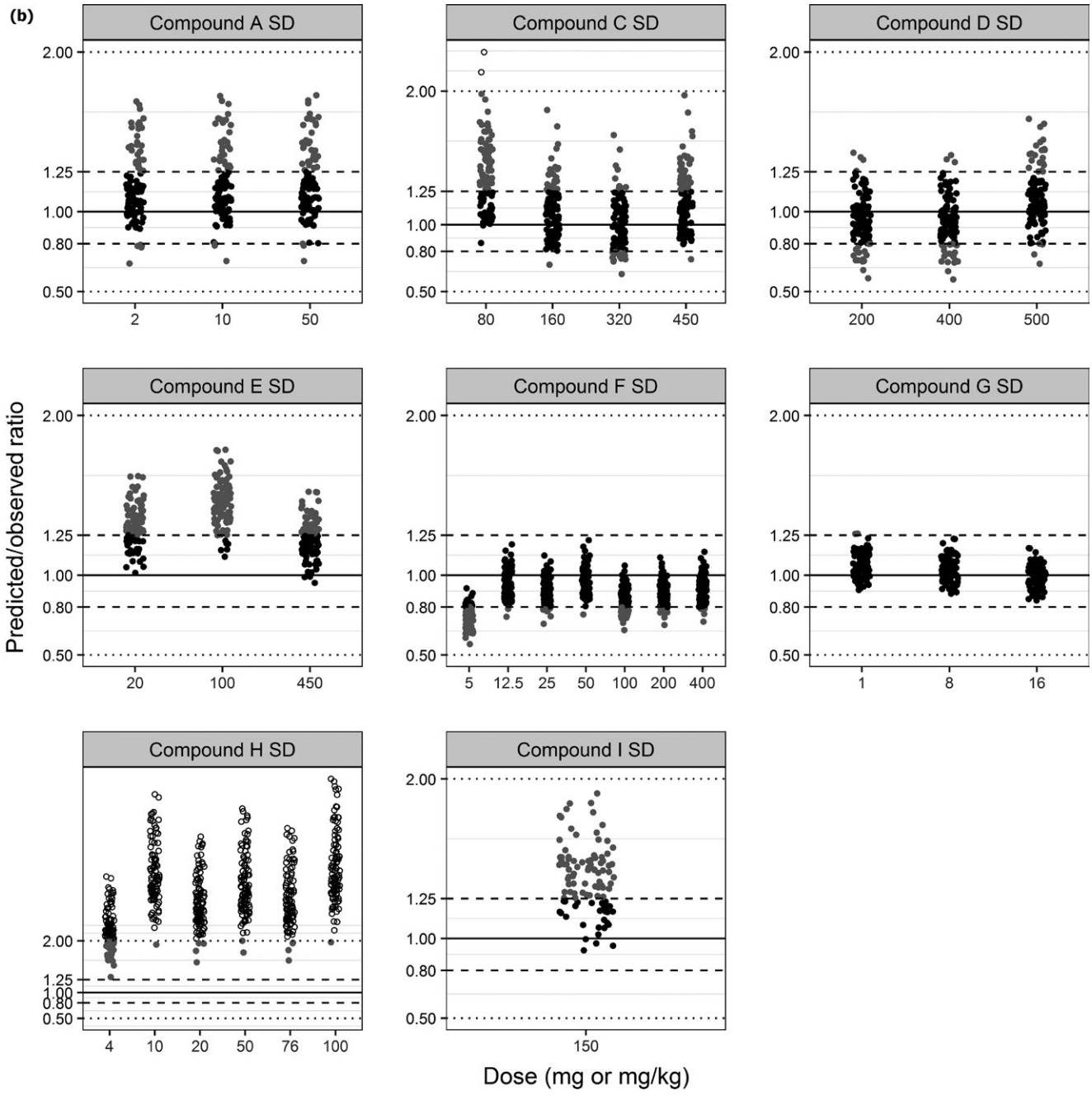

Figure 3 continued

respectively, from 1,000 individual virtual subjects were within 2.0-fold range of observed values, demonstrating that the PBPK models were, in general, sufficiently qualified. The metrics used for qualification of a given compound should be based on the known safety and efficacy profile of a compound. For example, if a compound has shown to be safe over the studied dose range in non-Japanese subjects, then a twofold qualification criterion may be appropriate. However, if a compound has a safety issue observed in early phase I studies, the qualification criterion may need to be more stringent.

When the PBPK models were used to simulate the PKs in the Japanese population, 87% of the simulations were categorized into categories 1 and 2, suggesting the predicted C_{max} and AUC values were comparable to observed values. It was prespecified that if >80% of simulations indicated prediction errors in category 1 or 2, the simulation of the trial was considered successful. For C_{max}, in 43 of 46 dosing regimens, >80% of simulations were categorized into category 1 or 2. For AUC_{0-inf}, 23 of 30 single-dosing regimens were successful. In multiple-dosing regimens, the AUC_{0-t} for all compounds was successfully predicted. Overall, this retrospective analysis demonstrated that Japanese PKs can be accurately predicted using qualified PBPK models.

For C_{max}, across 46 dosing regimens, >20% of the predictions were placed into category 3 (**Figure 3**). These regimens were generally at the lowest or highest dosages, whereas the rest of the

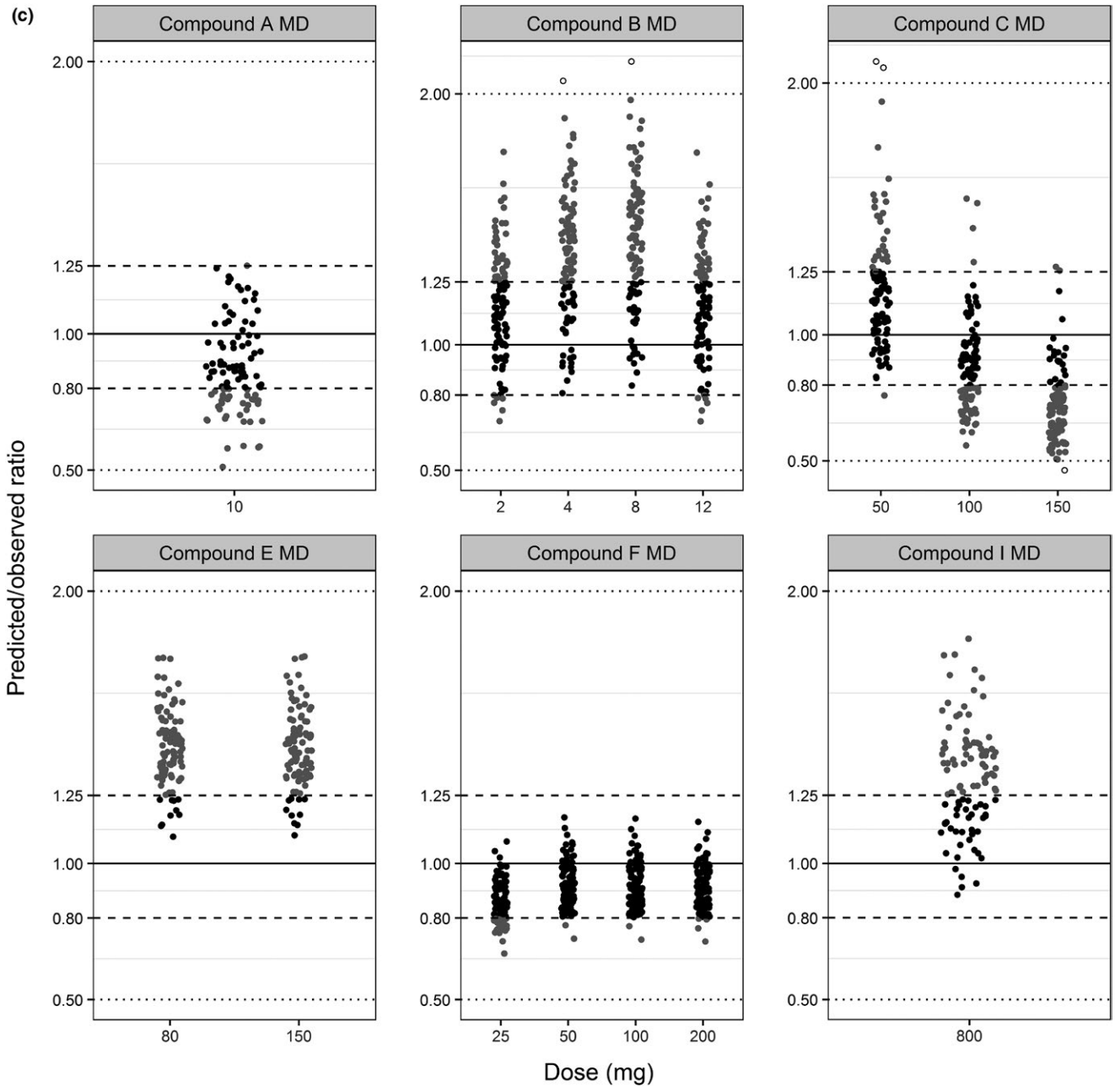

Figure 3 continued

46 regimens, including target therapeutic clinical dosage, were grouped into categories 1 or 2. For AUC_{0-inf}, >70% of the simulations for all six regimens of compound H and one of two regimens at a lower dosage for compound I were overpredicted, with errors of >2.0-fold (**Figure 3**).

For compound H, no difference in PKs was observed between Japanese and non-Japanese subjects in clinical studies, yet PBPK modeling predicted a 2.9-fold higher AUC_{0-inf} and 1.7-fold longer half-life in the Japanese population. On the basis of *in vitro* CYP phenotyping and clinical absorption, metabolism, and excretion data, compound H is predominately cleared by CYP3A-mediated metabolism, with a minor contribution from CYP2C19. In addition to being qualified with non-Japanese PK data, the model was able to capture the observed AUC_{0-inf} and C_{max} when coadministered with ketoconazole, a potent CYP3A inhibitor (data not shown). This adds confidence that the CYP3A f_m is correctly specified in the model ($f_m = 0.7$), leaving the remainder of the f_m assigned to CYP2C19 ($f_m = 0.3$). CYP2C19 is a polymorphic enzyme with reduced activity in poor metabolizers. In SimCYP, this is accounted for with a higher frequency of poor metabolizers in the Japanese population (18%) vs. the white population (2.4%) and a 14-fold lower abundance of CYP2C19 in Japanese EMs compared with white EMs. It is possible that the overpredicted exposure and half-life for compound H is attributable to an overestimated f_m of

Table 2 Major elimination route, key characteristics, and dosing regimen in Japanese healthy subjects for each compound

Compound	Physicochemical properties	Major elimination route	Dosing regimen in Japanese healthy subjects	SimCYP models used
Compound A	MW: 500–600; log P: >5 Diprotic acid, p*K*a 2.7, 5.8 P_{eff}: 0.69×10^{-4} cm/second Solubility: 0.2 μg/mL f_u: 0.005	CYP2C8 metabolism with CYP2C9, CYP3A4, and CYP3A5 as minor route	Dosing route: oral SD: 2, 10, and 50 mg MD: 10 mg q.d. for 7 days	Absorption: ADAM Distribution: minimal PBPK Elimination: enzyme kinetics (CYP2C8, CYP2C9, CYP3A4, and CYP3A5)
Compound B	MW: 300–400; log P: <5 Monoprotic base, p*K*a 5.7 P_{eff}: $1–10 \times 10^{-4}$ cm/second Solubility: 3.3 mg/mL in stomach and 0.14 mg/mL in each intestinal segment f_u: 0.038	CYP3A4 metabolism with CYP2C9 as minor route	Dosing route: oral SD: 2 mg MD: 2, 4, 8, and 12 mg q.d. for 4 days	Absorption: ADAM Distribution: full PBPK Elimination: enzyme kinetics
Compound C	MW: 500–600; log P: <5 Ampholyte, p*K*a 5.0, 3.0 P_{eff}: not applicable Solubility: not applicable f_u: 0.021	UGT1A3 metabolism	Dosing route: oral SD: 80, 160, 320, and 450 mg MD: 50 and 100 mg b.i.d. for 10 days	Absorption: first order Distribution: minimal PBPK Elimination: enzyme kinetics (UGT1A3)
Compound D	MW: 400–500; log P: <5 Neutral P_{eff}: not applicable Solubility: not applicable f_u: 0.080	CYP3A4 metabolism	Dosing route: oral SD: 200, 400, and 500 mg MD: not conducted	Absorption: first order Distribution: minimal PBPK Elimination: enzyme kinetics (CYP3A4 and CYP3A5)
Compound E	MW: 400–500; log P: <5 Monoprotic base, p*K*a 7.6 P_{eff}: 2.65×10^{-4} cm/second Solubility: 5 mg/mL at pH 2, 10.7 mg/mL at pH 4.5, and 0.66 mg/mL at pH 7.4 f_u: 0.450	CYP3A4 metabolism with minor contribution of esterase metabolism	Dosing route: oral SD: 20, 80, 100, 150, and 450 mg MD: 80 and 150 mg q.d. for 14 days	Absorption: ADAM Distribution: minimal PBPK Elimination: enzyme kinetics (CYP3A4) with human liver microsomal and renal clearance
Compound F	MW: 400–500; log P: <5 Neutral P_{eff}: not applicable Solubility: not applicable f_u: 0.600	Renal clearance with CYP3A4 and CYP2C8 metabolism	Dosing route: oral SD: 5, 12.5, 25, 50, 100, 200, and 400 mg MD: 25, 50, 100, and 200 mg q.d. for 10 days	Absorption: first order Distribution: minimal PBPK Elimination: renal clearance and enzyme kinetics (CYP3A4 and CYP2C8)
Compound G	MW: >1,000; log P: <5 Monoprotic acid, p*K*a 5 P_{eff}: not applicable Solubility: not applicable f_u: 1.00	Renal clearance	Dosing route: intravenous infusion SD: 1, 8, and 16 mg/kg MD: not conducted	Absorption: not applicable Distribution: minimal PBPK Elimination: renal clearance and whole organ metabolic clearance
Compound H	MW: 400–500; log P: <5 Neutral P_{eff}: not applicable Solubility: not applicable f_u: 0.005	CYP3A4 metabolism with CYP2C19 minor route	Dosing route: oral SD: 4, 10, 20, 50, 76, and 100 mg MD: not conducted	Absorption: first order Distribution: full PBPK Elimination: enzyme kinetics (CYP3A4 and CYP2C19)
Compound I	MW: 500–600; log P: <5 Monoprotic acid, p*K*a 3.9 P_{eff}: 3.45×10^{-4} cm/second Solubility: solution f_u: 0.001	UGT1A3 and CYP3A4 metabolism	Dosing route: oral SD: 150 and 800 mg MD: 800 mg q.d. for 10 days	Absorption: ADAM Distribution: full PBPK Elimination: enzyme kinetics (CYP3A4) with human liver microsomal clearance (as UGT1A3)

Unbound fraction of drug in enterocytes for all compounds was the default value of 1.00.
ADAM, advanced dissolution, absorption, and metabolism; b.i.d., twice daily; CYP, cytochrome P450; f_u, fraction unbound in plasma; MW, molecular weight; MD, multiple dose; P_{eff}, effective permeability; q.d., once daily; SD, single dose; UGT, uridine diphosphate–glucuronosyltransferase.

0.3 for CYP2C19. Although the CYP3A component is qualified in the model, because CYP2C19 is a relatively minor component, no DDI studies were conducted with CYP2C19 inhibitors that could be used for further model qualification.

For compound I, the kinetics were similar in Japanese and non-Japanese subjects. Although C_{max} and AUC were 1.4- and 1.2-fold higher, respectively, in Japanese compared with non-Japanese subjects, this difference was not considered meaningful, and the PBPK model predictions were consistent with this finding. We, however, identified some limitations of the model in that it did not describe all the kinetics in the non-Japanese population and, therefore, it could not be fully qualified. At doses <75 mg, the phase I data from non-Japanese healthy volunteers are suggestive of more than dose proportional exposure, which the model was unable to capture. Thus, simulations in Japanese populations were not run at the lower dose ranges. Compound I is known to be a substrate of CYP3A and P-glycoprotein, and saturation at the gut level could contribute to the observed nonlinearity. However, the kinetics of CYP3A metabolism and P-glycoprotein–mediated transport of compound I have not been characterized.

Given that exposure is a determinant factor for the safety profile of a compound, it is possible that underprediction of exposure of a drug could lead to underestimation of safety margins of a given drug. To ensure the safety and tolerability in clinical studies, a conservative approach should be taken. If there is a safety concern in early phase I studies, more stringent criteria may need to be applied for interpretation of results. Further prospective and retrospective evaluation on the feasibility of PBPK modeling and simulation approaches for compounds in development and for launched products is necessary across the pharmaceutical industry to increase confidence in predicting PKs in untested populations.

The MHLW guideline for conducting phase I trials in the Japanese population before enrolling Japanese subjects in global phase II or III trials requests the conduct of a phase I study to evaluate safety and tolerability in Japanese subjects.[14] If there is no major concern relating to the tolerability and safety of a drug in non-Japanese subjects, the phase I study in Japanese subjects can be conducted in parallel with global phase II or III trials to establish tolerability and safety in Japanese subjects. PBPK simulations can help provide accurate PK profiles in Japanese subjects to ensure optimal drug exposure at the selected dosages that may demonstrate safety and efficacy in phase II or III studies.[15] There is a plethora of information in the literature supporting use of PBPK models to address various clinical pharmacology questions, such as assessment of risk of DDIs, absorption-related issues, and selection of optimal dose in hepatic or renal impaired, obese, pregnant, and pediatric populations.[11,12,23,26,27] Our study also demonstrates that qualified PBPK models can, in certain cases, substitute actual clinical data through robust simulations that help estimate PK profiles in Japanese subjects. As a result, PBPK approaches can help contribute to a more streamlined study design for clinical trials and accelerate drug development programs in Japan.

METHODS

This study consisted of four steps, as outlined in **Figure 4**. First, a PBPK model for each compound was developed using physicochemical properties, *in vitro* and *in vivo* preclinical ADME data, and phase I clinical PK data in healthy non-Japanese volunteers. Next, qualification of the PBPK models was performed by comparing the simulated PKs with the observed PKs in the non-Japanese population across a wide dose range after single- and multiple-dose administration. The simulated concentration–time profiles were overlaid with the observed data to assess the ability of the models to describe the overall central tendency and variability of the clinical PK data. In addition, the simulated PK parameters were tabulated and compared with the observed PK data. Once qualified, the PBPK models were used to simulate the PK profiles in Japanese healthy subjects. The prediction accuracy in the Japanese population was assessed by comparing the predicted PK parameters with the observed PK data obtained in Japanese phase I studies. The details of each step are elaborated in the following subsections.

PBPK modeling and simulation were conducted using SimCYP v13, v14, and v15 (SimCYP, Sheffield, UK). There are no significant differences in population-related parameters between these versions. Phoenix WinNonlin Version 6.3.0.395 (Certara, Princeton, NJ) was used for PK parameter calculation when the simulated data were obtained from SimCYP v13. Microsoft Excel 2010 (Microsoft, Redmond, WA), R version 3.1.0, and Rstudio Version 0.98.1091 (Rstudio, Inc., Boston, MA) were used for data set integration, data analysis, and drawing figures and tables.

COMPOUND SELECTION AND PROPERTIES

A total of nine compounds were selected from the MRL development pipeline for this study. The compounds spanned various stages of development from phase I to launched products and had PK data in both Japanese and non-Japanese subjects. The selected compounds were chemically diverse and from different therapeutic areas. The key characteristics of each compound are demonstrated in **Table 2**. Of the nine compounds, seven were eliminated primarily through metabolism by CYPs or UGTs; the major elimination pathway for the other two compounds (compounds F and G) was urinary excretion. All compounds were administered orally, except compound G, which was administered intravenously.

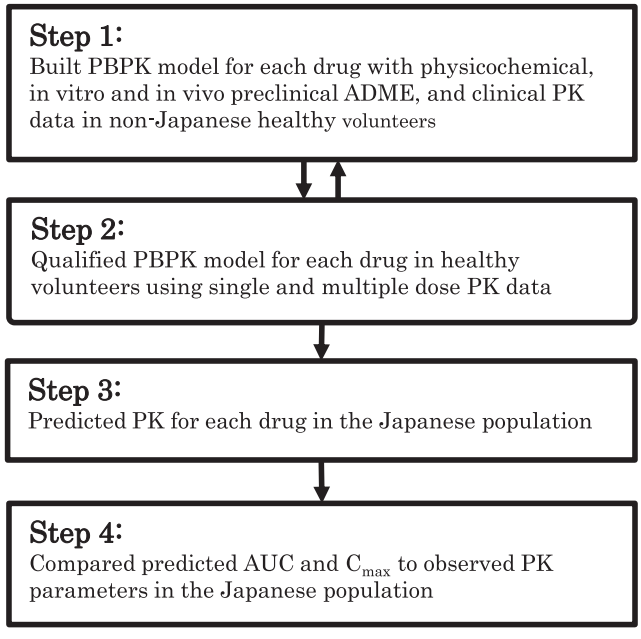

Figure 4 Schematic workflow of prediction of PKs in Japanese subjects using PBPK models built on the basis of preclinical and phase I data in non-Japanese subjects. PBPK, physiologically based pharmacokinetic.

CLINICAL PHASE I STUDY DATA

Each compound was studied in a placebo-controlled, double-blind, clinical trial with at least six subjects or a bioequivalence study with up to 120 subjects in each dosing group. All subjects provided written informed consent. The studies were conducted in accordance with ethical principles based on the Declaration of Helsinki, Good Clinical Practice. Validated bioanalytical methods (e.g., high-performance liquid chromatography with tandem mass spectrometry) were used to quantify the concentration of the compounds in human plasma. Single- or multiple-dose administration of each compound was performed, and noncompartmental analysis of plasma concentration was conducted to estimate PK parameters for each compound.

PBPK model building

PBPK models were built according to a "middle-out" approach.[4,16,21,28] Each model was parameterized with physicochemical data; *in vitro*, *in vivo*, and preclinical ADME data; and PK data from healthy non-Japanese subjects obtained from phase I studies. In particular, the *in vitro* and *in vivo* ADME information allowed for the predicted mechanisms of elimination in humans to be incorporated into each PBPK model. The input parameters for each compound are displayed in **Table 2**.

Absorption

With the exception of compound G, which was administered intravenously, advanced dissolution, absorption, and metabolism (ADAM)[29] (compounds A, B, E, and I) or first-order absorption (compounds C, D, F, and H) models were selected for absorption modeling, on the basis of availability of solubility and permeability data and the ability of the ADAM model to capture the observed PK profiles in non-Japanese subjects. In the ADAM model, compounds were modeled as immediate release, consistent with the formulations used for the early clinical studies, and parametrized with measured solubility data. Absorption rate constants (k_a) were predicted from *in vitro* permeability data using calibrated cell lines. In the first-order absorption model, fraction absorbed and k_a for compounds D, F, and H were estimated from clinical single oral dose PK data. For compound C, fraction absorbed was estimated from preclinical PK data and k_a was predicted from *in vitro* permeability data.

Distribution

Minimal PBPK models were used to describe the volume of distribution for all compounds, except compounds B, H, and I, in which full PBPK models were used. When the minimal PBPK model in SimCYP was selected, the distribution parameters were based on clinical PK data obtained from studies in non-Japanese subjects. For compounds C, D, F, and G, these parameters were obtained from population PK models. For compound E, distribution parameters were obtained by fitting the simulated PK profile to single oral dose PK data using the parameter estimation tool in SimCYP. For compound A, the steady-state volume of distribution was predicted from physicochemical properties. In cases in which the full PBPK model was used, tissue partition coefficients were predicted from LogP, p*K*a, and plasma protein binding, and distribution parameters were fit to the non-Japanese PK data by adjusting the tissue to plasma scaler.

Elimination

Total systemic clearance was obtained from intravenous PK data in the non-Japanese population for compounds A, F, G, and H, and from oral PK data for compounds B, C, E, and I. For compound D, clearance was obtained from a population PK model. The enzyme kinetic model in SimCYP was used to simulate the hepatic clearance for each compound, except for compound G, in which the whole organ clearance model was used. The f_m values were estimated from *in vitro* CYP or UGT phenotyping data, combined with *in vivo* preclinical studies. Intrinsic clearance values were assigned to each enzyme involved using SimCYP's retrograde calculator. The CYP3A4 f_m assignment was validated with a ketoconazole DDI study for compounds D and H. For compounds F and G, renal clearance determined in non-Japanese populations was used for the renal elimination component.

Simulation of PK parameters for Japanese and non-Japanese populations

A total of 100 trials of 10 subjects (n = 1,000 individual subjects) per dosing regimen were simulated using "Japanese" (Japanese healthy subjects) and "healthy volunteers" (non-Japanese healthy volunteers) populations in virtual population mode contained in the database within SimCYP. The age ranges (20–44 years) and proportion of female subjects (0 in most studies, 0.5 in some studies if female subjects were enrolled in the actual clinical trial) were matched to the actual clinical study design for each compound.

Dosage, dosing regimen, and the last blood sampling time were set to match the actual clinical trial in phase I studies in Japanese and non-Japanese healthy subjects. Single-dose simulations were conducted under fasted conditions. After each simulation, the AUC, C_{max}, and plasma concentration at a specified time were averaged and treated statistically within each trial (n = 100 for each parameter). Then, the geometric mean of the predicted C_{max} and AUC values for each Japanese population trial (10 subjects each) for each regimen were obtained, where AUC_{0-inf} was estimated for single-dose administration and AUC_{0-t} was used for multiple-dose administration.

Comparison of PK parameters

The error in predicted parameters (prediction error), relative to the observed parameter values obtained in actual clinical trials, was estimated according to Eq. 1.[30–34]

$$\text{Prediction error} = X_{\text{predicted}}/X_{\text{observed}}. \quad (1)$$

where $X_{predicted}$ represents the simulated geometric mean C_{max}, AUC_{0-inf}, or AUC_{0-t} values for 100 simulated clinical trials, and $X_{observed}$ is the observed geometric mean values obtained in the actual clinical trial.

Furthermore, prediction errors were grouped into three categories: category 1, prediction error fell within 0.8–1.25; category 2, prediction error fell within 0.5–2.0; and category 3, prediction error was <0.5 or >2.0. Then, the percentage of each category in each dosing regimen was estimated. If >80% of simulations indicated prediction errors in category 1 or 2, it was concluded that the simulation of the trial was successful.[30–34]

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

Figure S1. Simulated concentration–time curves overlaid with actual observed plasma concentration of each compound in non-Japanese subjects.

Figure S2. Simulated concentration–time curves overlaid with actual observed plasma concentration of each compound in Japanese subjects.

Table S1. Number of single- and multiple-dose regimens simulated for each compound in a non-Japanese population.

Table S2. Predicted and observed exposures after single oral and intravenous administration to non-Japanese and Japanese healthy subjects at the clinical dose.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

Y.M., T.C., P.S., G.H., T.I., H.Y., C.G., and N.U. wrote the manuscript; H.Y., C.G., and N.U. designed the research; Y.M., T.C., P.S., G.H., and T.I. performed the research; Y.M. and T.I. analyzed the data.

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