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Assessing pharmacokinetic differences in Caucasian and East Asian (Japanese, Chinese and Korean) populations driven by CYP2C19 polymorphism using physiologically-based pharmacokinetic modelling

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ABSTRACT

Understanding the influence of ethnicity on drug exposure is key to patient safety and could minimize repetitive clinical studies. This analysis aimed to evaluate the ability of physiologically-based pharmacokinetic modelling to predict exposure of CYP2C19 substrates (lansoprazole, (es)citalopram, voriconazole) across Caucasian and East Asian populations. CYP2C19 abundance levels in Japanese and Chinese populations have been re-assessed based on clinical evidence. Model performance in each population was evaluated by predicted-over-observed AUC ratios and comparison of observed data with simulated plasma concentration profiles. Exposures in 84.4% (76 out of 90) of the clinical studies were predicted within 1.5-fold of observed values. The reported concentration-time profiles were well-captured within the 90% prediction intervals. With specified CYP2C19 phenotype, PBPK modelling is capable to predict systemic exposure of drugs largely metabolized by CYP2C19 in different ethnic populations. This study demonstrated PBPK modelling can be applied to assess genotype-dependent exposure difference across ethnicities.

1. Introduction

East Asian countries, including Japan and the key emerging market China, are of great importance to global drug development. Potential inter-ethnic difference in pharmacokinetics (PK), pharmacodynamics (PD), safety and efficacy derived from a variety of genetic, physiological, demographic or environmental factors is a major concern in global drug development. International Conference on Harmonization (ICH) E5 guidance on "Ethnic Factors in the Acceptability of Foreign Clinical Data" highlighted the importance of ethnicity assessments for "ethnically" sensitive drugs, such as drugs metabolized by polymorphic enzymes with varying allele frequencies across ethnic groups. It is well known that Japan and China have a time lag in drug approval due to the regulatory requirement for stand-alone phase I/II studies in Japanese or Chinese subjects to assess potential ethnic differences (Zhou et al., 2019). Modelling and simulation have many successful applications in clinical development and regulatory review process (Al-Huniti et al., 2017; Bui et al., 2016; Johnson et al., 2014; Zhou et al., 2018). To promote timely participation of East Asian countries in global clinical trials and avoid a lag in drug approval as compared with those in the US and EU, modelling and simulation could act as a powerful approach to evaluate potential inter-ethnic differences without duplication of clinical trials.

The hepatic enzyme CYP2C19 plays an important role in the metabolism of various therapeutic drugs such as proton pump inhibitors and benzodiazepine anxiolytics. A significant number of allelic variants of the CYP2C19 gene have been discovered (https://www.pharmvar.org/gene/CYP2C19), and some genetic mutations can profoundly influence CYP2C19 expression and/or activity. CYP2C19*1 represents the wild-type allele. The most common loss-of-function allele CYP2C19*2 with allelic frequencies of 12–17% in Caucasians and 29–35% in Asians causes aberrant mRNA splicing and leads to a truncated non-functional protein (Desta et al., 2002; Scott et al., 2012). Another common loss-of-function allele in Asians (2–9%) is CYP2C19*3, resulting in premature termination codon, while the reported frequency of CYP2C19*3 in Caucasians is < 1% (Desta et al., 2002; Scott et al., 2012). In contrast,

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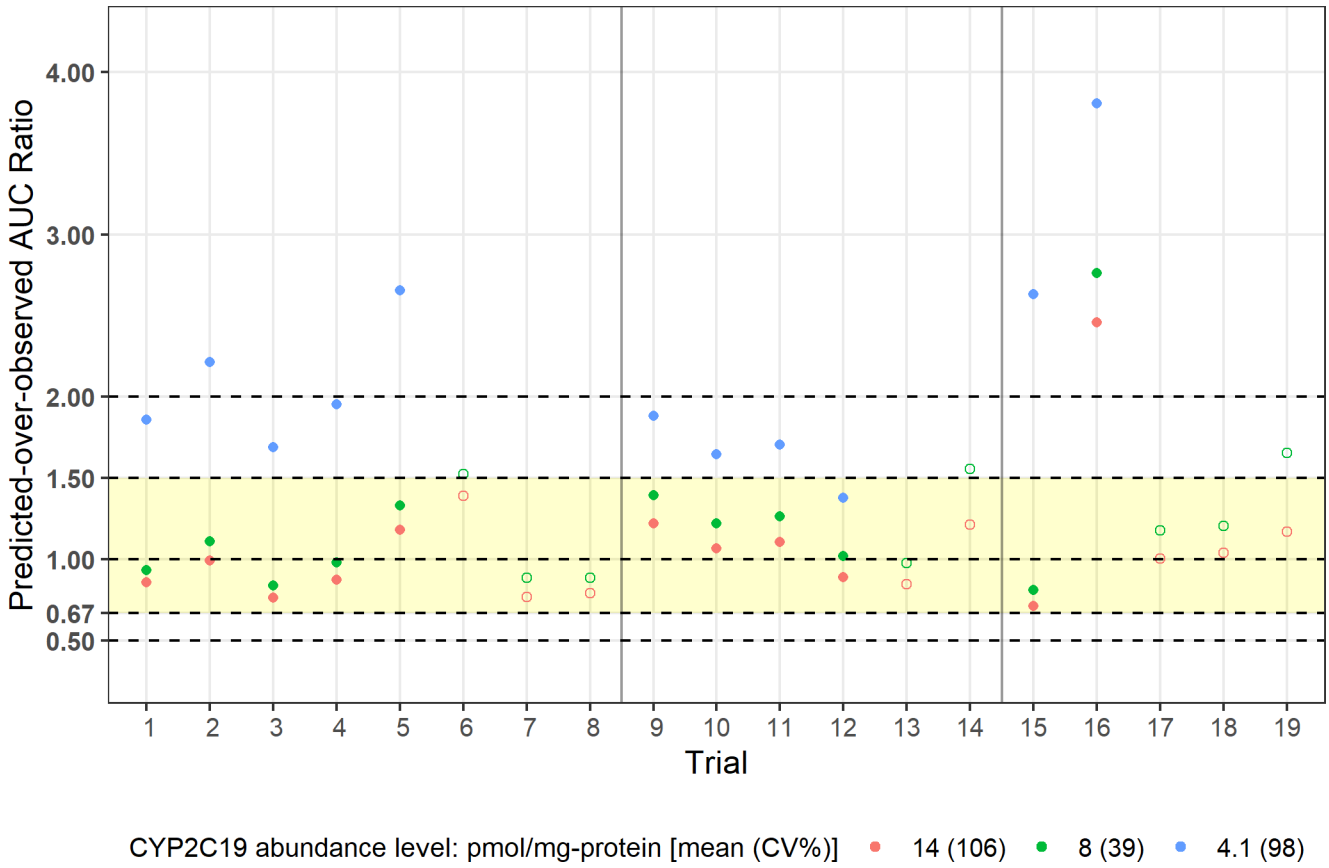

Fig. 1. Sensitivity analysis of CYP2C19 abundance on PBPK modelling performance.
The forest plot shows the predicted-over-observed AUC ratios of 19 reported trials on lansoprazole (trial 1–8), (es)citalopram (trial 9–14) and voriconazole (trial 15–19) in Japanese (solid fill dots) and Chinese (hollow fill dots) CYP2C19 extensive metabolizers.

the CYP2C19*17 allele, with a high prevalence in Caucasians (~21%) but low frequency in Asians (< 5%), is associated with an increase in transcriptional activity and increased CYP2C19 expression (Li-Wan-Po et al., 2010). CYP2C19 genotype well correlates with phenotype and is routinely used in phenotype stratification, including ultra-rapid metabolizer (UM, *1/*17 or *17/*17), homozygous extensive metabolizer (EM, *1/*1), heterozygous extensive metabolizer (HEM, *1/*2 or *1/*3) and poor metabolizer (PM, *2/*2, *2/*3 or *3/*3) (Desta et al., 2002; Li-Wan-Po et al., 2010), and the different allelic frequencies in each ethnic populations drive the observed difference of CYP2C19 activity (Myrand et al., 2008). Higher CYP2C19 PM incidences have been shown in Japanese (15–23%), Chinese (15–17%) and Koreans (13%) compared with Caucasians (1–6%) (Desta et al., 2002). In contrast, Caucasians (25.6%) have shown a higher CYP2C19 UM prevalence rate than Asians (7.2%) (Martis et al., 2013).

The objective of this study was to evaluate the use of physiologically-based pharmacokinetic (PBPK) modelling to predict clinical exposure of CYP2C19 substrates across different ethnic populations (Caucasians, Japanese, Chinese and Koreans). This was accomplished by incorporating physiologic, CYP2C19 genotypic and phenotypic differences among Caucasian and Asian populations to predict drug exposure by PBPK model and then comparing predictions with clinical observations (Supplementary Fig. 1).

Three drugs were selected to serve for this purpose. Lansoprazole, a proton-pump inhibitor treating acid-related diseases, is mainly metabolized by CYP2C19 and 3A4 (Horn, 2000). It is recommended to increase dose by 200% in *H. pylori* eradication and monitor for insufficient response in CYP2C19 UMs (Swen et al., 2011). Citalopram and its isomer escitalopram are selective serotonin reuptake inhibitors (SSRIs) widely used for the treatment of depression and anxiety disorders. Both drugs are primarily metabolized by CYP2C19 and to a lesser extent via CYP3A4 and 2D6. Plasma concentration monitoring and dose titration to a maximum of 150% in response to efficacy and adverse events or selecting alternative drug are recommended for CYP2C19 UMs (Swen et al., 2011). Voriconazole, a widely-used antifungal drug, is extensively metabolized in the liver primarily by CYP2C19 and 3A4. Serum concentration monitoring is recommended in CYP2C19 PMs and HEMs (Swen et al., 2011).

2. Material and methods

2.1. Drug selection

Extensive literature was reviewed to search for clinical studies of CYP2C19 substrates with genotype/phenotype information in Caucasian and East Asian populations. Only 4 drugs fulfilled such selection criteria: omeprazole, lansoprazole, citalopram and voriconazole. As omeprazole has been extensive studied using PBPK approach (Feng et al., 2015; Wu et al., 2014), the rest 3 drugs were selected to test the predictive performance of PBPK models using Simcyp® (Certara, Sheffield, UK).

2.2. Simcyp® set-up

PBPK modelling and simulations were performed in Simcyp® V17. Virtual populations for Caucasian (*Sim-Healthy Volunteers*), Chinese (*Sim-Chinese Healthy Volunteers*), and Japanese (*Sim-Japanese*) were applied for subject sampling. The simulation trial designs (e.g. dosing regimen, number of subjects, age range, proportion of females, etc.) matched the corresponding reported trials (Supplementary Table 3).

Specifically, 20 trials were applied for each simulation if the number of subjects was > 5, otherwise 100 subjects (20 trials with 5 subjects for each trial) were sampled virtually.

The Simcyp default liver CYP2C19 abundances in Caucasian and Chinese and Japanese EMs were 14(106), 8(39), and 4.1(98) pmol/mg-protein [mean(CV%)], respectively. The default GI tract CYP2C19 abundances in Caucasian and Chinese and Japanese EMs were 1.5(60), 0.85(60), and 0.4(60) pmol/mg-protein [mean(CV%)], respectively. The abundances in Japanese EMs and Chinese EMs were eventually assigned to be the same as that in Caucasian EMs in the current analyses. The abundances of IM or HEM (*1/*2 or *1/*3), UM (*1/*17 or *17/*17) in these virtual populations were calculated using the scaling factor estimated by Steere et al. (2015): 5.3(130) pmol/mg-protein for IM, 25(155) pmol/mg-protein for UM. Caucasian abundances of CYP2C19 in GI tract were also applied to Chinese and Japanese populations: 1.5(60) pmol/mg-protein for EM, 0.57(60) for IM and 2.685(60) pmol/mg-protein for UM.

2.3. Workflow of model development

The general workflow of model development is summarized in Fig. 1. To avoid the complication from disease factors, only reported PK studies in healthy volunteers with genotype/phenotype information on CYP2C19 in each ethnic population were used. PBPK models were firstly established based on physiochemical data, Caucasian data and in vitro metabolism data. Then simulations were conducted by sampling from the virtual population module *Sim-Healthy Volunteers*. The parameters were optimized based on the reported Caucasian data to match observed PK parameters and plasma concentration profiles. Available drug-drug interaction (DDI) studies were also simulated for confirmation. The developed models were verified with additional Caucasian studies. The optimized models were then applied to predict PK in Japanese and Chinese by using the virtual population modules, *Sim-Japanese* and *Sim-Chinese Healthy Volunteers*, and compared to the reported Japanese and Chinese PK data. Korean population is genetically and culturally similar to other East Asians, but virtual Korean population module is not available, so both *Sim-Japanese* and *Sim-Chinese Healthy Volunteers* were used for simulation. Trial designs of the reported studies used in this analysis were summarized in Supplementary Table 3.

2.4. PBPK modelling of lansoprazole

A full PBPK model of lansoprazole was developed (Table 2). First-order absorption with a lag time of 1 h was used to capture the delayed-release profile of enteric-coated capsule formulation of this Biopharmaceutical Classification System (BCS) class II drug. Human permeability (P_{eff},man) predicted by quantitative structure-activity relationship (QSAR) model was applied (Wu et al., 2013). DDI study with clarithromycin indicated the fm of CYP3A4 in PMs was 0.55 (Saito et al., 2005), and the fm of CYP2C19 was 0.836 in Caucasian EMs (Table 1). The initial CLint values of CYP2C19, CYP3A4 and additional clearance were determined in Simcyp by retrograde modelling using fm values of 0.836, 0.090 and 0.074, respectively (Saito et al., 2005). To incorporate population variability that is not considered by the retrograde modelling tool, minor adjustments were made to fit the reported Caucasian data (Andersson et al., 1998). Other published Caucasian PK studies were used to verify the model predictions. DDI with clarithromycin was also simulated for verification. Then the verified model was applied to predict lansoprazole PK in Japanese, Chinese and Korean populations.

2.5. PBPK modelling of escitalopram

Advanced Dissolution, Absorption and Metabolism (ADAM) model was used to capture the oral absorption of escitalopram. P_{eff},man was estimated by polar surface area (PSA) and number of hydrogen bound donors (HBD). Minimal PBPK model was chosen to estimate the distribution of escitalopram. A Kp scalar of 2.62 was applied to all tissue compartments to keep consistency between predicted volume of distribution at steady state (Vss) and the reported value of 12 L/kg from package insert. An average total clearance from reported Caucasian studies on escitalopram, 34.65 L/h and renal clearance of 4 L/h from the label were used for retrograde modelling (Celexa® package insert, Noehr-Jensen et al., 2009; Ohlsson Rosenborg et al., 2008). The mean fm of CYP2C19 was 0.52 (Table 1) and the fm of CYP2D6 was 0.19 based on exposure data stratified with CYP2C19 and CYP2D6 genotypes (Fudio et al., 2010). The rest fm of hepatic clearance was assigned to CYP3A4. The CLint values of CYP2C19, 2D6 and 3A4 were determined by retrograde modelling (Table 2). Escitalopram PK studies in Caucasian were used to verify the model predictions. Then the verified model was applied to predict citalopram PK in Caucasians and Chinese, and escitalopram PK in Japanese population. Default CYP2D6 phenotype frequencies in each population modules were used when phenotype information was not reported.

2.6. PBPK modelling of voriconazole

A full PBPK model of voriconazole with first-order absorption was developed (Table 2). The Vmax of CYP3A4 and 2C19 kinetics were obtained by parameter estimation using clinical data in Caucasian PMs and EMs based on in vitro Ki values (Mikus et al., 2006). Model verification was performed by simulating DDI study with ritonavir (Mikus et al., 2006) and other published voriconazole PK studies in Caucasians. Then the verified model was applied to predict voriconazole PK in Japanese, Chinese and Korean populations.

2.7. Model evaluation

The predictive performance was evaluated for each drug in different ethnic groups by overlaying the observed concentration-time profile with the model-predicted profile and 90% predictive interval. The prediction accuracy was determined by assessing ratio of mean predicted values over mean observed values.

3. Results

3.1. Sensitivity analysis of CYP2C19 abundance on model performance

In default population library of Simcyp V17, liver abundances of CYP2C19 assigned to Caucasian, Japanese and Chinese EMs are different, 14(106), 4.1(98) and 8(39) pmol/mg-protein [mean(CV%)], respectively. Significant over-estimations of exposure in Japanese and Chinese were observed for all three drugs using the default CYP2C19 abundance settings (Fig. 1). Using the default Japanese abundance, the models only predicted 1 out of 11 cases in EM subjects within 1.5-fold of observed AUC. By adjusting the CYP2C19 Japanese abundance to default Caucasian level in the models, all the trials were predicted within 1.5-fold range (Fig. 1), suggesting the CYP2C19 EM abundance should be similar across Caucasian and Asian populations.

3.2. Meta-analysis on fm in different ethnic populations

The fraction of drug metabolized (fm) by CYP2C19 for four substrate drugs was calculated based on reported clinical studies of paired trials in CYP2C19 EMs and PMs (Table 1). Average fm values showed no significant differences between Caucasian and East Asian populations [mean ± SD]: 0.84, 0.78 ± 0.04, 0.76 ± 0.08 and 0.78 for lansoprazole; 0.65 ± 0.02, 0.71, 0.66 and 0.70 for voriconazole, and 0.84 ± 0.07, 0.88 ± 0.04, 0.66 ± 0.18 and 0.82 for omeprazole, in Caucasians, Japanese, Chinese and Koreans, respectively. The average fm values for (es)citalopram are 0.52 and 0.52 ± 0.02 in Caucasian

Table 1
Summary of CYP2C19 fm[a] in reported clinical trials of four substrate drugs.

Lansoprazole			Voriconazole			Escitalopram			Omeprazole		
Ethnicity	fm	Reference	Ethnicity	fm	Reference	Ethnicity	fm	Reference	Ethnicity	fm	Reference
Caucasian	0.84	Andersson et al. (1998)	Caucasian	0.63	Mikus et al. (2006)	Caucasian	0.51	Noehr-Jensen et al. (2009)	Caucasian	0.92	Andersson et al. (1992)
				0.67	Scholz et al. (2009)		0.54	Fudio et al. (2010)[d]		0.78	Böttiger et al. (1997)
				0.64	Weiss et al. (2009)					0.82	Román et al. (2014)[c]
Mean	*0.84*		*Mean*	*0.65*		*Mean*	*0.52*		*Mean*	*0.84*	
SD	–		*SD*	*0.02*		*SD*	–		*SD*	*0.07*	
Japanese	0.82	Ieiri et al. (2001)	Japanese	0.82	VFEND® package insert[b]	Japanese	0.52	LEXAPRO® package insert	Japanese	0.93	Furuta et al. (1999)
	0.73	Sakai et al. (2001)		0.60	Ikeda et al. (2004)[c]		0.53	LEXAPRO® package insert		0.87	Sakai et al. (2001)
	0.82	Saito et al. (2005)					0.49	LEXAPRO® package insert		0.90	Yasui-Furukori et al. (2004)
	0.76	Yasui-Furukori et al. (2004)					0.54	LEXAPRO® package insert[b]		0.80	Ieiri et al. (2005)
	0.78	Uno et al. (2005)								0.90	Yasumori et al. (2006)
										0.89	Uno et al. (2007)
Mean	*0.78*		*Mean*	*0.71*		*Mean*	*0.52*		*Mean*	*0.88*	
SD	*0.04*		*SD*	–		*SD*	*0.02*		*SD*	*0.04*	
Chinese	0.71	Yu-rong et al. (2004)	Chinese	0.62	Wang et al. (2009)				Chinese	0.80	Andersson et al. (1992)
	0.75	Hai-Ling et al. (2006)		0.71	Shi et al. (2010)					0.81	Ophelia et al. (2004a)
	0.88	Xu et al. (2010)								0.82	Ophelia et al. (2004b)
	0.78	Zhang et al. (2011)								0.40	Lan et al. (2006)
	0.68	Li et al. (2014)								0.87	Nan et al. (2003)
										0.51	Chen et al. (2009)
										0.58	Li-Jun et al. (2009)
										0.49	Tu et al. (2010)
Mean	*0.76*		*Mean*	*0.66*					*Mean*	*0.66*	
SD	*0.08*		*SD*	–					*SD*	*0.18*	
Korean	0.78	Kim et al. (2002)	Korean	0.70	Lee et al. (2012)				Korean	0.82	Joo-Youn et al. (2002)
Mean	*0.78*		*Mean*	*0.70*					*Mean*	*0.82*	
SD	–		*SD*	–					*SD*	–	

SD: standard deviation.
[a] $fm = 1 - AUC_{EM} / AUC_{PM}$.
[b] Multiple dosing.
[c] Limited number of subjects (Ikeda et al., 2004, EM: 3, PM: 1; Román et al., 2014, PM:1).
[d] Citalopram.

and Japanese, respectively. The results indicated that the metabolic contributions of CYP2C19 were similar across these ethnic populations, except 4 omeprazole studies in Chinese, further supporting that CYP2C19 EM abundance should be similar across Caucasian and Asian populations. The standard deviations of fm suggested low intra-study variabilities in the studies conducted within each ethnic population. Based on these clinical studies and sensitivity analyses, the CYP2C19 abundances in Japanese and Chinese were eventually assigned to be the same values as those in Caucasians for all the simulations.

3.3. Modelling and simulations of lansoprazole

The PBPK model of lansoprazole was initially developed and verified in Caucasian population and then extrapolated to Asian populations. Simulation of DDI studies in Japanese population with clarithromycin (CYP3A4 inhibitor) and fluvoxamine (CYP2C19 inhibitor) reproduced the observed exposure changes, suggesting the assigned fm for CYP2C19 (0.78) and CYP3A4 (0.12) were reasonable (Supplementary Fig. 2, Supplementary Tables 1&2). Among the 12 published studies with 31 CYP2C19 phenotype subgroups, the majority of the predicted-over-observed AUC ratios (28 out of 31) were within 1.5-fold range (Fig. 2, Supplementary Table 3). The mean(range) AUC ratios of the EM, HEM, PM and UM subgroups of Caucasians were 1.09(0.91–1.35) (n = 3), 1.15 (n = 1), 1.00 (n = 1) and 1.55 (n = 1), respectively. The mean AUC ratios of the EM, HEM and PM subgroups of Japanese were 0.93(0.76–1.18) (n = 5), 1.26(1.16–1.41) (n = 5) and 1.24(1.09–1.50) (n = 5), respectively. The mean AUC ratios of the EM, HEM and PM subgroups of Chinese were 0.98(0.77–1.39) (n = 3), 1.36(0.95–1.77) (n = 2) and 1.71(1.23–2.52) (n = 3), respectively. The simulated plasma concentration profiles well predicted the observed values (Fig. 3). The Korean population is unavailable in current Simcyp version. Therefore, the Korean study (Kim et al., 2002) was simulated using both Japanese and Chinese populations. The simulations showed predicted-over-observed AUC ratios of 0.93 (EM) and 1.25 (PM) when using Japanese population-module. The simulations using Chinese population-module generated similar results (1.03 in EM and 1.32 in PM). Because lansoprazole has a very short half-life of 1–2 h in EMs and 4–5 h in PMs and there was no dose accumulation observed during once daily dosing (Andersson et al., 1998; Ieiri et al., 2001), multiple dosing cases were expected to be the same as single dose scenarios and they are not presented here.

3.4. Modelling and simulations of (es)citalopram

The PBPK model of (es)citalopram was first developed and verified in Caucasian population, then extrapolated to Asian populations. The mean fm of CYP2C19 was assigned as 0.52 (Table 1) and exposure data stratified with CYP2C19 and CYP2D6 genotypes indicated a fm of 0.19 for CYP2D6 (Fudio et al., 2010). Among the 8 published studies with 26 CYP2C19 phenotype subgroups, the majority of the predicted-over-observed AUC ratios (21 out of 26) were within 1.5-fold range (Fig. 2, Supplementary Table 3). The mean(range) AUC ratios of the EM, HEM, PM and UM subgroups of Caucasians were 1.26(0.98–1.63) (n = 5), 1.03 (n = 1), 1.04(0.90–1.20) (n = 3) and 1.67 (n = 1), respectively. The mean AUC ratios of the EM and PM subgroups of Japanese were 1.07(0.89–1.22) (n = 4) and 1.13(0.90–1.28) (n = 4), respectively. The

Table 2
Summary of input parameters for PBPK models.

Parameters	Lansoprazole	Escitalopram	Voriconazole
Physicochemical properties			
Molecular weight (g/mol)	369.4[a]	324.39[a]	349[a]
Log P	1.9[a]	3.76[a]	1.8[a]
Compound type	Monoprotic base	Monoprotic base	Monoprotic base
pKa	4.15 (Kristl, 2009)	9.78[a]	1.76
fu	0.03 (Landes et al., 1995)	0.44 (LEXAPRO® package insert)	0.42 (VFEND® package insert)
B/P	0.59 (Zhou et al., 2018)	1.086 (Overø, 1982)	1.23 (predicted)
Absorption			
Absorption model	First-order	ADAM	First-order
fa	0.998 (predicted)	1.00 (predicted)	0.96 (Zane and Thakker, 2014)
ka	3.12 (predicted)	4.96 (predicted)	0.85 (Zane and Thakker, 2014)
$P_{eff,man}$ (10^{-4} cm/s)	7.15 (Wu et al., 2013)	11.35 (predicted)	3.03 (predicted)
Lag time (h)	1	0	0
fu_{Gut}	0.096 (predicted)	1 (Steere et al., 2015)	0.117 (predicted)
Caco-2 (10^{-6} cm/s)	–	–	28.10 (Damle et al., 2011)
PSA	–	36.26 (Steere et al., 2015)	–
HBD	–	0 (Steere et al., 2015)	–
Distribution			
Distribution model	Full PBPK	Minimal PBPK	Full PBPK
Vss (L/kg)	0.187 (Method 2)	12 (Method 2)	1.23 (Method 1)
Kp Scalar	–	2.62	–
Elimination			
CLint, CYP2C19 (μl/min/pmol)	14.0	0.774	–
Vmax, CYP2C19 (pmol/min/pmol)	–	–	5
Km, CYP2C19 (μM)	–	–	3.5 (Hyland et al., 2003)
CLint, CYP2D6 (μl/min/pmol)	–	0.505	–
CLint, CYP3A4 (μl/min/pmol)	0.107	0.0155	–
Vmax, CYP3A4 (pmol/min/pmol)	–	–	0.075
Km, CYP3A4 (μM)	–	–	0.15 (Yamazaki et al., 2010)
Additional HLM CLint (μl/min/mg protein)	12.0	–	–
CL_R (L/h)	0	4 (Celexa® package insert)	0.096 (Zane and Thakker, 2014)

[a] drugbank (https://www.drugbank.ca/) or pubchem (https://pubchem.ncbi.nlm.nih.gov/).

mean AUC ratios of the EM, HEM and PM subgroups of Chinese were 1.03(0.84–1.21) (n = 2), 1.43(0.98–1.87) (n = 2) and 2.13 (n = 1), respectively. Minor over-prediction was observed in Chinese PMs when administered with a high single oral dose of citalopram (40 mg). The plasma concentration profiles reasonably recovered clinical observations (Supplementary Fig. 3). Slight under-prediction of peak concentration was observed in the plasma concentration profiles of two Chinese studies administering a 20 mg single oral dose of citalopram. Both escitalopram and citalopram studies have been included in the analysis because of the limited number of reported clinical studies with CYP2C19 genotype/phenotype information.

3.5. Modelling and simulations of voriconazole

The PBPK model of voriconazole was first developed and verified in Caucasian population, then extrapolated to Asian populations. Simulation of DDI study with ritonavir (CYP3A4 inhibitor) in Caucasians recovered the voriconazole exposure changes in both EMs and PMs at a single oral dose of 400 mg (Supplementary Fig. 4, Supplementary Table 4). There are 9 published studies with 33 CYP2C19 phenotype subgroups. The majority (27 out of 33) of the predicted-over-observed AUC ratios were within 1.5-fold range (Fig. 2, Supplementary Table 3). The mean(range) AUC ratios of the EM, HEM, PM and UM subgroups of Caucasians were 1.07(0.91–1.24) (n = 4), 1.02(0.87–1.17) (n = 4), 1.18(1.01–1.53) (n = 4) and 0.99 (n = 1), respectively. The mean AUC ratios of the EM, HEM, PM and UM subgroups of Chinese were 1.16(1.00–1.45) (n = 3), 1.36 (n = 1), 0.92(0.80–1.05) (n = 3) and 1.63 (n = 1), respectively. The exposures in Japanese HEMs and PMs after multiple dosing were well-captured by the model, with AUC ratios of 1.17 and 1.18. Slight under-prediction was observed in Japanese EMs after multiple dosing (AUC ratio = 0.71), which warrants further model investigations. The model over-predicted a single dose Japanese study (AUC ratio = 2.10–2.57), however, the clinical data were from a very limited number (n = 1–3) of subjects with no demographic information. The Korean study (Lee et al., 2012) was simulated using both Chinese and Japanese population modules and the results were similar. The AUC ratios on day 1 using Chinese or Japanese modules were 1.40 vs 1.37 (EM), 1.26 vs 1.40 (PM) and 1.32 vs 1.35 (HEM), while the AUC ratios on day 7 were 0.46 vs 0.43 (EM), 1.07 vs 1.06 (PM) and 0.51 vs 0.49 (HEM). The plasma concentration profiles recovered the observed values in single dose settings except the said Japanese single dose study (Supplementary Fig. 5).

4. Discussion

Many factors, including genetic polymorphism, epigenetic influences and non-genetic host factors, are found to influence CYP450 expression and function (Zanger and Schwab, 2013). Host factors, such as age, sex and environmental factors can also influence epigenetic patterns, further complicating the real situation in human subjects. Most of the variability in CYP450 activity results from single nucleotide polymorphisms (SNPs) that may alter the sequence of the transcribed protein leading to altered activity, gene transcription or even translation/splicing of mRNA depending on their locations (McGraw and Waller, 2012). The abundance differences among different ethnic populations discovered by previous studies that didn't have genotypic information could be largely led by polymorphism of the related metabolic enzymes. However, more validations are warranted to determine how the current abundance parameters in Simcyp could be appropriately used in the PBPK models with phenotype/genotype stratification.

The PBPK model presumes that intrinsic activity per unit amount of enzyme variant, as well as tissue composition, is the same across different ethnic populations. The current assumption that different ethnic

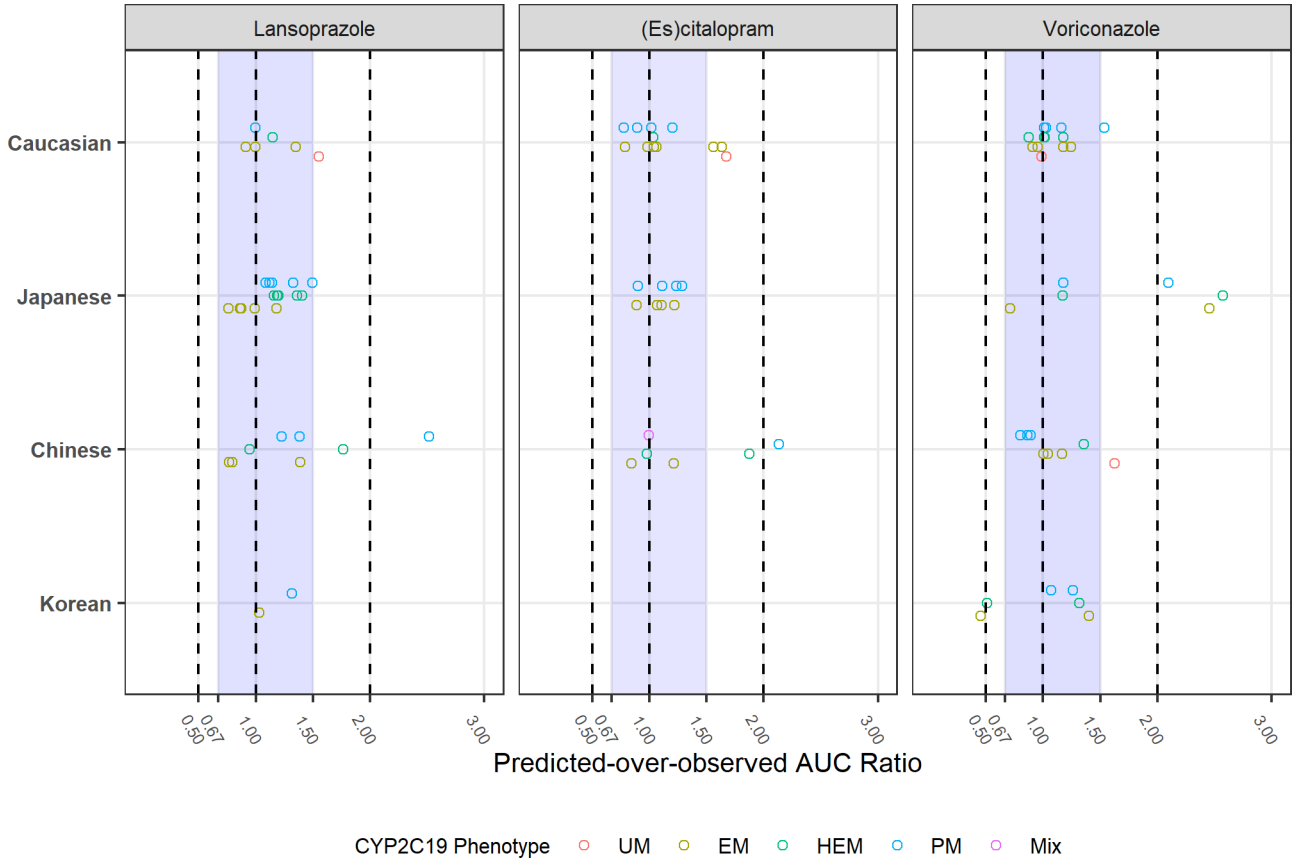

Fig. 2. PBPK modelling performance in Caucasian, Japanese, Chinese and Korean populations.
The forest plot shows the predicted-over-observed AUC ratios of the three example drugs, lansoprazole, (es)citalopram and voriconazole, in CYP2C19 ultra-rapid metabolizers (UM), extensive metabolizers (EM), heterozygous metabolizers (HEM) and poor metabolizers (PM) in Caucasian, Japanese, Chinese and Korean populations. The predicted-over-observed AUC ratio of one Chinese citalopram PK study on a mixture of 9 EMs and 14 HEMs was 0.99. The data of Korean trials were from the simulations using *Sim-Chinese Healthy Volunteers* for subject sampling.

populations have different abundance levels is not well grounded. The Simcyp default liver CYP2C19 abundance value in Caucasians was developed from a meta-analysis (Barter et al., 2013). The value in Chinese was based on a single report on 42 Chinese liver samples (Barter et al., 2013; Shu et al., 2000). In that study, Chinese liver samples were not genotyped (Shu et al., 2000). Some samples were excluded in the abundance calculation due to their low S-mephenytoin 4′-hydroxylation rates. The calculated abundance could be lower than the actual abundance of Chinese CYP2C19 EM because of the inclusion of CYP2C19 HEM samples. The value in Japanese was estimated by a paired study on 29 Japanese and 35 Caucasian liver samples (Inoue et al., 1997). The Japanese abundance calculation didn't distinguish CYP2C19 genotypes. The expression levels of CYP2C19 in samples with two mutated alleles were below the detection limit but included in the calculation. Japanese wild-type samples showed very similar % of total CYP450 as Caucasian wild-type samples: 1.4 ± 0.7 (n = 4) vs 1.4 ± 0.4 (n = 21) (Inoue et al., 1997). Moreover, the about 2-fold difference in total CYP450 levels between Caucasian and Japanese was also included in the abundance calculation. However, the authors attributed the higher levels of total CYP450 in Caucasian samples than those of Japanese samples to differences in the storage conditions of liver samples before microsome preparation. Therefore, the Japanese abundance was largely underestimated. Besides, significant variabilities were observed in these in vitro enzyme activity data based on measurement in human liver microsomes (HLM).

Based on the assumption of consistent enzyme intrinsic activity and tissue composition, we hypothesized that the CYP2C19 abundance levels should be the same or very similar among Caucasian, Japanese and Chinese populations. This hypothesis was supported by the model performance evaluations using different abundance levels (Fig. 1), as well as the fm meta-analysis (Table 1). Model performance was significantly improved by adjusting the CYP2C19 abundance in Japanese to be the same level as Caucasians, resulting in within 1.5-fold prediction accuracy in all trials in EMs. The simulation results in all three drugs show that the default Japanese CYP2C19 abundance was too low to provide reliable predictions. Less difference was observed for Chinese by applying default Chinese and Caucasian CYP2C19 abundances, probably due to the large CV% (106%) of Caucasian default abundance. There were some limitations in the data used in the fm meta-analysis. Japanese studies of voriconazole were limited. Ikeda et al. (2004) only reported one PM subject. The studies reported in Japanese package insert were multiple dosing studies. Non-linear PK of voriconazole might contribute to the large differences in fm of CYP2C19 when the dosing regimens were different. Omeprazole PK in Chinese subjects showed large inter-study differences. Half of the studies (4 out of 8) showed fm values slightly higher than 0.8, while others were around 0.5. However, these limitations are not expected to adversely influence the finding that metabolic contributions of CYP2C19 were similar across these ethnic populations. That being said, CYP2C19 abundance across Caucasian, Japanese and Chinese population still warrants further investigation. From an in vitro perspective, a large number of HLM samples from the three populations analyzed by the same method in the same laboratory could provide consistent values for modelling. From an in vivo perspective, more CYP2C19 substrates should be evaluated in well-controlled clinical studies in the three populations, which only focuses on CYP2C19 genotype and rule outs other potential

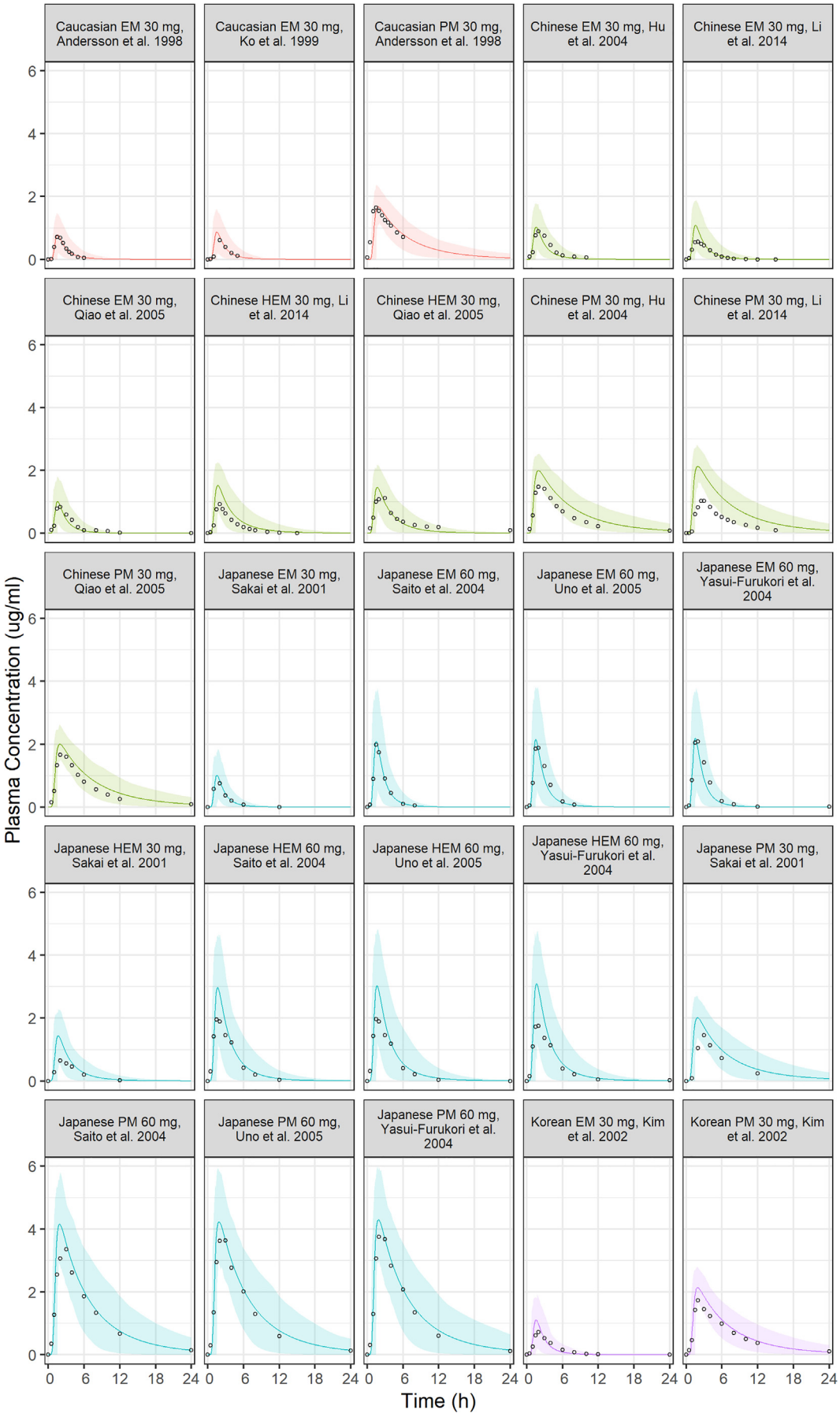

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Fig. 3. PBPK model predicted and clinical observed concentration-time profiles of lansoprazole.
Mean simulated (solid lines) and observed (circles) plasma concentrations of lansoprazole in healthy volunteers from different ethnic populations were plotted. The shaded areas represent 90% prediction interval of the simulations. Trial design of the simulations matched the demographic information and dosing regimen in the corresponding literature.

confounding factors. Hasunuma et al. (2016) performed a strictly controlled study of moxifloxacin, simvastatin and meloxicam on which ethnic PK differences had been reported. With body weight normalization and stratification of polymorphism of major metabolic enzymes or transporters, no significant differences in PK parameters among East Asian and Caucasian populations were found, which is consistent with our findings.

The established PBPK models of the three CYP2C19 substrates demonstrated the feasibility to assess genotype-dependent exposure difference across ethnicities using PBPK modelling. Continuous verifications of this approach are encouraged when clinical data is available for other CYP2C19 substrates. Some limitations still exist in our current models due to data availability and quality. Lansoprazole is a typical BCS class II drug and acid-labile, so enteric-coated formulations are applied to prevent gastric decomposition and increase oral bioavailability (Wu et al., 2013). Our model was built on the data from studies using the Takeda brand name capsule, so the absorption model may not capture the behavior of a different formulation. Zhang et al. (2011) used generic enteric-coated tablets. The Tmax values in all phenotype groups were much longer than those reported from other studies and the plasma concentration profiles indicated a slower absorption compared with the data from the originator capsules. Xu et al. (2010) didn't provide information on the drug manufacture, but the Cmax and AUC values in their study were much higher than the other Chinese studies using 30 mg dose and were close to the data of 60 mg dose data in Japanese subjects. According to originator package insert, the bioavailability was reported as over 80%. Data reliability from this study is of great concern. Therefore, these two studies were excluded from our analysis. The rest of the Chinese studies and all of the Japanese studies used the Takeda capsule. All reported Caucasian studies with phenotype information used generic drugs, so they are still included in the analysis.

Citalopram is a racemic mixture of *R*-enantiomer and biologically active form *S*-enantiomer (escitalopram). An in vitro study using HLM and recombinant enzymes (Olesen and Linnet, 1999) showed that the enzymes involved in the first demethylation step of citalopram, CYP3A4, 2C19 and 2D6, all favored the conversion of the *S*-enantiomer. This is consistent with the population PK analysis in Alzheimer's patients showing that the clearance of the *R*-enantiomer was slower than the *S*-enantiomer (Akil et al., 2016) and the study in healthy Swedes comparing the PK of the *R*- and *S*-enantiomers in different CYP2C19 and 2D6 phenotype combinations (Herrlin et al., 2003). This multiple dosing study in healthy Swedes was simulated using our escitalopram model assuming that escitalopram accounted for 50% of the citalopram dose. Although we know the existence of stereoselective metabolism in citalopram, available data in East Asian populations are not enough for us to model citalopram and escitalopram separately. Plasma protein binding is another major difference between citalopram (80%) and escitalopram (56%) according to their package inserts. This is possibly one of the reasons for stereoselective metabolism. Thus, we simulated all the reported studies using the escitalopram model. Additionally, both in vitro and in vivo data showed that citalopram had little effect on the major CYP isoforms (Alex and Frans, 2002). The slightly higher (21–39%) AUC_{tau} (AUC from dosing to the time point of the next dosing) compared with AUC_{inf} in both EM and PM groups in the two multiple dosing studies of escitalopram (LEXAPRO® package insert; Noehr-Jensen et al., 2009) might result from the weak inhibition of CYP2D6 by citalopram and its metabolite desmethylcitalopram. This inhibitory effect was not included in our model because of the large variation in the reported Ki values (Alex and Frans, 2002).

Multiple dosing studies on voriconazole indicated non-linear PK and high dose accumulation. The ratio of AUC_{tau} measured on day 7 over AUC_{inf} of the 1st dose was around 3 in Korean healthy volunteers across all CYP2C19 phenotypes (Lee et al., 2012). Two Caucasian studies without genotyping also showed similar accumulation patterns (Geist et al., 2013; Purkins et al., 2003). In vitro literature data suggested that voriconazole was not only a substrate of CYP2C19 and 3A4, but also an inhibitor of both CYP enzymes (Hyland et al., 2003; Jeong et al., 2009; Niwa et al., 2005; Yamazaki et al., 2010). Auto-inhibition, mechanism-based inhibition and an inhibitory metabolite are common causes of dose accumulation. However, pre-incubation assays indicated that voriconazole was not a mechanism-based inhibitor of both enzymes (Niwa et al., 2005; Yamazaki et al., 2010). Literature reported IC_{50} values of voriconazole N-oxide were 146 μmol/L for CYP3A4 and 40.2 μmol/L for CYP2C19 (Hohmann et al., 2017), which are too high to be clinically meaningful. Another possible reason is reversible conversion between parent and its metabolites, but there is no reported evidence to support. The mechanism underlying significant dose accumulation warrants further investigations. Our current voriconazole model only incorporates auto-inhibition. The model predicts no dose accumulation in EMs and a slight dose accumulation in HEMs and PMs.

5. Conclusions

Despite the minor limitations in these PBPK models, reasonable predictive performance of PBPK models in Caucasian and East Asian populations has been demonstrated. In conclusion, the analysis on clinical data suggests similar CYP2C19 abundance levels in Caucasian and East Asian populations. By applying the same level of CYP2C19 abundance in three populations, the PBPK models successfully predicted AUC within 1.5-fold in 84.4% (76 out of 90) reported studies across Caucasian and East Asian populations over four different phenotypes. With specified CYP2C19 phenotype, PBPK modelling is capable to predict systemic exposure of drugs largely metabolized by CYP2C19 in different ethnic populations.

Author contributions

D.Z., L.Z., P.S., K.R.Y., M.H., H.X., and N.A-H. wrote the manuscript; D.Z., L.Z., P.S., and K.R.Y. designed the research; D.Z., L.Z., and P.S. performed the research and analyzed the data.

Declaration of competing interest

This study was funded by AstraZeneca Pharmaceuticals LP. K.R.Y. is an employee of the Simcyp Division of Certara UK Ltd. L.Z., P.S., H.X., N.A.-H. and D.Z. are employees of AstraZeneca Pharmaceuticals LP.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejps.2019.105061.

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