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Utilizing PBPK Absorption Modeling to Evaluate Impact of Single-Sex on Bioequivalence Evaluation of Atorvastatin Immediate Release Tablets

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PURPOSE

Atorvastatin is β-hydroxy β-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor indicated in both sexes along with proper diet to reduce elevated cholesterols, fats, and triglycerides to lower the risk of heart disease and stroke. Females have approximately 20% higher Cmax and 10% lower AUC than male subjects as indicated in the reference listed drug (RLD) labeling for atorvastatin calcium immediate release (IR) tablets **[1]**. Per the newly revised FDA's draft Guidance for Industry–*Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA* (August 2021) **[2]**, if a drug product is intended for use in both sexes, the applicant should include both males and females in the pharmacokinetic bioequivalence (BE) study or provide a justification supporting the use of a single-sex population.

OBJECTIVE(S)

This study aimed to evaluate the use of physiologically based pharmacokinetic (PBPK) absorption model with virtual BE (VBE) simulations to investigate sex differences in drug exposure and assess whether BE results can be extrapolated to the entire population of both sexes from a single-sex BE study for atorvastatin IR tablets.

METHOD(S)

Physicochemical properties, disposition and absorption parameters based upon literature and PK data in healthy male subjects following oral administration with single-dose atorvastatin calcium IR tablet of EQ 80 mg base were used for model development using ADMET Predictor™ and PBPKPlus™ from the GastroPlus™ software (Version 9.8.2, Simulations Plus Inc., CA, USA). Dissolution data, CYP3A4-mediated metabolism, and transporter kinetics (i.e., BCRP, MRP3, OATP1B1, OATP1B3, and P-gp) were incorporated to characterize plasma concentration of atorvastatin considering the formulation differences, pre-systemic absorption, and first-pass metabolism under fasting condition. Metabolite tracking was not enabled according to the recommendations provided in the current product-specific guidance (PSG) **[3]**. Km and Vmax scaling factors of gut metabolism in the female subjects were optimized to capture the PK differences between male and female subjects. The PBPK model was further validated with PK data containing both sexes for 80 mg IR tablets under the fasting state. VBE simulations were carried out under fasting condition considering different sample sizes and various proportions of female subjects to support that BE results from a single-sex population can be extrapolated to the general population of both sexes.

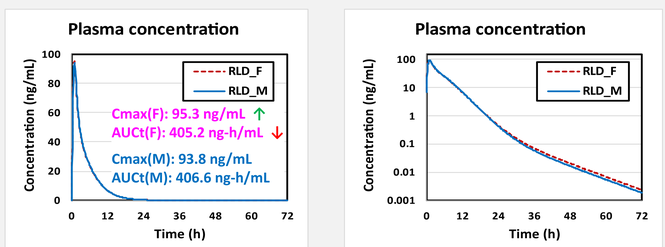
RESULT(S)

- The PBPK model which incorporated dissolution data, enzyme and transporter kinetics adequately predicts the PK profiles of atorvastatin under fasting condition with prediction error (PE) estimates of <20% (**Table 1**).
- The PBPK model is also able to capture the general trend that the female population has higher Cmax and lower AUC under fasting condition as indicated by the RLD labeling **[1]** (**Figure 1**).

Table 1. PBPK absorption modeling results in healthy male/female subjects following oral administration with single-dose atorvastatin calcium IR tablets of EQ 80 mg base.

Drug	Prediction error for PK parameters (%)		
	Cmax	AUCt	AUCinf
Model development			
RLD (Study 1)	5.71	14.92	14.90
Generic (Study 1)	-7.99	16.70	16.71
Model validation			
RLD_M (Study 2)	-0.61	-4.49	-4.43
RLD_F (Study 2)	15.72	-14.34	-14.29
RLD_M (Study 3)	-2.84	12.78	13.06
RLD_F (Study 3)	-15.96	1.74	4.86

Figure 1. PBPK model prediction captures RLD drug exposures in both sexes.

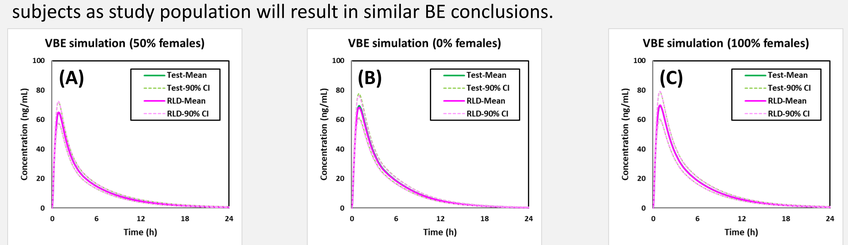


- VBE simulation in **Table 2** shows that when 50% of females and males are included in the BE studies with sample size of 70 subjects, the Cmax and AUC T/R ratios [90% CI] are predicted to be 1.00 [0.89–1.12] and 1.00 [0.91–1.09], respectively, which are within the 0.8–1.25 BE criteria. Similar VBE simulation results are obtained for the sample size of 40 subjects as well.
- As demonstrated in **Table 2 and Figure 2**, when using male- or female-only subjects in VBE simulations for the sample size of 70 subjects, results demonstrate that Cmax and AUC T/R ratios [90% CI] are predicted to be 1.01 [0.91–1.12] and 1.01 [0.92–1.11], respectively, for males, and 1.00 [0.89–1.12] and 1.00 [0.90–1.11], respectively, for females.
- As such, VBE simulation results can be used to justify that BE results from male-only subjects can be relevant to the entire population of both sexes.

Table 2. Comparisons of VBE simulations between test (T) and reference (R) atorvastatin calcium IR tablets of EQ 80 mg base with various sample sizes and female proportions under fasting condition.

VBE simulation	Sample size	Female (%)	Cmax T/R ratio [90% CI]	AUCt T/R ratio [90% CI]	AUCinf T/R ratio [90% CI]
1	40	50	0.94 [0.81, 1.10]	0.94 [0.83, 1.07]	0.94 [0.83, 1.07]
2	70	50	1.00 [0.89, 1.12]	1.00 [0.91, 1.09]	1.00 [0.91, 1.09]
3	70	0	1.01 [0.91, 1.12]	1.01 [0.92, 1.11]	1.01 [0.92, 1.11]
4	70	100	1.00 [0.89, 1.12]	1.00 [0.90, 1.11]	1.00 [0.90, 1.11]

Figure 2. VBE simulations between test and reference 80 mg atorvastatin IR tablets with (A) 50%, (B) 0%, and (C) 100% females contained in the 70 healthy subjects. Using male- or female-only subjects as study population will result in similar BE conclusions.



CONCLUSION(S)

- The developed oral PBPK model for atorvastatin could adequately capture PKs of RLD and test drug products with different formulations in healthy male and female subjects under fasting condition.
- For this atorvastatin IR tablet case example, PBPK modeling approach along with VBE simulations could support the scientific justification that the risk of having different BE results is low by using single-sex subjects compared to using subjects with both sexes in BE studies.

FUNDING / GRANTS / ENCORE / REFERENCE OR OTHER USE

References: [1] RLD Labeling for NDA 020702 (December 2022); **[2]** Guidance for Industry–Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA (August 2021); and **[3]** Draft Guidance on Atorvastatin Calcium (October 2010).

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