Modelling of Atorvastatin Pharmacokinetics in relation to *SLCO1B1* genotype and Simulations for Bioequivalence Study

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Abstract

Objectives: This study aimed to assess atorvastatin pharmacokinetic profile and variability in relation to SLCO1B1 genotype by population pharmacokinetic modelling and to build up a clinical trial simulation approach for optimal bioequivalence (BE) design considering the genotype.

Methods: The population pharmacokinetic analysis was performed using NONMEM7 based on plasma samples from a single dose PK with genotyping study in 28 healthy subjects. With the use of a two-compartment model with first order absorption, the influence of SLCO1B1 genotype on absorption rate constant and oral bioavailability was examined. The final pharmacokinetic model was used for clinical trial simulation of bioequivalence study. Simulation scenario consists of varying the sample size from 40 to 80 and variant genotype frequencies from 0 to 100%. Each study was simulated 300 times using TrialSimulator2.2.1 and the percent of successful BE results was calculated as a statistical power.

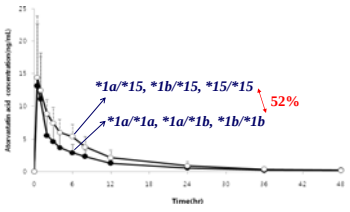
Results: The SLCO1B1 genotype showed a significant influence on atorvastatin pharmacokinetics. Oral clearance was 23 L/h, volume of distribution of steady-state was 180.5 L, inter-compartmental clearance was 43 L/h, the absorption rate constant was 1.51 h-1 for wild-type and 0.82 for variant-type, and bioavailability was 7.2% for wild-type and 10.9% for variant-type. A large intersubject variability was found to affect atorvastatin absorption (CV 54.7%), and the residual variability was large (CV 48%). An inverse correlation between the percentage of SLCO1B1 variant-type and the success rate (power) of average BE were detected by clinical trial simulation. For achieving 80% power, about 45 subjects would be necessary and cut off for variant-type frequency in study population was 25%.

Conclusion: The SLCO1B1 genotype frequency in study population may influence the success rate of bioequivalence study. Applying genotyping to subject screening could be a valuable option for a more efficient and successful approach to the BE study design of atorvastatin.

SLCO1B1 and Atorvastatin PK

Subjects & Methods

- **Objectives: To evaluate the association of genetic polymorphism of *SLCO1B1* with the pharmacokinetics (PK) of atorvastatin**
- **Genotype Screened: 290 unrelated healthy Korean → 28 subjects enrolled**
- ***SLCO1B1* genotyped: c.388A>G and c.521T>C**
- **Single oral dosing of 20 mg atorvastatin (Lipitor®)**
- **Blood sampling: 0, 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 36, 48 hr after dosing**



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Modeling of Atorvastatin PK

- **Two Compartment First order absorption & elimination model**
- **NONMEM® 7 FOCE with Interaction**
- **SLCO1B1 genotype group is a significant covariate on both Ka and F1**
- **Bioavailability was increased by 50% in variant type group.**

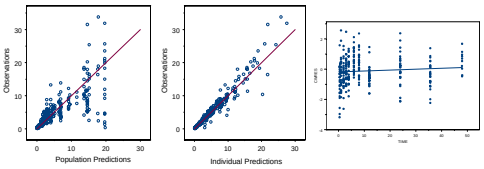
Population PK parameters of the final model

Parameter	Parameter Value (95% CI)*	Inter-Individual Variability (CV%) (95% CI)*
CL (L/h)	23 (19.3~28.7)	31.9 (24.0~41.5)
V1 (L)	16.5 (13.8~22.9)	169 (96.9~249)
Q (L/h)	43 (30.1~53.5)	57.6 (32.5~70.4)
V2 (L)	164 (139~174.5)	39.5 (25.5~51.0)
Ka_wild (1/h)	1.51 (1.03~3.33)	54.7 (16.2~76.0)
Ka_var (1/h)	0.92 (0.56~1.12)	
F_wild %	7.3% (5.5%~9.3%)	
F_var %	11.0% (7.7%~13.4%)	
Add. Error	0.0371 (0.006~0.061)	
Prop. Error	0.235 (0.174~0.275)	

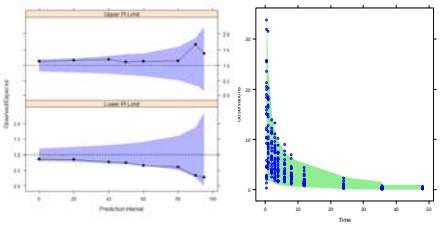
*Obtained by Bootstrap 1000 times
Wild = Without *SLCO1B1*15* allele
VaR = Including *SLCO1B1*15* allele

Evaluation of the Population PK Model

Basic goodness-of–fit plots



Predictive Check plots



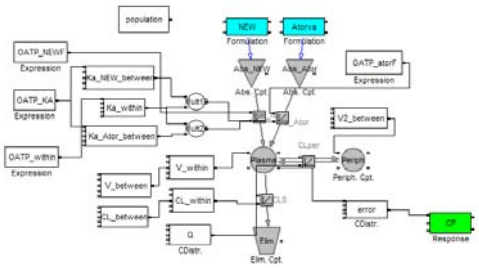
Numerical predictive check | Visual predictive check

Simulations of Bioequivalent study (1)

Simulations

- **Trial Simulator® 2.2.1 (Pharsight Ltd.)**
- **Total number of simulated study: 300X6X5 = 9,000**
- **Total number of simulated plasma concentrations: 9,000x16x2 = 288,000**

Drug Model



Simulations of Bioequivalent study (2)

Study Design

Sequence	Period 1	Period 2
Sequence # 1	NEW	Atorva
Sequence # 2	Atorva	NEW

- **Single oral dose of atorvastatin 20 mg tablet**
- **NEW: New generic formulation of atorvastatin**
- **Atorva: Reference Listed Drug of atorvastatin**
- **CP: Plasma Concentrations of atorvastatin**
- **Observations ("Sampling2"): 0(pre), 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 24, 36, 48 Hr post dose**

Study Subject Enrollment

- **Genotype population according to SLCO1B1 variant allele frequency**
- **Variant allele percent: 0% (wild type), 25%, 50%, 75%, and 100%**

Simulations of Bioequivalent study (3)

Analysis Variables

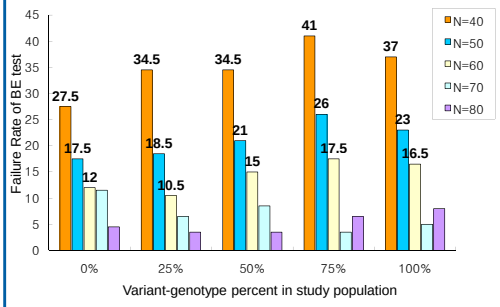
Variable	Missing Policy	BQL Policy	Summarization	Method(s)
CP	Missing	BQL = 0	Cmax	ANOVA BE test
CP	Missing	BQL = 0	Partial AUC from time 0 to 48	ANOVA BE test

Simulation Scenario (Each genotype population)

Name	Replications	Observation	No. of Subjects
N40	300	Sampling2	40
N50	300	Sampling2	50
N60	300	Sampling2	60
N70	300	Sampling2	70
N80	300	Sampling2	80

Simulation Results

Failure Rates of Bioequivalence (%)



Simulation Scenario	Variant Genotype Percent in Study Population 0%	25%	50%	75%	100%
N40	**27.5**	34.5	34.5	41	37
N50	**17.5**	**18.5**	**21**	**26**	**23**
N60	12	10.5	15	17.5	16.5
N70	11.5	6.5	8.5	3.5	5
N80	4.5	3.5	3.5	6.5	8

Conclusion

- **The Failure rates of 75% variant genotype group are 1.5 fold greater than those of 0% variant group.**
- **For achieving 80% power, about 45 subjects would be necessary and cut off for variant-type frequency in study population was 25%.**
- **The *SLCO1B1* genotype frequency in study population may influence the success rate of atorvastatin bioequivalence study**
- **Applying genotyping to subject screening could be a valuable option for a more efficient and successful approach to the Bioequivalence study of highly variable drug such as atorvastatin.**