POPULATION PHARMACOKINETIC MODEL DEVELOPMENT FOR LONG-ACTING INTRAMUSCULAR INJECTION OF DRUG X IN HEALTHY SUBJECTS

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BACKGROUND

- As a result of the aging population, the proportion of the population who suffer from dementia is rising year by year around the world.
- And poor patient compliance is one of the major factors for treatment failure in dementia patients.
- In hope to improve patient compliance, Drug X, a new long-acting intramuscular (IM) injection formulation is currently under development for extension of the dosing frequency to once several weeks in contrast to the currently available once daily oral regimen.

OBJECTIVE

- A population pharmacokinetic (PK) analysis was carried out for characterisation of Drug X after IM injection in healthy subjects.

METHODS

Study Design

- A total of 36 healthy male subjects were enrolled in a randomised, double-blind, placebo-control, dose-escalation, single-dose, phase I study. (*N.B. 16 additional subjects were included in the analysis since the abstract written date*)
- Single IM injection of Drug X of 35, 70, 140, 210 or 280 mg were administered to each subjects. (*N.B. 210 mg and 280 mg dosage group data obtained from the additional 16 subjects were included in the analysis since the abstract written date*)
- PK blood sampling for determination of plasma Drug X concentration was performed at following time points.
  - Pre-dose, 0.5, 1, 2, 4, 6, 8, 12, 24(2d), 48(3d), 72(4d), 96(5d), 120(6d), 168(8d), 240(11d), 312(14d), 360(16d), 408(18d), 432(19d), 456(20d), 480(21d), 504(22d), 528(23d), 552(24d), 600(26d), 648(28d), 720(31d), 816(35d), 888(38d), 960(41d) and 1056(45d) h post-dose.
- This clinical study was approved by the Institutional Review Board of Seoul National University Bundang Hospital.

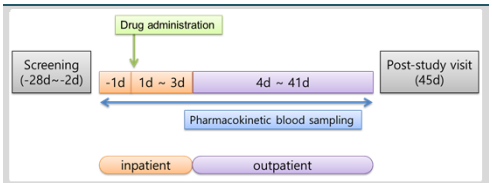

Figure 1. Design of the clinical study.

Analytical Methods

- The plasma concentrations of Drug X were determined using the liquid chromatography-tandem mass spectrometry.

Population PK Dataset

- A nonlinear mixed effect modelling for population PK analysis was performed with 1114 plasma concentration-time records obtained from 36 healthy subjects.

Population PK Model Structure and Assumptions

- Base model assumptions
  - A one-compartmental model structure with two independent first-order absorptions with lag time in the secondary absorption phase was assumed for IM injection of Drug X.
- Optimization of model parameterisation
  - Different model parameterisation scenarios were tried using nonlinear mixed-effects method in NONMEM version 7.3.0 (Icon Development Solutions, Hanover, MD, USA).
- Covariate analysis
  - Individual model parameters were obtained by Bayesian estimation implemented in NONMEM. Age, height, weight, BMI, and the following base measures of the laboratory test were included in the covariate screening: ALT and AST levels, serum creatinine level, creatinine clearance (estimated by Cockcroft-Gault equation), total bilirubin level.

Population PK Model Structure and Assumptions (Cont.)

- Covariate analysis (Cont.)
  - Covariates were entered into the model using a forward selection significance level of 0.05 and a backwards deletion criterion of 0.01.
- Numerical method
  - First-order conditional estimation with interaction (FOCE INTERACTION) was used in all runs for estimation of the PK parameters.

Model Validation

- The standard basic model diagnosis plots, including individual fittings, goodness-of-fit plots and visual predictive check (VPC) plots for the observed and predicted plasma concentrations were examined to assess for the model fitting and the performance of the predictions.

RESULTS

- The mean±standard deviation of the age, height and weight of the subjects enrolled were 29.21±6.72 years, 174.26±5.83 cm and 70.93±8.72 kg, respectively.
- A one-compartment with two independent first-order absorptions with lag time in the secondary absorption phase and combined error model adequately described the concentration–time profiles of Drug X.
- Within the combined error model, the interindividual variability (IIV) for the apparent clearance (CL/F), volume of distribution (Vd/F), the primary absorption rate constant (Ka1), and the lag time in the secondary absorption phase (ALAG2) were included.
- The effect of weight on CL/F and Vd/F with fixed exponents of 0.75 and simple allometry were selected, respectively.
- The goodness-of-fit plots showed good adequacy between the observed and the predicted Drug X concentrations.

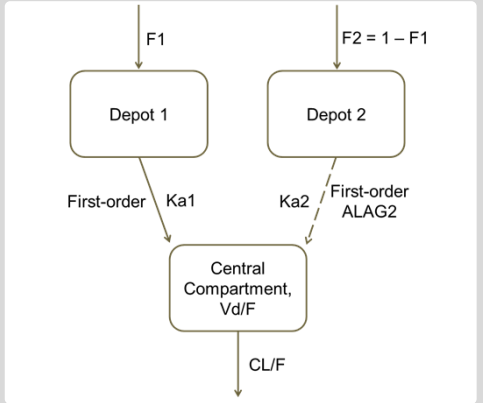

Figure 2. The schematic illustration of the base model structure.
Abbreviations: CL/F: apparent clearance, Vd/F: apparent volume of distribution, Ka1: primary absorption rate constant, Ka2: secondary absorption rate constant, ALAG2: lag time in the secondary absorption phase, F1: proportion of the primary absorption phase, F2: proportion of the secondary absorption phase.

Table 1. The initial pharmacokinetic model parameter estimates of the partial dataset (N=20).

Parameters	Population estimates	RSE (%)	Inter-individual variability (%)
θ1; CL/F (L/h)	9.01	11	21.8
θ2; Vd/F (L)	1270	24	27.2
θ3; Ka1, primary absorption (h^{-1})	0.0023	31	17
θ4; Ka2, secondary absorption (h^{-1})	0.0113	46	47.6
θ6; ALAG2, secondary absorption (h)	352	1	0 (fixed)
θ7; F1	0.338	20	17.6
θ8; $\sigma_{additive}$	0.442	8	-
θ9; $\sigma_{proportional}$	0.161	7	-

Model constructed with the data from 20 subjects after single IM injection of 35, 70 or 140 mg Drug X obtained at the time of the abstract written date.
Abbreviations: CL/F: apparent clearance, Vd/F: apparent volume of distribution, Ka1: primary absorption rate constant, Ka2: secondary absorption rate constant, ALAG2: lag time in the secondary absorption phase, F1: proportion of the primary absorption phase, $\sigma_{additive}$: additive error, $\sigma_{proportional}$: proportional error, RSE: relative standard error

Table 2. The final pharmacokinetic model parameter estimates of the full dataset (N=36)

Parameters	Population estimates	RSE (%)	Inter-individual variability (%)
θ1*(WT/70.5)$^{0.75}$; CL/F (L/h)	8.78	5	25.7
θ2*(WT/70.5); Vd/F (L)	1250	13	23.9
θ3; Ka1, primary absorption (h^{-1})	0.00204	11	11.7
θ4; Ka2, secondary absorption (h^{-1})	0.0101	8	0 (fixed)
θ6; ALAG2, secondary absorption (h)	373	2	7.6
θ7; F1	0.38	4	0 (fixed)
θ8; $\sigma_{additive}$	0.777	3	-
θ9; $\sigma_{proportional}$	0.157	4	-

Model constructed with the data from 36 subjects after single IM injection of 35, 70, 140, 210 or 280 mg Drug X.
Abbreviations: CL/F: apparent clearance, Vd/F: apparent volume of distribution, Ka1: primary absorption rate constant, Ka2: secondary absorption rate constant, ALAG2: lag time in the secondary absorption phase, F1: proportion of the primary absorption phase, $\sigma_{additive}$: additive error, $\sigma_{proportional}$: proportional error, RSE: relative standard error

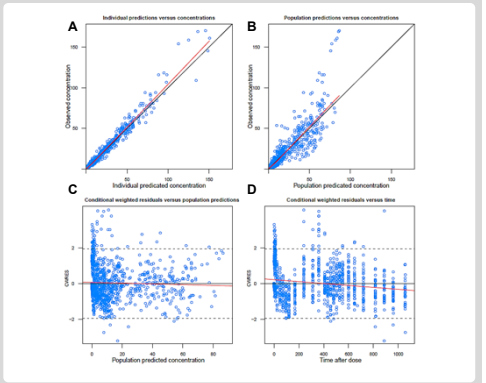

Figure 3. Basic model diagnosis plot produced using the final pharmacokinetic model. A Observed concentration (DV) vs. individual predictions (IPRED), B DV vs population predictions (PRED), C Conditional weighted residuals (CWRES) vs PRED, and D CWRES vs time after dose.

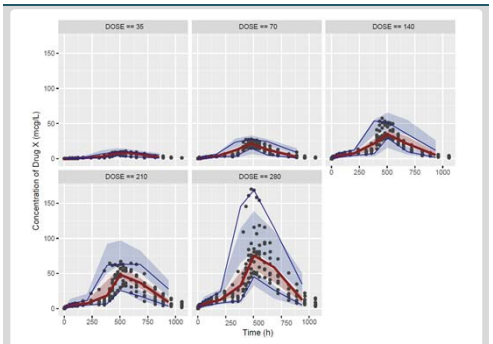

Figure 4. Visual prediction of the final pharmacokinetic model by dose in mg.

CONCLUSION

- A population PK model of the IM Drug X injection was developed and the corresponding PK parameters were estimated in healthy subjects.
- We hope that such model predictions may contribute towards selection of the dose for the dose finding phase II clinical study.

REFERENCES

- Beal SL, Sheiner LB, Boeckmann AJ & Bauer RJ (Eds.) NONMEM Users Guides. 1989-2015. Icon Development Solutions, Gaithersburg, Maryland, USA.

CONFLICT OF INTEREST

- The authors declare no conflict of interest to disclose.