I-45

Population Pharmacokinetic Analysis of Fampridine in Japanese Patients with Multiple Sclerosis in a Phase 3 Study

Hu X, Mehta LR, Prasad P

Biogen, Inc. Cambridge, MA, USA

25th Population Approach in Europe Meeting
7-10 June, 2016
Lisbon, Portugal

INTRODUCTION

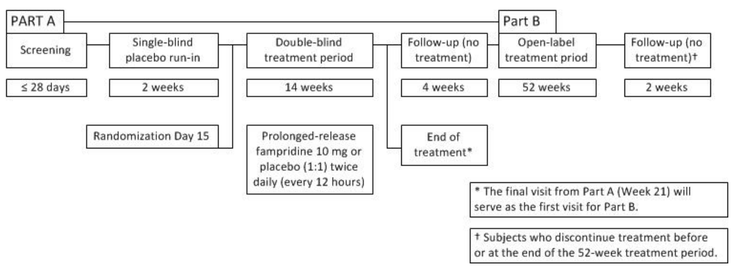
- Multiple sclerosis (MS) is an inflammatory condition that damages the myelin of the central nervous system (CNS) and causes neurological impairment, often leading to severe disability. Walking disability has been ranked by both MS patients and neurologists as having the greatest negative impact on quality of life. Fampridine has been extensively studied in Caucasian MS patient populations and approved in US and EU.[1] However, there are no drug therapies currently available in Japan to treat walking impairment in people with MS. Study 218MS304 was to assess the effect of prolonged-release fampridine 10 mg twice daily on walking ability in Japanese subjects with MS, as well as gather information about the safety and tolerability of long term fampridine treatment. Pharmacokinetic (PK) samples were collected in the study, to characterize PK in Japanese subjects, using population PK analysis. Herein we report the PK results of fampridine in Japanese MS patients.

OBJECTIVES

- The objective of the population PK analysis was to characterize the PK of fampridine in Japanese patients with MS.

METHODS

Figure 1. Study schematic (n= 24 males and 26 females)



PK sampling schedule

- Two blood samples were collected from each subject at the Week 9 Visit during Part A of the study: one at the beginning of the visit and the other 2 to 3 hours later. The time of the most recent dose and the sampling times were recorded. PK samples were also taken during unscheduled visits to enrich PK data.

Data Analysis

PK Structural model

$$P_i = \hat{P}\, exp(\eta_{P_i}) \qquad \text{(Eq. 3)}$$

$$C_{ij} = \hat{C}_{ij} + \varepsilon_{aij} \qquad \text{(Eq. 4)}$$

P_i: PK parameter; $\hat{P}$: typical value; η_{Pi}: inter-individual variabililty; C_{ij}: observed concentration; $\hat{C}_{ij}$: model-predicted concentration; ε_{ij}: random residual error.

Stochastic Model

$$\frac{d\,A_a}{dt} = -K_a * A_a \qquad \text{(Eq. 1)}$$

$$\frac{d\,Ac}{dt} = K_a * A_a - K_e * A_c \qquad \text{(Eq. 2)}$$

A_a: amount in absorption compartment; K_a: absorption rate; A_c: amount in central compartment; K_e: elimination rate.

Covariate screening

- A forward addition ($p \le 0.05$) followed by a backward deletion ($p \le 0.001$). The following covariates were tested based on previous PK modeling[1]:
  - Creatine clearance, sex, and age for CL
  - Sex for V

Modeling Software

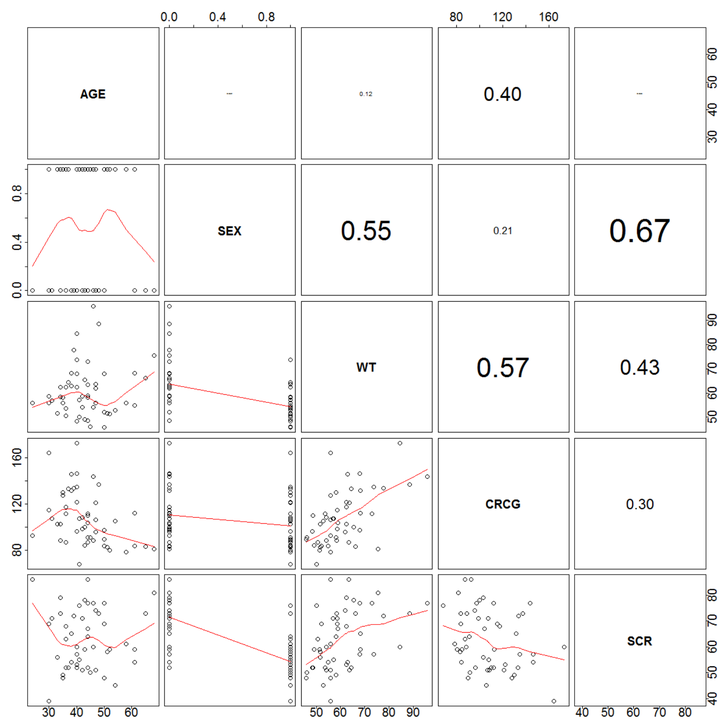
- SAS, R, NONMEM[2], Perl-speaks-NONMEM (PsN)[3,4]

RESULTS

Summary of Covariate Characteristics

- The baseline covariate correlation is shown in Figure 2. The summary of the continuous demographics at baseline are listed in Table 1.

Figure 2. Scatter plot matrix of covariates



From left to right, the x-axis represents age, sex, weight,creatinine clearance, and serum creatine concentration in the respective panel; from bottom to top, the y-axis represents serum creatine concentration, creatinine clearance, weight, sex, and age in the respective panel. Numbers in right upper panels represent correlation coefficient (r) between corresponding covariates for the intersecting panel.
WT: weight; CRCG: creatinine clearance; SCR: serum creatinine concentration.

Table 1. Summary of continuous covariates

Parameter	Mean	SD	Median	Low95	Up95	Low99	Up99	RANGELOW	RANGEUP
AGE (y)	43.3	9.07	42.5	30.0	64.1	25.5	67.3	24.0	68.0
WT (kg)	60.7	10.6	58.3	46.5	87.6	45.8	94.0	45.8	95.8
CRCG (mL/min)	108	23.4	105	78.7	160	70.5	171	68.0	173
SCR (mg/dL)	62.6	11.5	60.0	45.7	84.9	40.5	86.0	39.0	86.0

Population PK Model

PK Model

- The structural PK model was a one-compartment linear model with a first-order absorption rate.
- None of the covariates met criteria to be included in the final model ($p<0.001$).
- PK parameters are summarized in Table 2.

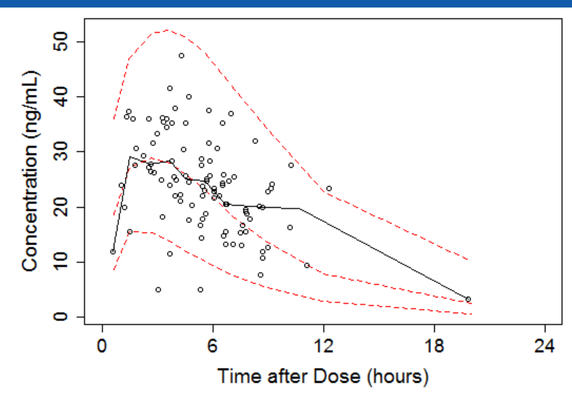
Table 1. Summary of continuous covariates

Parameter	Definition	Estimated value	Relative standard error (%)	Shrinkage
CL (L/h)	Clearance	41.3	5.12	2.1
V (L)	Volume of Distribution	91.1	20.5	NA
Ka (h-1)	Absorption Rate	0.168	11.7	NA
ω2CL	Intersubject Variance Of Cl	0.121	21.5	NA
σ2	Additive Random Error for Log-Transformed Data	0.0160	19.9	25.8

PK Model Evaluation

- The visual predictive check (VPC) of the final PK model is shown in Figure 3.
- VPC showed that the final structural and stochastic model described the data well.

Figure 3. PK model visual predictive check

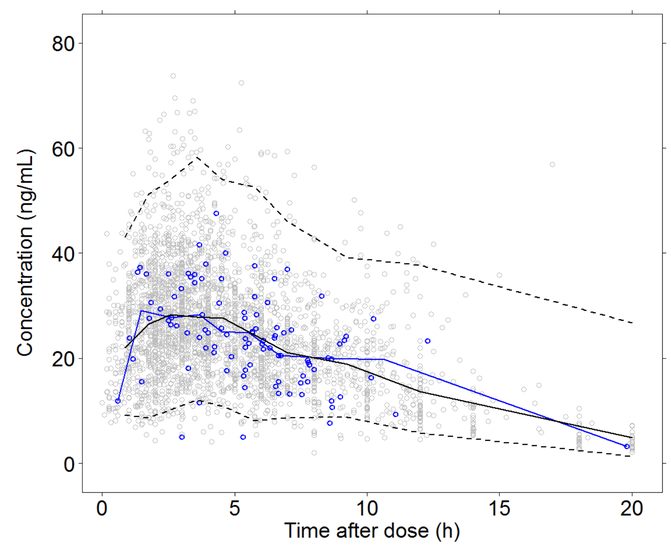


Circles represent observed data; solid line represent medians of observed data; dashed lines from bottom to top represent the 2.5th, 50th and 97.5th percentiles of the simulated data using the final PK model.

Data Comparison to Caucasian Patients

- The PK profiles from Study 218MS304 were compared to earlier historic data, as shown in Figure 4.
- The median data from study 218MS304 overlapped with those of earlier data, and almost all data fell within the [2.5th, 97.5th] range of historic data.
- All patients in study 218MS304 were Japanese, whereas one percent of the patients in the historic studies were Asian. Based on the comparison, the PK profiles from study 218MS304 were consistent with PK profiles observed in historic studies, despite differences in race composition.

Figure 4. Data comparison between historic data and data from Study 218MS304



Blue circles represent observed concentrations in Japanese subjects from Study 218MS304; solid blue line represents median concentration in Japanese subjects; grey circles present concentrations from historic studies AN751-102, MS-F201, MS-F202, MS-F203, and MS-F204;black lines from bottom to top represent the 2.5th, 50th and 97.5th percentiles, respectively, of the concentrations in historic studies.

CONCLUSIONS

- The disposition of fampridine in Japanese patients was well described by a one-compartment linear model with a first-order absorption rate. The PK profiles in Japanese MS patients from study 218MS304 were consistent with the PK profiles observed in earlier clinical trials, consisting mostly of Caucasian MS patients.

References

1. Weir S, Gao Y, Henney HR 3rd, Population pharmacokinetics and pharmacodynamics of dalfampridine-ER in healthy volunteers and in patients with multiple sclerosis. Curr Med Res Opin. 2013 Dec;29(12):1637-45. doi: 10.1185/03007995.2012.749222. Epub 2013 Sep 25.
2. Beal, SL and Sheiner, LB, NONMEM Users Guides – Part I-VII. NONMEM Project Group C255, University of California at San Francisco, San Francisco, 1988-1998.
3. Lindbom L, Pihlgren P, Jonsson EN. PsN-Toolkit--a collection of computer intensive statistical methods for non-linear mixed effect modeling using NON MEM. Comput Methods Programs Biomed. 2005, 79(3):241-57.
4. Lindbom L, Ribbing J, Jonsson EN. Perl-speaks-NONMEM (PsN)--a Perl module for NONMEM related programming. Comput Methods Programs Biomed, 2004, 75(2):85-94.

Disclosures

This research was supported by Biogen. All authors are employees of and hold stock/stock options in Biogen.