Population Pharmacokinetic Analysis of Fampridine in Japanese Patients with Multiple Sclerosis in a Phase 3 Study
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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. 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
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
\[ \frac{dC}{dt} = -\frac{CL}{V} C + \frac{F \cdot Dose}{V} \] (Eq. 1)
\[ \frac{dC}{dt} = -\frac{CL}{V} C + \frac{F \cdot Dose}{V} \] (Eq. 2)
\[ \frac{dC}{dt} = \frac{CL}{V} C + \frac{F \cdot Dose}{V} \] (Eq. 3)
\[ \frac{dC}{dt} = -\frac{CL}{V} C + \frac{F \cdot Dose}{V} \] (Eq. 4)
PK parameters: CL, clearance; V, volume of distribution; Dose, dose; F, bioavailability; C, concentration; t, time; C0, observed concentration; C, model predicted concentration; ε, random residual error.

Stochastic Model
\[ \frac{dA}{dt} = \frac{bA}{kA} - kA A \] (Eq. 5)
\[ \frac{dC}{dt} = \frac{bC}{kC} - kC C \] (Eq. 6)
\[ \frac{dC}{dt} = \frac{bC}{kC} - kC C \] (Eq. 7)
\[ \frac{dC}{dt} = \frac{bC}{kC} - kC C \] (Eq. 8)
A, amount in absorption compartment; C, amount in central compartment; k, elimination rate; b, absorption rate.

Covariate analysis
A forward addition (p ≤ 0.05) followed by a backward deletion (p ≤ 0.001). The following covariates were tested based on previous PK modeling:
- Creatinine clearance, sex, and age for CL
- Sex for V

Modeling Software
- SAS, NONMEM, Perl-speaks-NONMEM (PsN)

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.

Table 1. Summary of continuous covariates
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean</th>
<th>SD</th>
<th>Median</th>
<th>Lower95</th>
<th>Upper95</th>
<th>LowerSD</th>
<th>UpperSD</th>
<th>Lower99</th>
<th>Upper99</th>
<th>Lower.range</th>
<th>Upper.range</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGE (y)</td>
<td>43.3</td>
<td>9.67</td>
<td>42.5</td>
<td>30.0</td>
<td>64.1</td>
<td>25.5</td>
<td>67.3</td>
<td>24.0</td>
<td>66.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WT (kg)</td>
<td>60.7</td>
<td>10.6</td>
<td>58.3</td>
<td>45.6</td>
<td>67.4</td>
<td>43.8</td>
<td>49.4</td>
<td>45.8</td>
<td>95.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRCCG</td>
<td>156</td>
<td>23.4</td>
<td>105</td>
<td>78.7</td>
<td>179</td>
<td>70.9</td>
<td>171</td>
<td>60.0</td>
<td>172</td>
<td>32.4</td>
<td>108.6</td>
</tr>
<tr>
<td>SCR (mg/dL)</td>
<td>62.6</td>
<td>11.5</td>
<td>60.0</td>
<td>45.7</td>
<td>84.0</td>
<td>40.5</td>
<td>90.0</td>
<td>35.0</td>
<td>85.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Population 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
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition</th>
<th>Estimated value</th>
<th>Relative standard error (%)</th>
<th>Skewness</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL (L/h)</td>
<td>Clearance</td>
<td>41.0</td>
<td>5.12</td>
<td>2.1</td>
</tr>
<tr>
<td>V (L)</td>
<td>Volume of Distribution</td>
<td>91.1</td>
<td>28.5</td>
<td>NA</td>
</tr>
<tr>
<td>F(%)</td>
<td>Absorption Rate</td>
<td>0.168</td>
<td>11.7</td>
<td>NA</td>
</tr>
<tr>
<td>t1/2 (h)</td>
<td>Elimination half-life</td>
<td>1.021</td>
<td>21.5</td>
<td>NA</td>
</tr>
<tr>
<td>Amax (mg)</td>
<td>Additive Random Error for Log-transformed Data</td>
<td>0.0148</td>
<td>19.9</td>
<td>23.8</td>
</tr>
</tbody>
</table>

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
4. Canale J, Strauss H, Meza R, et al. A forward addition (p ≤ 0.05) followed by a backward deletion (p ≤ 0.001). The following covariates were tested based on previous PK modeling:

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