Introduction

Lacosamide (R-2-acetamido-N-benzyl-3-methoxypropionamide, formerly known as 5-acetamido-2-benzyl-3-methoxypropionamide) is a new drug under clinical development by Schwarz Biosciences for the treatment of epilepsy and neuropathic pain. About 40% of the drug is renally excreted as unchanged compound. Major metabolic pathway is demethylation, the inactive O-desmethyl-metabolite is excreted with the urine and represents about 30% of the dose.

Objectives

To characterize population pharmacokinetics of unchanged lacosamide in healthy elderly males and females (>65 years) in comparison to young healthy males (18–45 years)

To identify possible covariates that may have an influence on the pharmacokinetics (PK) of lacosamide in the trial population of healthy subjects to explain inter-individual variability

Study Design

Double-blind, placebo-controlled, parallel group trial

47 subjects in 3 groups: 15 elderly males (EM), 16 elderly females (EF), 16 young males (YM)

Day 1, 8: 100 mg lacosamide oral single dose administration

Day 4, 5, 6, 7: 100 mg lacosamide bid oral administration

Day 1, 8: 100 mg lacosamide oral single dose administration

33 blood samples were taken from Day 1 to Day 11 at the following time points:

- 0 (pre-dose), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72, 96, 120, 132, 144, 156 hours following first dose on Day 1

- 0 (pre-dose), 0.5, 1, 1.5, 2, 3, 4, 6, 12, 24, 36 and 72 hours following last dose on morning of Day 8

Tested Covariates

- Age
- Sex
- Body weight (BW)
- Height
- Body Mass Index (BMI)
- Creastinine Clearance (Clcrea)
- Calculated using Cockcroft-Gault equation based on serum creatinine, age, weight and sex

Pharmacokinetic Methods

- Software: NONMEM Version 5 in combination with PDxPop Version 1.1

- Subroutine ADVAN2: One-compartment model with first-order absorption and elimination with the parameters:
  - \( k_a \) rate constant of absorption
  - \( k_e \) rate constant of elimination
  - \( V/f \) apparent volume of distribution

Bioanalytical Method

- Highly sensitive and selective LC-MS/MS method for lacosamide with deuterated internal standard (solid-phase extraction)
- Calibration range: 0.01 – 10 µg/mL

Results

The following model was chosen as base model for the evaluation of possible covariates during the final model development:

- Combined residual random error model (proportional and additive component)
- No lag-time

Final Model Development

**Diagnostic Plots Covariates vs. Individual PK Parameters**

**Statistical Testing of Covariates**

The following table summarizes important steps of covariate testing on the base model (without covariates) during final model development:

<table>
<thead>
<tr>
<th>Description of covariates</th>
<th>OBF</th>
<th>IV of ( k_a ) [%]</th>
<th>IV of ( k_e ) [%]</th>
<th>IV of ( V/f ) [%]</th>
<th>Residual Error [Prop/Add.]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base Model</td>
<td>–1600.0</td>
<td>19.2</td>
<td>112</td>
<td>21.4</td>
<td>7.9%/0.06</td>
</tr>
<tr>
<td>Body weight on ( V/f )</td>
<td>–1415.1</td>
<td>21.5</td>
<td>123</td>
<td>40.9</td>
<td>7.6%/0.08</td>
</tr>
<tr>
<td>Height on ( V/f )</td>
<td>–1718.7</td>
<td>18.6</td>
<td>117</td>
<td>11.9</td>
<td>7.9%/0.06</td>
</tr>
<tr>
<td>Sex on ( V/f )</td>
<td>–1701.7</td>
<td>19.4</td>
<td>115</td>
<td>14.0</td>
<td>7.9%/0.06</td>
</tr>
<tr>
<td>Age on ( k_e )</td>
<td>–1222.2</td>
<td>35.4</td>
<td>119</td>
<td>25.0</td>
<td>7.4%/0.13</td>
</tr>
<tr>
<td>( \text{Cl}_{\text{Cr}} ) on ( k_e )</td>
<td>–1720.1</td>
<td>16.4</td>
<td>112</td>
<td>21.5</td>
<td>8.2%/0.06</td>
</tr>
<tr>
<td>Height on ( \text{Cl}_{\text{Cr}} ) on ( k_e )</td>
<td>–1783.0</td>
<td>15.9</td>
<td>117</td>
<td>10.3</td>
<td>8.2%/0.06</td>
</tr>
<tr>
<td>( \text{Cl}_{\text{Cr}} ) on ( k_e )</td>
<td>–1805.8</td>
<td>14.7</td>
<td>117</td>
<td>10.2</td>
<td>8.2%/0.05</td>
</tr>
</tbody>
</table>

**Statistical Testing of Covariates**

- **OBF** = Objective Function, **IV** = inter-individual variability

Final Model Development

**Statistical Testing of Covariates**

The following model was chosen as final model with the following characteristics:

- 1-comp-model with first-order absorption and elimination without lag-time (ADVAN2, FOCE)

- Height and sex as covariates on \( V/f \)

- \( \text{Cl}_{\text{Cr}} \) and sex as covariates on \( k_e \)

- Low inter-individual variability (~15 %) for \( V/f \) and \( k_e \)

- Low residual variability: 8.2 % (proportional error)

- 0.05 µg/mL (additive error)

- Predominantly high precision of final estimates (RSE<25 %)

**Final Population PK Parameter Estimates**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Final Estimate [%RSE]</th>
<th>IV [%RSE]</th>
</tr>
</thead>
<tbody>
<tr>
<td>( V/f ) [mg]</td>
<td>42.4 ± 4.4 with ( \text{Height}:69 ) + ( \text{Sex}:5 ) + Gender ( (2.7) )</td>
<td>10.2% [27.9]</td>
</tr>
<tr>
<td>( k_a ) [h⁻¹]</td>
<td>0.0225 + 0.6 ( \text{Cl}_{\text{Cr}} ) + + ( \text{Sex}:5 ) + Gender ( (17.2) )</td>
<td>14.7% [17.5]</td>
</tr>
<tr>
<td>( k_e ) [h⁻¹]</td>
<td>4.20 [122]</td>
<td>117% [29.1]</td>
</tr>
<tr>
<td>( C_{\text{ss}} ) [mg]</td>
<td>7.415 [23.7]</td>
<td>–</td>
</tr>
<tr>
<td>( C_{\text{ss}} ) [mg]</td>
<td>6.90 [23.5]</td>
<td>–</td>
</tr>
<tr>
<td>( C_{\text{ss}} ) [mg]</td>
<td>0.0004 [17.4]</td>
<td>–</td>
</tr>
<tr>
<td>( C_{\text{ss}} ) [mg]</td>
<td>0.0019 [23.9]</td>
<td>–</td>
</tr>
</tbody>
</table>

**Residual Error [%]**

- 8.15% / 0.0532 µg/mL [8.58, 35.1] –

**Statistical Testing of Covariates**

- A major part of inter-individual variability of \( V/f \) (~10 %) could be explained by differences in height and sex

- Observed higher plasma concentrations of lacosamide in females are the result of the smaller \( V/f \) in this subgroup

- Lacosamide is highly soluble in water and mainly distributed in extracellular fluid, changes in height are linked with changes in \( V/f \)

- A smaller part of inter-individual variability of \( k_e \) (~5 %) could be explained by differences in \( \text{Cl}_{\text{Cr}} \) and sex

Conclusion

- Adequate population PK model was developed for the description of plasma concentrations of lacosamide in healthy subjects.

- Inter-individual variability of \( V/f \) and \( k_e \) can be explained to a large extent by differences in height, sex and \( \text{Cl}_{\text{Cr}} \)

- Exposure of lacosamide is highly predictable in individuals.

- Current population PK model will be used as basis for PopPK evaluations in Phase 2/3 to verify the results in the target population.