INTRODUCTION

Zervia is a combination of 2 approved drugs, Dextromethorphan (DM) and Quinidine (Q), and is being developed for the treatment of Pseudobulbar Affect (PBA). The limited systemic delivery to the central nervous system (CNS) of DM may be a limiting factor of its efficacy in the treatment of different neurological disorders. Q is used as an inhibitor of DM metabolism by CYP2D6 enzymes to increase its bioavailability. A dose combination of 30 mg DM with 30 mg Q b.i.d. was used during the early development of Zervia. In order to improve the safety profile of the drug, the dose of Q was subsequently reduced to 10 mg b.i.d. The current dose formulations of Zervia in development for the treatment of PBA are DM 20 mg/Q 10 mg, and DM 30 mg/Q 10 mg. This dose of Q in Zervia is 1-3% of that used to treat arrhythmias.

OBJECTIVE

The objectives of this study were to determine the population pharmacokinetic (PK) parameters of Q, DM and its metabolite Dextrorphan (DX) in plasma after single and multiple doses of Zervia and to identify the impact of demographic covariates on the population parameter estimates.

DATA

The results of a series of Phase I – III studies were combined in order to perform a population PK analysis of Q, DM and its metabolite DX in plasma. Phase I: double-blind, randomized, placebo-controlled study in healthy volunteers.

• Dosing regimens (for 8 days): 45 mg DM/Q b.i.d., 30/10 mg DM/Q b.i.d., 20/10 mg DM/Q b.i.d., 20/10 mg DM/Q b.i.d., 10/5 mg DM/Q t.i.d. and a single dose of 30 mg DM/Q t.i.d. and once daily and placebo b.i.d.

• Plasma samples on Day 1 and Day 8.

• 60 subjects receiving active treatment were included.

• All subjects had extensive metabolizer (EM) genotype for CYP2D6.

Phase I: thorough QT trial (50 healthy volunteers)

• Clinical dose of 30 mg DM and 10 mg Q b.i.d.

• Plasma samples on Day 4.

• All subjects had the EM genotype for CYP2D6.

Phase II: multicenter safety and efficacy study in patients

• Dosing regimens were 30/10 mg DM/Q b.i.d. and 20/10 mg DM/Q b.i.d.

• 24 of the 326 patients had a rich PK sampling schedule at steady-state on Day 29.

• 22 were EM, 1 was ultra-metabolizer (UM) and 1 was intermediate-metabolizer (IM) of CYP2D6.

Data from 133 subjects were analyzed using a total of 5730 plasma samples on Day 4.

Phase I: double-blind, randomized, placebo-controlled study in healthy volunteers.

1 compartment for DX. The metabolic conversion of DM to DX was described by a sigmoidal Michaelis-Menten model related to Q concentrations, both at first-pass and systemically.

Figure 1: Structural PK Model for Q, DM and DX in Plasma

Table 1: Population PK Parameters for Quinidine

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean</th>
<th>Inter-subject variability (%CV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>tlag (h)</td>
<td>0.357</td>
<td>101</td>
</tr>
<tr>
<td>Ka (h⁻¹)</td>
<td>2.32</td>
<td>38.9</td>
</tr>
<tr>
<td>CL/F (L/h)</td>
<td>20.7</td>
<td>33.1</td>
</tr>
<tr>
<td>Vo/F (L)</td>
<td>173</td>
<td>30.1</td>
</tr>
<tr>
<td>Vc/F (L)</td>
<td>3.02</td>
<td>64.9</td>
</tr>
<tr>
<td>Vp (L)</td>
<td>33.3</td>
<td>38.7</td>
</tr>
</tbody>
</table>

Table 2: Population PK Parameters for DM and DX

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean</th>
<th>Inter-subject variability (%CV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aborption</td>
<td>0.597</td>
<td>38.9</td>
</tr>
<tr>
<td>Ka1 (h⁻¹)</td>
<td>0.791</td>
<td>57.7</td>
</tr>
<tr>
<td>Ka2 (h⁻¹)</td>
<td>0.555</td>
<td>47.6</td>
</tr>
<tr>
<td>CL/F (L/h)</td>
<td>11.7</td>
<td>43.2</td>
</tr>
<tr>
<td>CL/F (L/h)</td>
<td>431.5</td>
<td>31.1</td>
</tr>
<tr>
<td>Vo/F (L)</td>
<td>66.4</td>
<td>55.8</td>
</tr>
<tr>
<td>Vp/F (L)</td>
<td>459</td>
<td>52.0</td>
</tr>
<tr>
<td>Vc/F (L)</td>
<td>9.59</td>
<td>14.3</td>
</tr>
<tr>
<td>Vp/F (L)</td>
<td>17.4</td>
<td>31.7</td>
</tr>
<tr>
<td>Vc/F (L)</td>
<td>1.21</td>
<td>58.7</td>
</tr>
</tbody>
</table>

The residual error model was proportional and additive and parameters were normally distributed in the final model presented in Figure 1. The key feature of this model is the inhibition of both first-pass and systemic metabolism.

The model discrimination and selection for DM/DX was based on data from EM only (studies 1 and 2). A maximum posterior Bayesian (MAPB) analyses was performed on data from study 3 where there was one IM and one UM subjects. The model was adequate to fit these 2 subjects. Not enough data from genotypes other than EM were available to build a model with genotype as a covariate but the results of the MAPB analysis show that it would be something to explore in the future, pending data availability.

Table 2: Population PK Parameters for DM and DX

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean</th>
<th>Inter-subject variability (%CV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DM - Intra-subject variability (%CV)</td>
<td>5.81</td>
<td></td>
</tr>
</tbody>
</table>

Figure 3: Predicted Metabolic Clearance of DM

Figure 4: External Validation – Distribution of the Percentiles of Observed Concentrations

The PK of Q, DM and DX are well described by the population PK model developed. None of the available covariates were considered significantly correlated with any of the PK parameters. The external validation results show that the model predicts well the plasma PK of Q, DM and DX and can be used for the MAPB analysis of other sets of data or to predict the outcome of different dosing regimens for future clinical use.

CONCLUSION

The model PK of Q, DM and DX are well described by the population PK model developed. None of the available covariates were considered significantly correlated with any of the PK parameters. The external validation results show that the model predicts well the plasma PK of Q, DM and DX and can be used for the MAPB analysis of other sets of data or to predict the outcome of different dosing regimens for future clinical use.

REFERENCE


POPULATION PHARMACOKINETIC META ANALYSIS: INHIBITION BY QUINIDINE OF THE FIRST-PASS AND SYSTEMIC METABOLISM OF DEXTROMETHORPHAN TO DEXTORPHAN

J. Grenier & Ph.D., JR. Lavigne & M.Sc., LE. Pope & Ph.D.

Clinical Pharmacology Department, Celerion, Montréal, QC, Canada

Avanir Pharmaceuticals, Aliso Viejo, CA, USA

www.celerion.com

Figure 3: Predicted Metabolic Clearance of DM

Figure 4: External Validation – Distribution of the Percentiles of Observed Concentrations

Quinidine

Dextromethorphan

Dextrorphan

CONCLUSION

The model discrimination and selection for DM/DX was based on data from EM only (studies 1 and 2). A maximum posterior Bayesian (MAPB) analyses was performed on data from study 3 where there was one IM and one UM subjects. The model was adequate to fit these 2 subjects. Not enough data from genotypes other than EM were available to build a model with genotype as a covariate but the results of the MAPB analysis show that it would be something to explore in the future, pending data availability.

REFERENCE


www.celerion.com

Figure 3: Predicted Metabolic Clearance of DM

Figure 4: External Validation – Distribution of the Percentiles of Observed Concentrations

Quinidine

Dextromethorphan

Dextrorphan

CONCLUSION

The model discrimination and selection for DM/DX was based on data from EM only (studies 1 and 2). A maximum posterior Bayesian (MAPB) analyses was performed on data from study 3 where there was one IM and one UM subjects. The model was adequate to fit these 2 subjects. Not enough data from genotypes other than EM were available to build a model with genotype as a covariate but the results of the MAPB analysis show that it would be something to explore in the future, pending data availability.

REFERENCE


www.celerion.com

Figure 3: Predicted Metabolic Clearance of DM

Figure 4: External Validation – Distribution of the Percentiles of Observed Concentrations

Quinidine

Dextromethorphan

Dextrorphan

CONCLUSION

The model discrimination and selection for DM/DX was based on data from EM only (studies 1 and 2). A maximum posterior Bayesian (MAPB) analyses was performed on data from study 3 where there was one IM and one UM subjects. The model was adequate to fit these 2 subjects. Not enough data from genotypes other than EM were available to build a model with genotype as a covariate but the results of the MAPB analysis show that it would be something to explore in the future, pending data availability.

REFERENCE


www.celerion.com