Clinical Trial Simulations Using a Pharmacokinetic/Enzyme-Occupancy/Pharmacodynamic Model of TAK-935, a Cholesterol 24S-Hydroxylase Inhibitor

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Introduction

TAK-935 is a potent and selective inhibitor of cholesterol 24S-hydroxylase (CYP27A1), which constitutes the enzyme that catalyzes the final step in cholesterol synthesis from 24-25-cholestadienol (CD243) and is involved in hepatic de novo cholesterol synthesis.

Based on adult clinical data, a population pharmacokinetic (PK)/pharmacodynamic (PD) model was developed to guide dose selection in children (aged ≥2 and <12 years), adolescents (aged ≥12 and ≤18 years), and adults (aged ≥18 years). The model was intended to allow for individualized dose assignment in adolescents and adults based on body size and pharmacokinetic parameters.

Methods

PK/PD database

1. A population PK/PD model was developed to describe the time course of 24HC in plasma. First, model parameters were estimated from the PK/PD model using a semi-mechanistic inhibitory indirect response model, which resulted in an EC50 of 5.44 ng/mL.

2. In addition, 24HC decreased by more than 60% from baseline (Figure 5). In addition, 24HC decreased by more than 60% from baseline (Figure 5).

3. The model database is a collection of 860 plasma measurements from 166 subjects and 2207 PB/PD measurements. From PB data, subjects, in addition to 25 individuals from 15 individuals are available.

Table 1. Overview of Phases Studied Included in the PK/PD Data Set

<table>
<thead>
<tr>
<th>Phase</th>
<th>Study Design</th>
<th>Study Size</th>
<th>Population Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 1</td>
<td>Double-blind, placebo-controlled</td>
<td>126 subjects</td>
<td>Aged 19 to 55 years, inclusive</td>
</tr>
<tr>
<td>Phase 2</td>
<td>Double-blind, placebo-controlled</td>
<td>108 subjects</td>
<td>Aged 18 to 55 years, inclusive</td>
</tr>
<tr>
<td>Phase 3</td>
<td>Double-blind, placebo-controlled</td>
<td>108 subjects</td>
<td>Aged 18 to 55 years, inclusive</td>
</tr>
</tbody>
</table>

Results

Population PK Model

A population PK/PD model was developed to describe the time course of 24HC in plasma. First, model parameters were estimated from the PK/PD model using a semi-mechanistic inhibitory indirect response model, which resulted in an EC50 of 5.44 ng/mL.

Parameter Estimates

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>Standard Error</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>EC50 (ng/mL)</td>
<td>5.44</td>
<td>NA</td>
<td>22</td>
</tr>
<tr>
<td>IIV on EC50</td>
<td>0.229</td>
<td>0.093</td>
<td>30</td>
</tr>
<tr>
<td>IIV on VC</td>
<td>0.3132</td>
<td>0.093</td>
<td>30</td>
</tr>
</tbody>
</table>

Figure 7. Simulated and Observed PD Parameters and PD Profiles for Different TAK-935 Dosing Regimens from 3 to 9 mg/kg.

Summary

In summary, the developed PK/PD model is a valuable tool for evaluating the potential of TAK-935 for the treatment of patients with rare epilepsies. The model is validated using a semi-mechanistic inhibitory indirect response model, which resulted in an EC50 of 5.44 ng/mL.

Acknowledgments

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References

