Population Pharmacokinetic and Exposure-Response Analysis of Linagliptin in Pediatric Patients with Type 2 Diabetes Mellitus

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Summary

• Linagliptin is a DPP-4 inhibitor approved for the treatment of type 2 diabetes mellitus (T2DM) in adults.
• Study 1218.91 [1] was a trial to evaluate the efficacy and safety of empagliflozin and linagliptin over 26 weeks, with a double-blind active treatment strategy. Safety extension period up to 52 weeks, with children and adolescents with T2DM.
• Models for linagliptin, previously developed with data from adults and adolescents with T2DM, were re-estimated in a Bayesian framework using only the pediatric data from 1218.91 to characterize pediatric pharmacokinetics (PK) and exposure-response (ER) and compare to adults. The ER-endpoint of interest was HbA1c.
• Slightly larger but more variable linagliptin exposures were achieved for a 5 mg dose in pediatric subjects relative to adults.
• Pediatric patients achieved a smaller, but highly variable, placebo-adjusted HbA1c decrease relative to adults at week 26 (Figure 4).
• The Bayesian estimation approach enabled the characterization of linagliptin PK and ER in a limited sample of pediatric patients, borrowing from what is already known about PK and ER in adults.

Demographics

Table 1: PK model: comparison of baseline continuous covariates by study

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adults</th>
<th>Pediatric</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>63</td>
<td>22</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>103</td>
<td>97.2</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.73</td>
<td>1.72</td>
</tr>
<tr>
<td>Estimated GFR (ml/min)</td>
<td>87.5</td>
<td>82.9</td>
</tr>
<tr>
<td>DPP-4 Activity (RFU)</td>
<td>981</td>
<td>1010</td>
</tr>
</tbody>
</table>

Table 2: ER model: comparison of baseline continuous covariates by study

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adults</th>
<th>Pediatric</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linagliptin AUCss (nmol*h/L)</td>
<td>458</td>
<td>40</td>
</tr>
<tr>
<td>Placebo-adjusted HbA1c change from baseline (%)</td>
<td>-0.5</td>
<td>-0.6</td>
</tr>
<tr>
<td>Hemoglobin A1c change from baseline (%)</td>
<td>-0.9</td>
<td>-0.6</td>
</tr>
</tbody>
</table>

Figure 2: PK model: Distributions of AUCss values from Monte Carlo simulations in adults and pediatric patients using the previous model and the current model respectively.

Methods

• The PK model included 227 observations from 63 patients receiving linagliptin 5 mg once daily. The ER model included 309 total observations from 99 patients receiving linagliptin (N=48) or placebo (N=51).
• The PK model included informative priors using the point and uncertainty estimates from the previous model for all parameters except CL/F and V2/F which used weakly informative priors during estimation.
• The ER model included an informative prior for the AUC, producing half-maximal inhibitory effect parameter (AUC50), while all other parameters used uninformative priors.
• Monte Carlo simulations were performed to compare population level endpoints for PK (AUC50) and ER (placebo-adjusted HbA1c change from baseline at 26 weeks) in adults and pediatric patients.
• All analyses performed on the Metworx™ computing platform using a suite of open-source tools [2].

Results

Figure 3: ER model: Visual predictive check for HbA1c change from baseline versus time after dose.

Figure 4: ER model: Box plot of placebo-adjusted HbA1c change from baseline at week 26 in pediatric subjects compared to adults (-0.41% vs. -0.61%) (Figure 2).

Figure 5: ER model: Impact of AUC50 at half-maximal inhibition of HbA1c production rate (AUC50) Bayesian prior variances and scale on typical linear estimates.

References


QR code

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