Comparison of Non-compartmental Analysis Estimation and Population Pharmacokinetic Predictions of Exposure Changes as a Function of Renal Impairment

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Disclaimer

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Research Objective

To compare exposure changes as a function of renal impairment utilizing
1. Non-compartmental analysis estimation
2. Population pharmacokinetics predictions
Methods: Inclusion/Exclusion Criteria

Survey of NMEs (2000 and 2015) (N=373)

Dedicated Renal impairment Study (Full Study Design) (N=100)

Dedicated RIS and PopPK from Phase II/III (N=44)

Reports available (N=28)

RFI is not significant covariate (N=10)

Combination drugs (N=1)

Total # of NMEs Included (N=17)
Excluded Cases
Methods

• Renal impairment classification was based on C-G equation as follows:
  – Normal: CrCL ≥ 80 mL/min
  – Mild: CrCL ≥ 50-<80 mL/min
  – Moderate: CrCL ≥ 30-<50 mL/min
  – Severe: CrCL<30 mL/min

• Submitted PopPK models were used to predict observed AUC for each subject enrolled in RIS
  – 1000 simulation per subject
  – The non-parametric prediction interval for AUC GMR was calculated by computing the 5\textsuperscript{th} and 95\textsuperscript{th} percentiles of the model-based predicted GMR based on the 1000 simulations
## Results: Description

### RIS

<table>
<thead>
<tr>
<th>Normal Renal Function</th>
<th>Mild Renal Impairment</th>
<th>Moderate Renal Impairment</th>
<th>Severe Renal Impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Number of Subjects Included</td>
<td>8</td>
<td>8</td>
<td>7</td>
</tr>
</tbody>
</table>

### PopPK

| Median Number of Subjects Included | 636 | 166 | 12 | 4 |
Results: Concordance

Number of Cases where AUC Geometric Mean Ratios (GMR) was not within the Same Fold

<table>
<thead>
<tr>
<th></th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obs</td>
<td>0/17 (0%)</td>
<td>4/16 (25%)</td>
<td>5/17 (29%)</td>
</tr>
<tr>
<td>Pred</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Symbols:
- fe<30%
- fe≥30%
Potential Factors for Differences

- Fraction excreted in urine.
- Inclusion of RIS data in PopPK model development
- Number of subjects with renal impairment in phase II/III trials
- Covariate model
  - Inclusion of correlated covariates
Results: Colinearity of Covariates was a Major Factor in Differences

Number of Cases where AUC Geometric Mean Ratios (GMR) was not within the Same Fold

<table>
<thead>
<tr>
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<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colinearity</td>
<td>0/7 (0%)</td>
<td>4/7 (57%)</td>
<td>4/7 (57%)</td>
</tr>
<tr>
<td>No colinearity</td>
<td>0/10 (0%)</td>
<td>0/9 (0%)</td>
<td>1/10 (10%)</td>
</tr>
</tbody>
</table>

fe<30%  fe≥30%
Conclusions

• In general, there is a good concordance between PopPK and NCA results

• Inclusion of correlated covariates in model development increases the discordance between PopPK predictions and NCA analysis
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