Final estimates of the population PK parameters for BU

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>Parameter</th>
<th>Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>θ_{CL,F} (L/h)</td>
<td>10.6 (11.1)</td>
<td>θ_{V,F}</td>
<td>0.328 (56)</td>
</tr>
<tr>
<td>θ_{CL,P} (L)</td>
<td>46.8 (11)</td>
<td>ω_{CL,P} (%)</td>
<td>25.2 (21)</td>
</tr>
<tr>
<td>θ_{V,P} (h⁻¹)</td>
<td>1.68 FIX</td>
<td>ω_{V,P} (%)</td>
<td>19.7 (51)</td>
</tr>
<tr>
<td>q_{UL}</td>
<td>-2.06 (60)</td>
<td>ω_{IOV-CL,F} (%)</td>
<td>19.1 (41.6)</td>
</tr>
<tr>
<td>q_{UL2}</td>
<td>0.418 (68)</td>
<td>σ² (%)</td>
<td>16.3 (24)</td>
</tr>
<tr>
<td>θ_{UL}</td>
<td>-10.2 (63)</td>
<td></td>
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</tr>
</tbody>
</table>

θ_{CL,F} = BU clearance for an individual with average age and weight; θ_{V,F} = BU volume of distribution for a male with average weight; θ_{CL,P} = absorption rate constant; θ_{UL} = multiplier of BU clearance for the rate (age/mean population age); ω_{CL,P} = power of weight in power function predicting BU clearance; ω_{V,P} = power of weight in power function predicting BU V/F; ω_{IOV-CL,F} = interoccasion PK parameter variance; σ² = residual error variance.

Precision (standard error of the estimate) expressed as fraction of estimate (in parenthesis).

The Goodness of fit plots for the final population PK model:

PK model and Individual Maximum a Priori Bayes BU predictions

Individual MAP Bayes BU predictions (solid line), population predictions (dashed line) and observed concentrations (dots), after the first dose of BU. BU concentrations (DV, PRED and IPRED) are in ng/mL.

**RESULTS**

- Basic popPK model: One-compartment model with first-order absorption and elimination.
- Parameter estimation:
  - FOCE with INTERACTION
  - Interindividual variability (IIV): (Lognormal)
    - Clearance (Cl/F) → 30%
    - Volume of distribution (V/F) → 27%
  - Intercocassion variability (IOV): (Lognormal)
    - It was only retained for Cl/F → 19%
  - Measurement error variability:
    - Proportional normal distribution → 16%
- Model covariates:
  - weight and age for Cl/F
  - sex and weight for V/F
- Final model: A 4% and 7% reduction in unexplained IIV was found for Cl/F and V/F, respectively.

**CONCLUSIONS**

- BU pop-PK parameters were consistent with those previously published.
- Body weight, sex and age were important determinants on Cl/F and V/F.
- Results from this study could be used to optimize the initial and maintenance oral BU dosage in daily practic.