The graphical PK-PD analysis aimed to assess and compare PK-safety and PK-relationships following IV and SC RTX in CLL patients.

**BACKGROUND**

- Rituximab (RTX) intravenous (IV) formulation is approved for treating many B-cell lymphomas. A subcutaneous (SC) formulation of rituximab has been developed and approved for non-Hodgkin’s lymphoma. SC dosing for patients with chronic lymphocytic leukemia (CLL) was investigated in a number of studies.
- The aim of the population PK analysis was to characterize the PK properties of RTX following IV and SC administration in CLL patients and to identify covariate factors that influence its disposition in this population.
- The graphical PK-PD analysis aimed to assess and compare PK-safety and PK-relationships following IV and SC RTX in CLL patients.

**PK METHODS**

**Data**

- 255 patients from 2 studies (Phase Ib and III) contributed 4739 serum concentration values (1777 and 2962 values following SC and IV administration). Of 255 subjects, 140 subjects received at least 1 SC dose.
- RTX dosing regimens (28-day cycles):
  - IV: Cycle 1: 375 mg/m² IV, Cycles 2-6 500 mg/m² IV;
  - SC1: 5 cycles of IV regimen, Cycle 6: various SC doses up to 2200 mg
  - SC2: Cycle 1: 375 mg/m² IV, Cycles 2-6 1600 mg SC
- RTX dosing:
  - Study 1: IV regimen,

**Modeling**

- Nonlinear mixed-effects modeling was performed using NONMEM 7.3.0 with FOCEI method.
- The full model approach was used for covariate model development. Multiple covariates chosen based on mechanistic plausibility, exploratory analysis and scientific interest were simultaneously added to model parameters.
- Tested covariates: body weight, BSA, BMI, gender, age, and baseline values of white blood cells (WBC), tumor size (BSIZ), and serum albumin. Other covariates: normalized creatinine clearance, markers of hepatic impairment, presence of anti-drug antibodies, and B-cell count at baseline (that was confounded with WBC but had more missing values) were evaluated by diagnostic plots.

**PK RESULTS & CONCLUSIONS**

The final population PK model:

- 2-compartment model with first order SC absorption and time-dependent clearance:
  \[ CL_{sc} + CL_{a} = CL_{c} \exp(-ka(t)) \]
- Steady-state PK parameters typical for a monoclonal antibody (Table 1);
- CL, declined with half-life of 17.4 days; simulation indicated that concentrations approached the steady-state levels after approximately six 28-day cycles;
- Clearance (both, \( CL_{a} \) and \( CL_{c} \) terms), \( V_{c} \), \( V_{p} \), and Q increased with BSA. In subjects with extreme values of BSA, clearance and central volume were within 25% and 16% of the corresponding values for subjects with mean BSA;
- Central volume was 9% lower in females compared to males;
- SC absorption parameters \( k_{a} \) and \( F_{sc} \) decreased with increasing BMI;
- Consistent with target-mediated elimination, \( CL_{c} \) was higher in subjects with higher WBC and BSIZ;
- Anti-drug antibodies were detected in 13 subjects; they did not influence the concentration-time course;
- Conditional simulations demonstrated that, while flat SC dosing leads to larger differences in exposure (\( C_{trough} \) and AUC) between subjects with low and high body sizes compared to body-weight-adjusted IV dosing, for SC2 regimen it allows to maintain \( C_{trough} \) and AUC values for all body-size groups at levels not lower than levels attained by IV regimen, thus achieving at least the same target saturation as for IV regimen.

**PKPD Results & Conclusions**

The analysis demonstrated that the RTX SC regimen (SC2) tested in CLL patients provides exposures that are equal or higher compared to the reference RTX IV regimen across the whole range of body sizes, while there are no differences between IV and SC treatments in exposure-safety relationships. The analysis supports the conclusion that switch to the SC route of administration does not impair the anti-B-cell activity of RTX.

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**Table 1. Parameter Estimates of the Final Model**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>%RSE</th>
<th>Parameter</th>
<th>Estimate</th>
<th>%RSE</th>
<th>Shrinkage</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL_{IV} (mL/day)</td>
<td>207</td>
<td>2.62</td>
<td>FSC,RTX</td>
<td>0.465</td>
<td>35.6</td>
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<tr>
<td>V_{c} (mL)</td>
<td>990</td>
<td>1.82</td>
<td>CL_{IV}</td>
<td>0.223</td>
<td>34.2</td>
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<tr>
<td>V_{p} (mL)</td>
<td>3700</td>
<td>1.97</td>
<td>CL_{SVASI}</td>
<td>0.261</td>
<td>21.1</td>
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<tr>
<td>Q (mL/day)</td>
<td>420</td>
<td>3.23</td>
<td>CV=59.7%</td>
<td>10.3</td>
<td>13.2%</td>
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<tr>
<td>k_{a} (1/day)</td>
<td>0.372</td>
<td>3.86</td>
<td>CV=43.1%</td>
<td>9.4</td>
<td>10.5%</td>
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<tr>
<td>F_{sc}</td>
<td>0.633</td>
<td>2.52</td>
<td>CV=32.5%</td>
<td>10.5</td>
<td>7.6%</td>
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<tr>
<td>CL_{SC} (mL/day)</td>
<td>1550</td>
<td>8.14</td>
<td>R=0.47</td>
<td>15.2</td>
<td>7.6%</td>
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<tr>
<td>k_{EGA} (1/day)</td>
<td>0.0399</td>
<td>5.19</td>
<td>CV=18.0%</td>
<td>11.3</td>
<td>9.9%</td>
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<tr>
<td>CL_{EGBA} / CV</td>
<td>1.37</td>
<td>12.3</td>
<td>CV=34.0%</td>
<td>17.7</td>
<td>9.1%</td>
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<tr>
<td>FSC</td>
<td>0.80</td>
<td>11.4</td>
<td>CV=21.3%</td>
<td>19.0</td>
<td>7.9%</td>
<td></td>
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<tr>
<td>CL_{EGBA}</td>
<td>0.909</td>
<td>2.96</td>
<td>CV=21.3%</td>
<td>19.0</td>
<td>7.9%</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 1: Model-Based Conditional Simulations**

Graphical PK-PD analysis showing IV and SC dosing regimens.