Rapid and sustained B-cell depletion with ofatumumab: Population pharmacokinetic B-cell modeling in relapsing multiple sclerosis patients

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Disclosures

Gordon Graham, Huixin Yu, Olivier J. David, Joseph Kahn, Marina Savelieva, Ratnakar Pingili, Roman Willi, Krishnan Ramanathan, Dieter A. Häring, and Morten Bagger are employees of Novartis

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Background and objective

- Ofatumumab, an FDA-approved, fully human anti-CD20 monoclonal antibody, with a 20 mg s.c. monthly dosing regimen, is indicated for the treatment of relapsing forms of MS, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.

- In the Phase 2b MIRROR dose finding study, ofatumumab s.c.:
  - depleted B cells in a dose- and frequency-dependent manner
  - reduced Gd+T1 lesions by over 90% (cumulative doses ≥30 mg) relative to placebo

- In the Phase 2 APLIOS study:
  - ofatumumab 20 mg s.c. resulted in rapid and close to complete B-cell depletion over 12 weeks
  - bioequivalence was demonstrated between prefilled syringe and auto injector pen

- In the Phase 3 ASCLEPIOS I/II trials, ofatumumab 20 mg s.c. resulted in rapid and sustained B-cell depletion over 96 weeks

Objective

To characterize the PK relationship of ofatumumab for B-cell counts in RMS patients, assess the PK and B-cell dynamics of the given Phase 3 dose regimen through PK B-cell simulations and explore the effect of selected covariates on PK and B-cells

**Data and methods**

**Model choice and covariate selection**

<table>
<thead>
<tr>
<th>Studies included</th>
<th>Phase</th>
<th>Population and sample size</th>
<th>Administration route and device</th>
<th>Ofatumumab dosage regimen</th>
<th>Study duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>OMS115102&lt;sup&gt;1&lt;/sup&gt;</td>
<td>2</td>
<td>RRMS; N=25</td>
<td>i.v.</td>
<td>100, 300 or 700 mg</td>
<td>48 weeks+FU</td>
</tr>
<tr>
<td>MIRROR&lt;sup&gt;2&lt;/sup&gt;</td>
<td>2</td>
<td>RRMS; N=231</td>
<td>s.c. by PFS</td>
<td>0, 3, 30, or 60 mg q12w or 60 mg q4w</td>
<td>48 weeks+FU</td>
</tr>
<tr>
<td>APLIOS&lt;sup&gt;3&lt;/sup&gt;</td>
<td>2</td>
<td>RMS; N=284</td>
<td>s.c. by PFS or AI</td>
<td>20 mg q4w after 20 mg initial doses at days 1, 7, and 14</td>
<td>12 weeks</td>
</tr>
<tr>
<td>ASCLEPIOS I and II&lt;sup&gt;4&lt;/sup&gt;</td>
<td>3</td>
<td>RMS; N=946</td>
<td>s.c. by PFS</td>
<td>20 mg q4w after 20 mg initial doses at days 1, 7, and 14</td>
<td>Up to 120 weeks (30 months)</td>
</tr>
</tbody>
</table>

- Nonlinear mixed effects modeling was performed using Monolix (v.2019R2) and R (v.3.6.1) programs
- Simultaneous fitting was performed to assess the relationship between PK and B-cells
- Only covariates with significant effect based on Wald test were included in the final model

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**Effect of following covariates on PK and B-cell parameters were evaluated:**

- Body weight
- Gender
- Baseline age
- Race
- Route of administration
- s.c. injection device
- Baseline B-cell count
- Study

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Results

Covariate summary statistics from the five pooled studies

<table>
<thead>
<tr>
<th>Administration route/ s.c. formulation*</th>
<th>Gender (% female)</th>
<th>Age, years</th>
<th>Weight, kg</th>
<th>Race (n)</th>
<th>CD19+ B-cell count (cell/µL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1461 patients (s.c. administration)</td>
<td>67.8</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Caucasian, n=1354</td>
<td>225.8 (127.5)</td>
</tr>
<tr>
<td>25 patients (i.v. administration)</td>
<td></td>
<td>Median [range]</td>
<td>Median [range]</td>
<td>Black, n=36</td>
<td>200.0 [0–1520]</td>
</tr>
</tbody>
</table>

*Total number of patients included from 5 studies: OMB115102 (IV; N=25), MIRROR (PFS; N=231), APLIOS (PFS; N=143 and AI; N=141), ASCLEPIOS I and II (PFS; N=946)
AI, autoinjector; i.v., intravenous; PFS, prefilled syringe; s.c., subcutaneous; SD, standard deviation; N, number of patients from each study included in this analysis, n, number of patients
Results
Final PK B-cell model and selected covariates for analysis

PK analysis
9168
Plasma concentrations
from 1440 patients

B-cell analysis
17158
B-cell counts
from 1486 patients

Final PK B-cell model

• PK model: a quasi-steady state binding model with two compartments and a first order absorption for s.c. administration with a time effect on the target synthesis rate
• Covariates included: weight, i.v. route of administration, AI device

• B cell model: an indirect response model to describe the stimulation of B-cell lysis by free ofatumumab concentrations
• Covariates included: weight, age, baseline B-cell counts, study

AI, autoinjector; i.v. intravenous; PK, pharmacokinetic; s.c., subcutaneous
Ofatumumab concentrations over time remained within the range needed for ensuring PD effect

- The ofatumumab initial dosing regimen ensured rapid attainment of relevant pharmacological levels.
- The q4w maintenance regimen ensured low and sustained levels of exposure.
- The simulated median concentration profile decreased below the LOQ ~66 days after the last dose.

Ofatumumab concentrations simulated below 0.05 mg/L were left censored at 0.05 mg/L. *Simulation is for subcutaneous route with PFS and using Phase 3 dosage regimen.

LOQ, lower limit of quantification; PD, pharmacodynamic; PFS, prefilled syringe; q4w, every 4 week.
Ofatumumab 20 mg s.c. demonstrated rapid B-cell depletion and repletion after treatment interruption.

Simulated median and 90% prediction interval*

- Median B-cell depletion to <10 cells/µL was achieved in 8.75 days, with negligible signs of B-cell repletion between doses.
- Over 94% of patients had <10 cells/µL at B-cell steady state and pre-dose.

- The median B cell profile returns to the LLN of 40 cells/µL ~23 weeks after the last dose.

B cell counts simulated below 0 cells/µL were left censored at 0. *Simulation is for subcutaneous route with PFS and using Phase 3 dosage regimen. LLN. Lower limit of normal; PFS, prefilled syringe; s.c. subcutaneous.
**Ofatumumab effect on B cells was independent of weight effect on PK**

- Effect of weight on the steady state $\text{AUC}_{\tau}$ (wks 104-108) was 71.8% higher and 52.0% lower for a 50 kg ($5^{\text{th}}$ weight percentile) and 110 kg ($95^{\text{th}}$ weight percentile) patients relative to a 70 kg patient (median), respectively.
- Steady state maximum concentration resulted in 66.8% increase and 51.1% decrease respectively.
- Baseline age, B-cell counts and injection device had negligible effect on PK exposure. While there is a weight effect on PK, B cell depletion is independent of weight.

*Simulation is for subcutaneous route with PFS and using Phase 3 dosage regimen.
AUC, area under the curve; LLN, lower limit of normal; PFS, prefilled syringe; PK, pharmacokinetic; wks, weeks
Conclusions

- The PK-B cell model demonstrates the rapid and sustained B-cell depletion with the ofatumumab 20 mg s.c., which is associated with the favorable efficacy and tolerability as shown in the phase 3 ASCLEPIOS studies\(^1\).

- The PK-B cell model confirmed the rationale for choosing ofatumumab 20 mg s.c. as the Phase 3 dosing regimen.

- No change in the dosing regimen is warranted based on body weight, baseline age, B-cell counts and injection device.

- While there is a weight effect on PK, B-cell depletion is independent of weight.

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PK, pharmacokinetic; s.c. subcutaneous


Thank you