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

Gordon Graham[1], Huixin Yu[1], Olivier J. David[1], Joseph Kahn[2], Marina Savelieva[1], Ratnakar Pingili[2], Roman Willi[1], Krishnan Ramanathan[1], Dieter A Häring[1], Morten Bagger[1]

Poster Number: P0396

[1]Novartis Pharma AG, Basel, Switzerland; [2]Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA

Poster Presentation at the 8th Joint ACTRIMS-ECTRIMS Meeting, MS Virtual 2020, September 11–13, 2020

Scan to download a copy of this presentation

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

The study was funded by Novartis Pharma AG, Basel, Switzerland

Medical writing support was provided by **Vimal Kumar Muthyala** and **Uma Kundu** (employees of Novartis Healthcare Pvt. Ltd., Hyderabad, India). The final responsibility for the content lies with the authors

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[1]
- In the Phase 2b MIRROR dose finding study, ofatumumab s.c.[2]:
  - 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[3]:
  - 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[4]

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**

FDA, Food and Drug Administration; Gd+, gadolinium-enhancing; PK, pharmacokinetic; MS, multiple sclerosis; s.c., subcutaneous

1. KESIMPTA® (ofatumumab) Prescribing Information. https://www.novartis.us/sites/www.novartis.us/files/kesimpta.pdf (accessed Aug 24, 2020).
2. Bar-Or A, et al. Neurology 2018; 90 (20) e1805-e1814.
3. Bar-Or A, et al. Presented at the *ACTRIMS* 2020; P#LB300.
4. Hauser SL, et al. Presented at the *AAN* 2020; P7.1-013.

Data and methods

Model choice and covariate selection

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

- 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

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**

AI, auto injector; FU, follow up; i.v. intravenous; PK, pharmacokinetic; RMS, relapsing multiple sclerosis; RRMS, relapsing-remitting MS; s.c., subcutaneous; q4w, every 4 weeks; q12w, every 12 weeks

1. Sorensen PS, et al. *Neurology*. 2014;82:573–581
2. Bar-Or A, et al. *Neurology* 2018; 90 (20) e1805-e1814.
3. Bar-Or A, et al. Presented at the *ACTRIMS* 2020; P#LB300.
4. Hauser SL, et al. *N Engl J Med* 2020;383:546−557.

Results

Covariate summary statistics from the five pooled studies

Administration route/ s.c. formulation*

1461 patients
(s.c. administration)
25 patients
(i.v. administration)

Age, years

Mean (SD)
Median [range]

37.9 (9.1)

38 [18–56]

Weight, kg

Mean (SD)
Median [range]

74.0 (18.8)

70.0 [40.5–171.6]

Gender (% female)

67.8

Race (n)

Caucasian, n=1354
Black, n=36
Asian, n=37
Unknown, n=11
Other, n=48

CD19+ B-cell count (cell/µL)

Mean (SD)
Median [range]

225.8 (127.5)

200.0 [0–1520]

Covariate summary statistics between studies were broadly similar

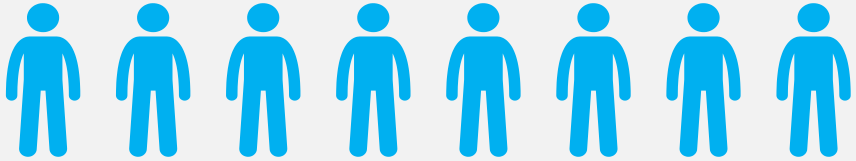
*Total number of patients included from 5 studies: OMB115102 (IV; N=25), MIRROR (PFS; N=231), APLIOS (PFS; N=143 and AI; N=141), ASCLEPIOS I and II (PFS; N=946)
AI, autoinjector; i.v., intravenous; PFS, prefilled syringe; s.c., subcutaneous; SD, standard deviation; N, number of patients from each study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

Results

Final PK B-cell model and selected covariates for analysis

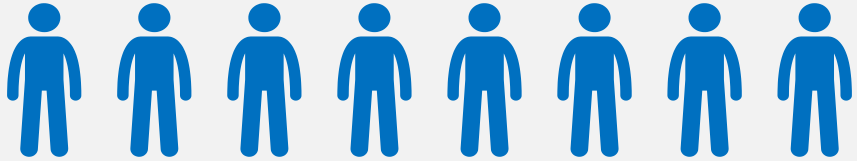
PK analysis
9168
Plasma concentrations

from **1440** patients



B-cell analysis
17158
B-cell counts

from **1486** patients



Final PK B-cell model

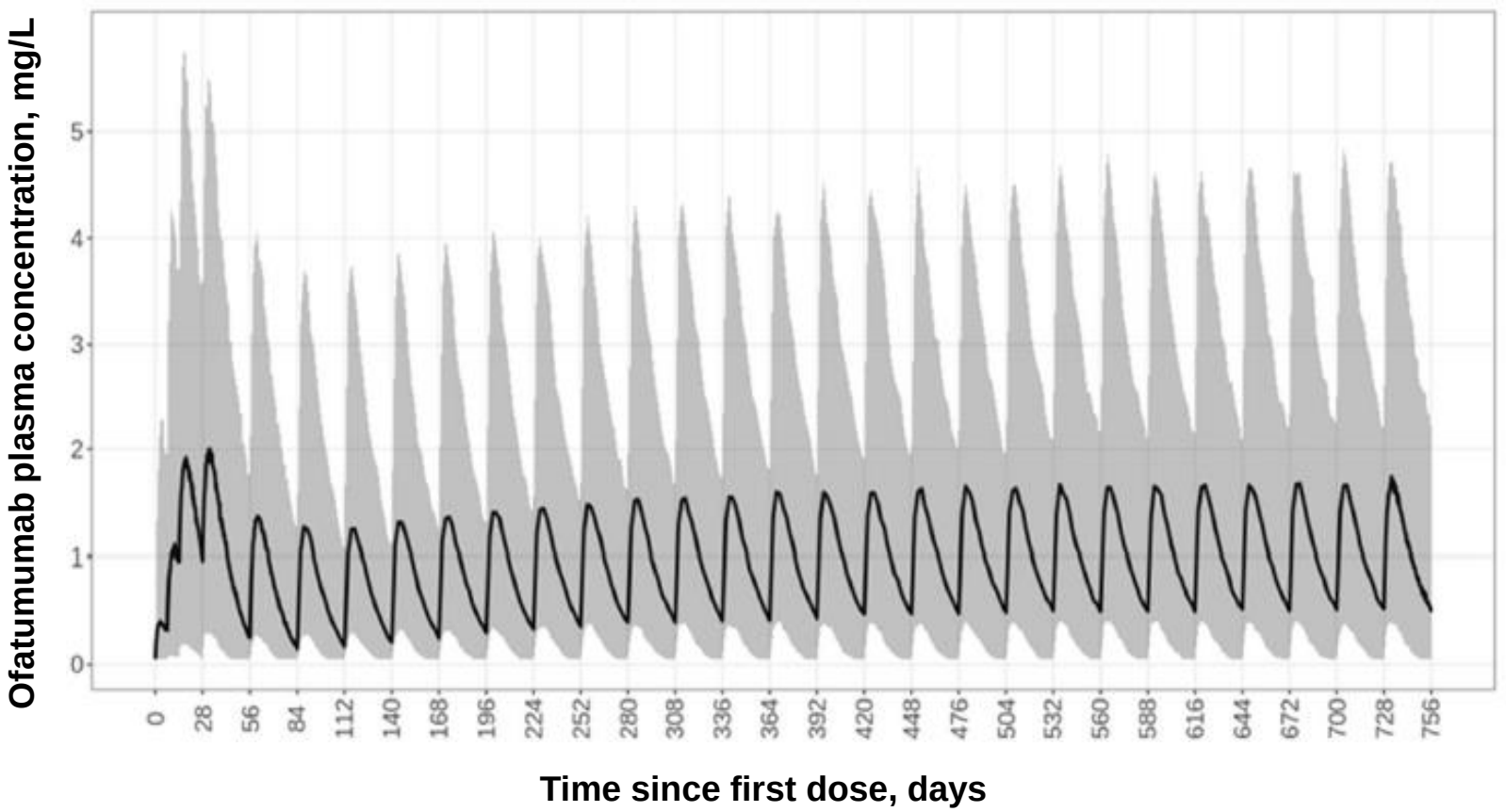
- PK model: a quasi-steady state binding model with two compartments and a first order absorption for s.c. administration with a time effect on the target synthesis rate
- Covariates included: **weight, i.v. route of administration, AI device**

- 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

Simulated median and 90% prediction interval*



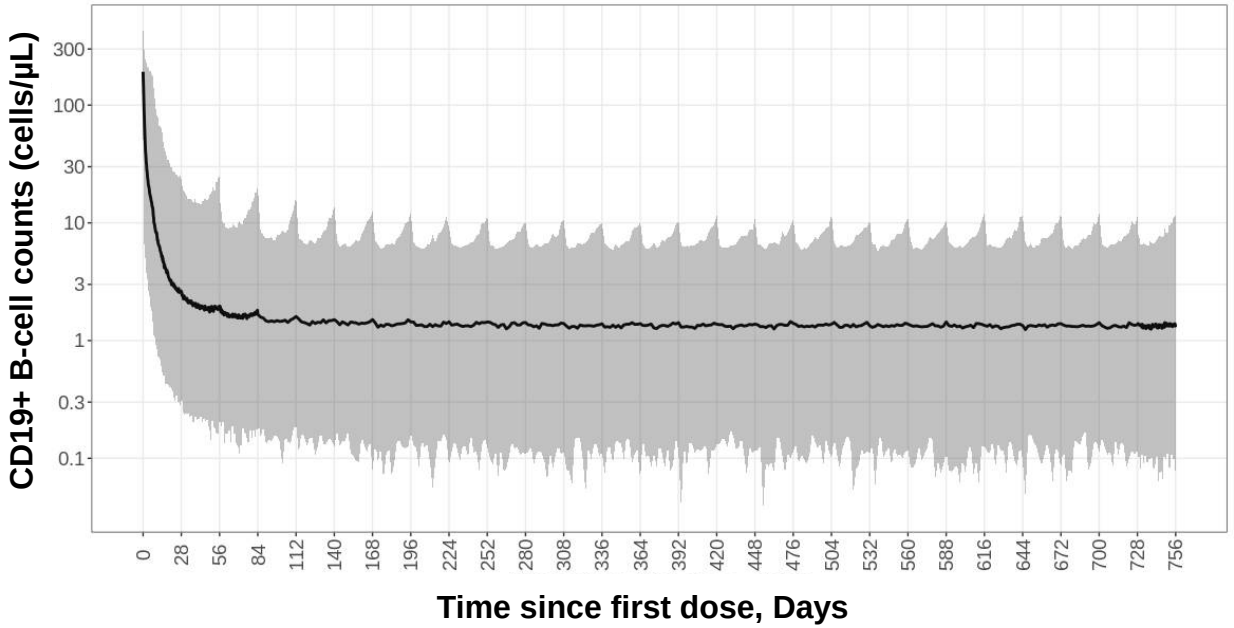
- The ofatumumab initial dosing regimen ensured rapid attainment of relevant pharmacological levels
- The q4w maintenance regimen ensured low and sustained levels of exposure
- The simulated median concentration profile decreased below the LOQ ~66 days after the last dose

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

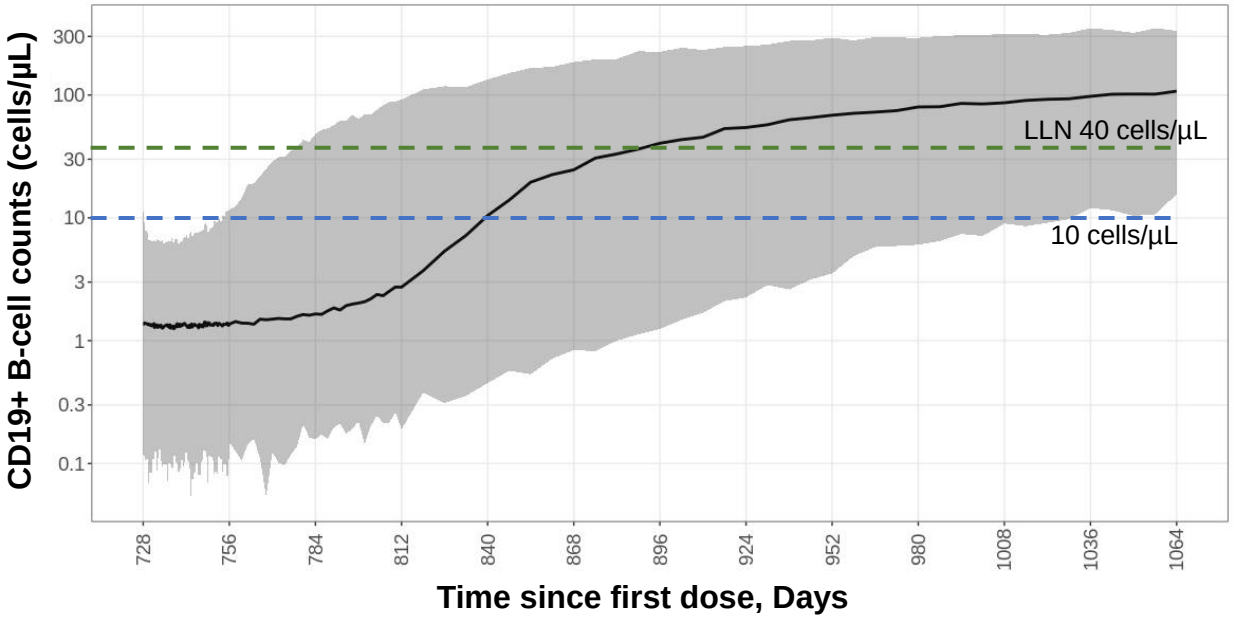
Ofatumumab 20 mg s.c. demonstrated rapid B-cell depletion and repletion after treatment interruption

Simulated median and 90% prediction interval*

B-cell depletion over 2 years of treatment



B-cell repletion after treatment interruption



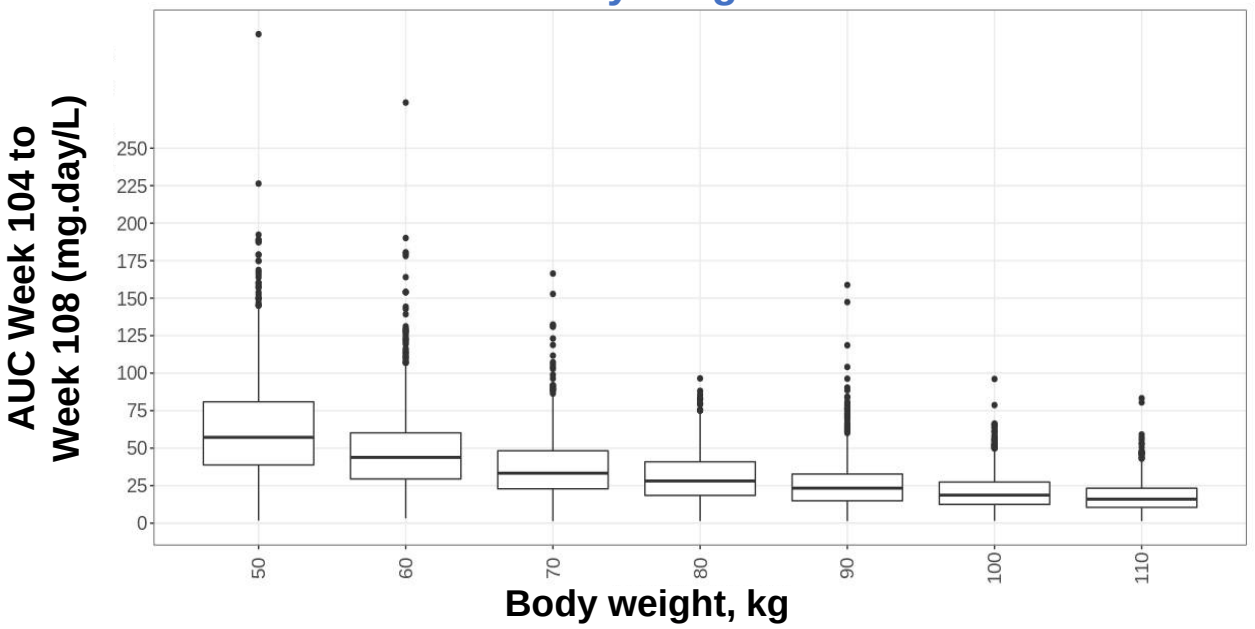
- Median B-cell depletion to <10 cells/µL was achieved in 8.75 days, with negligible signs of B-cell repletion between doses
- Over 94% of patients had <10 cells/µL at B-cell steady state and pre-dose

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

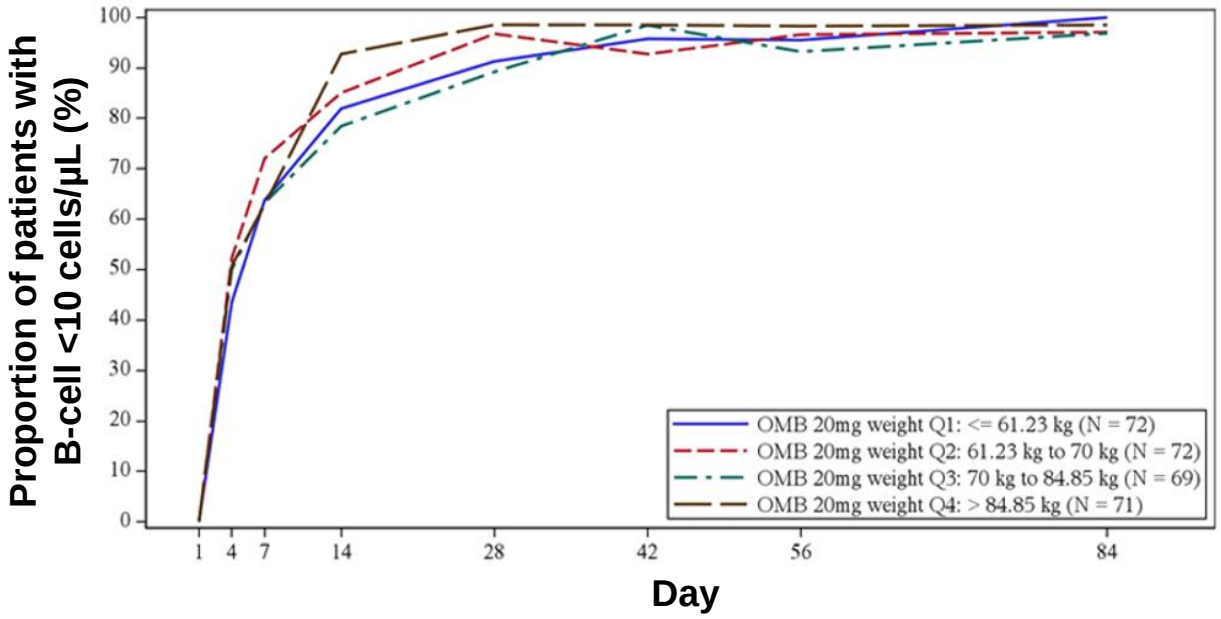
B cell counts simulated below 0 cells/µL were left censored at 0. *Simulation is for subcutaneous route with PFS and using Phase 3 dosage regimen
LLN. Lower limit of normal; PFS, prefilled syringe; s.c. subcutaneous

Ofatumumab effect on B cells was independent of weight effect on PK

Simulated steady state AUC Week 104 to Week 108 by weight*



Proportion of CD19+ B-cell depletion over time by patient weight quartile



- Effect of weight on the steady state AUC_{tau} (wks 104-108) was 71.8% higher and 52.0% lower for a 50 kg (5^{th} weight percentile) and 110 kg (95^{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

Thank you

PK, pharmacokinetic; s.c. subcutaneous

1. Hauser SL, et al. *N Engl J Med* 2020;383:546−557.