

Effect of Subcutaneous Ofatumumab on Lymphocyte Subsets in Patients with RMS: Analysis from the APLIOS Study

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Heinz Wiendl¹, Edward Fox², Alexandra Goodyear³, Inga Ludwig⁴, Morten Bagger⁴, Harald Kropshofer⁴, Martin Merschhemke⁴, Gisbert Weckbecker⁴, Amit Bar-Or⁵

¹University of Muenster, Muenster, Germany; ²Central Texas Neurology Consultants and Dell Medical School, The University of Texas at Austin, Round Rock, Austin, TX, USA; ³Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; ⁴Novartis Pharma AG, Basel, Switzerland; ⁵Center for Neuroinflammation and Experimental Therapeutics and Department of Neurology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

Background

- Ofatumumab, the first fully human anti-CD20 monoclonal antibody,¹ depletes CD20+ B cells and CD20+ T cells in the blood and lymphoid tissues through complement-dependent cytotoxicity and antibody-dependent cell-mediated cytotoxicity.^{2,3}
- In the Phase 3 ASCLEPIOS I and II trials, ofatumumab 20 mg (0.4 mL) subcutaneous (s.c.) demonstrated superior efficacy versus teriflunomide and a favourable safety profile in patients with relapsing multiple sclerosis (RMS)⁴
- The Phase 2 APLIOS study met its primary objective by demonstrating pharmacokinetic bioequivalence between an autoinjector pen (SensoReady[®]) versus prefilled syringe when ofatumumab 20 mg s.c. was administered at the abdomen site⁵
 - Systemic exposure to ofatumumab was similar across the injection sites (abdomen or thigh)⁵

Objective

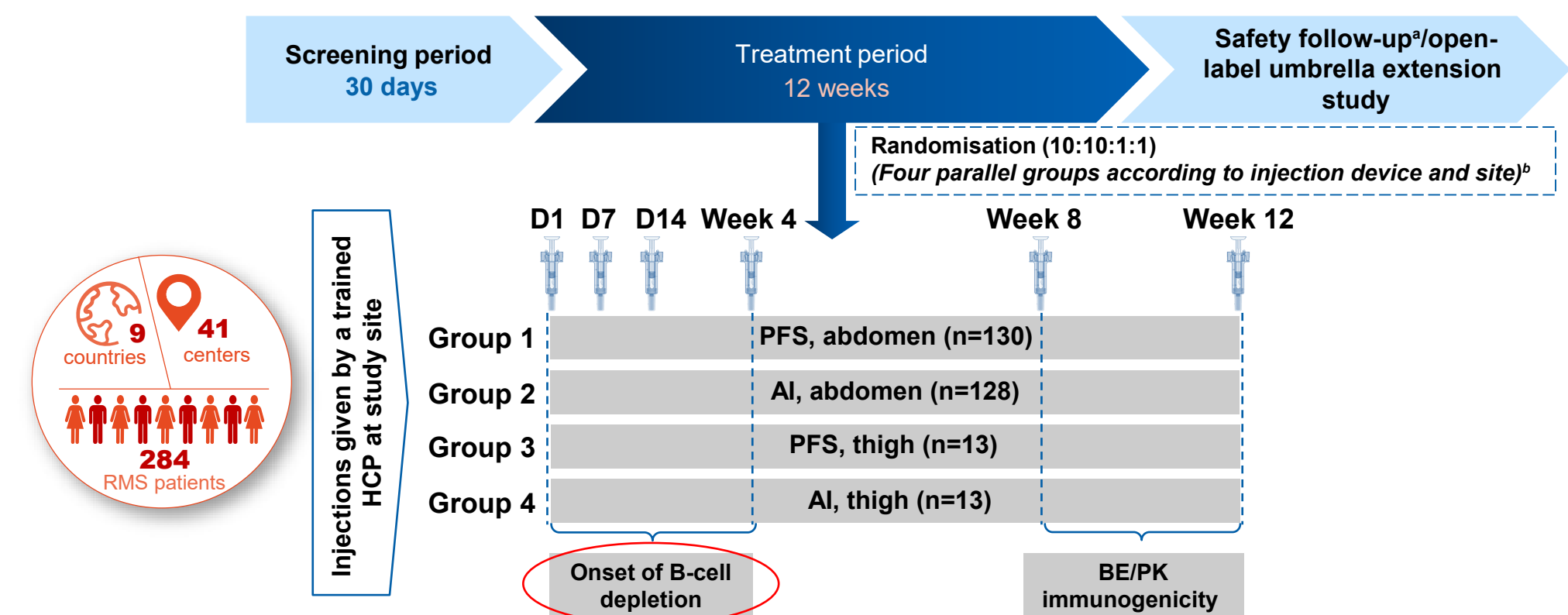
- To evaluate the effect of ofatumumab 20 mg s.c. dosing regimen on B- and T-cell subsets in RMS patients from the APLIOS study

Methods

Study design and treatment pattern

- APLIOS was a 12-week, randomised, open-label, multicenter, parallel-group, Phase 2 bioequivalence study conducted in 284 RMS patients from 41 study centers in 9 countries worldwide
- The study consisted of 3 parts: A screening period of up to 30 days, a treatment period of 12 weeks, and a safety follow-up/transition to open-label umbrella extension study (Figure 1)
- Patients received ofatumumab 20 mg (0.4 mL) s.c. injections on Days 1, 7, and 14 (initial doses) and thereafter every 4 weeks from Week 4 onwards (subsequent doses) via a prefilled syringe or an autoinjector pen (SensoReady[®])

Figure 1. Design of APLIOS study



*9 months or until the B cells returned to their baseline value or to LLN; *Randomisation was stratified by body weight (<60 kg, 60–90 kg, and >90 kg); † dose administration
AI, Autoinjector; AUC_{0-∞}, area under concentration-time curve over dosing interval; BE, bioequivalence; D, day; HCP, healthcare professional; LLN, lower limit normal; PK, pharmacokinetic; PFS, prefilled syringe

Study assessments and statistical analysis

- Blood samples were collected longitudinally at baseline and on Days 1, 4, 7, 14, 28, 42, 56, and 84 for assessment of CD19+ B-cell counts and CD20+ B-cell and CD20+ T-cell lymphocyte subsets
- Total CD20+ B-cell counts and the proportion of patients achieving B-cell counts <10 cells/μL were measured over 12 weeks and were summarized using descriptive statistics
- Lymphocyte B-cell and T-cell subset analysis was performed using fluorescence-activated cell sorting
- For all the lymphocyte subsets, the analysis considered data until 30 days after the last injection

Results

- Patient demographics and baseline disease characteristics were similar across treatment groups and representative of a typical RMS population (Table 1)
- Overall, the mean age of patients was 37.3 years, the majority of patients were white (96.8%) and female (70.1%); 68.3% of patients were treated with an MS disease-modifying therapy prior to the study, and 45.8% were on interferon β

Table 1. Patient demographics and baseline characteristics

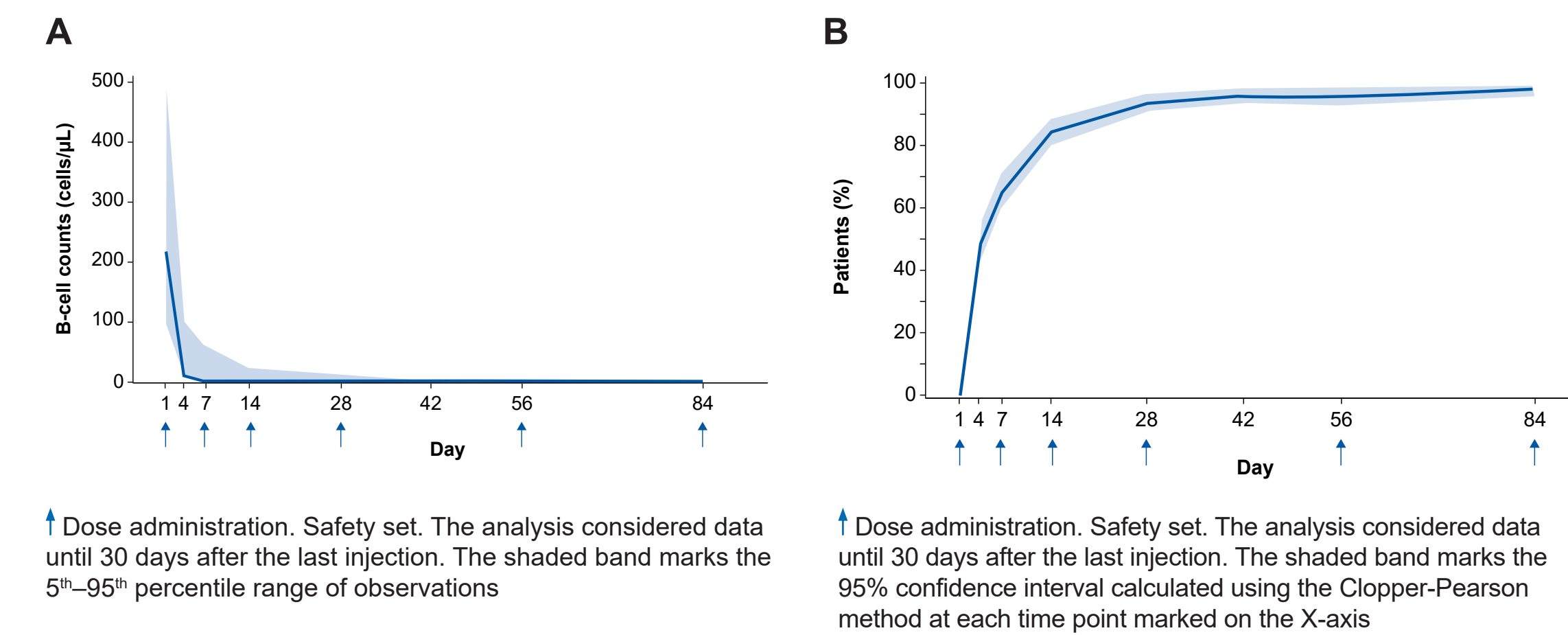
Parameter	All patients (N=284)
Age (years)	37.3±8.92
Sex, female, n (%)	199 (70.1%)
Race, white, n (%)	275 (96.8)
Weight (kg)	73.7±18.38
MS duration since first symptom (years)	9.3±7.75
No. of relapses in the year before the study	1.3±0.72
EDSS score	3.0±1.30
No. of Gd+ T1 lesions	1.5±4.97
B-cell counts (cell/μL), median (Q1, Q3)	214 (154, 286)
Treatment-naïve patients, n (%)	90 (31.7)

Data are expressed as mean±standard deviation, unless stated otherwise
EDSS, Expanded Disability Status Scale; Gd+ gadolinium-enhancing; MS, multiple sclerosis; RMS, relapsing MS; Q, quartile

Total CD20+ B-cell counts

- The baseline median B-cell count was 214 cells/μL in the total study population
- The initial doses of ofatumumab rapidly depleted B cells, with median B-cell counts of 2 cells/μL by Day 14 and sustained at ≤1 cell/μL up to Day 84⁵ (Figure 2A)
- Approximately 85% of patients achieved B-cell counts <10 cells/μL by Day 14, and 94% by Day 28, which was maintained in 98.1% of patients through to Day 84⁵ (Figure 2B)

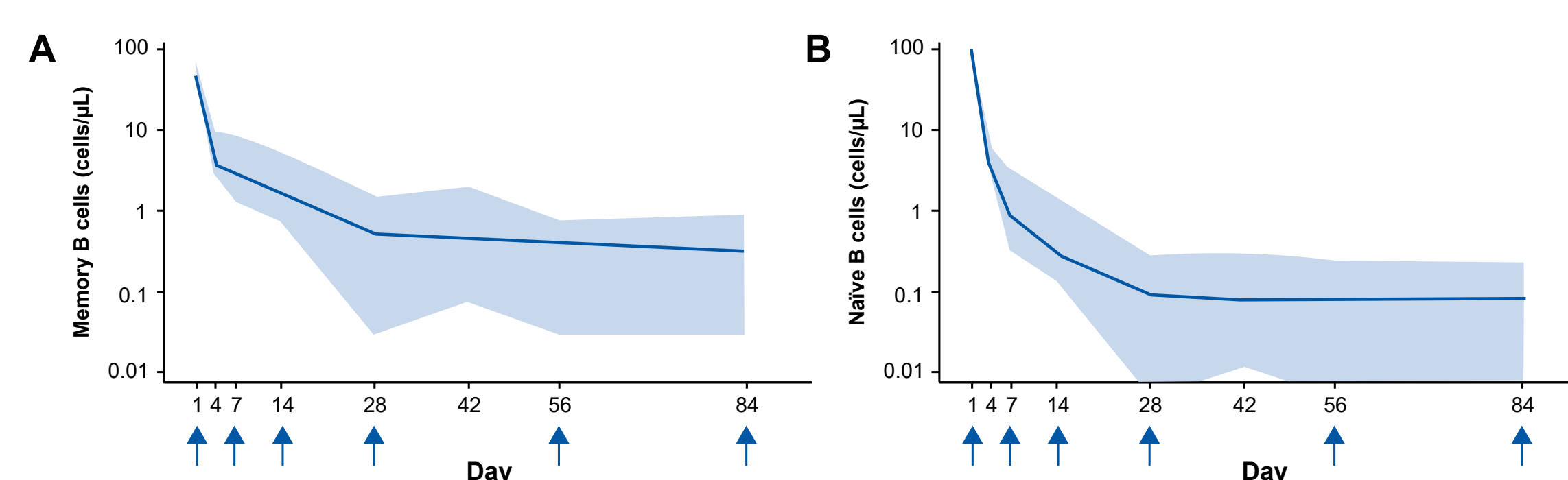
Figure 2. (A) Median number of B cells over 12 weeks with ofatumumab 20 mg (N=284), (B) Proportion of patients with B cells <10 cells/μL over time, total study population (safety set)



Memory and Naïve B cells

- Ofatumumab rapidly depleted memory B cells, with median B-cell counts of 1.8 cells/μL by Day 14 and sustained at ≤0.5 cell/μL up to Day 84 (Figure 3A)
- Ofatumumab also rapidly depleted naïve B cells, with median B-cell counts of 0.3 cells/μL by Day 14 and sustained at ≤0.1 cell/μL up to Day 84 (Figure 3B)

Figure 3. Median number of (A) memory B cells (CD19+CD45+CD27+) and (B) naïve B cells (CD19+CD45+IgD+CD27-CD38^{dim}) over 12 weeks (n=79)

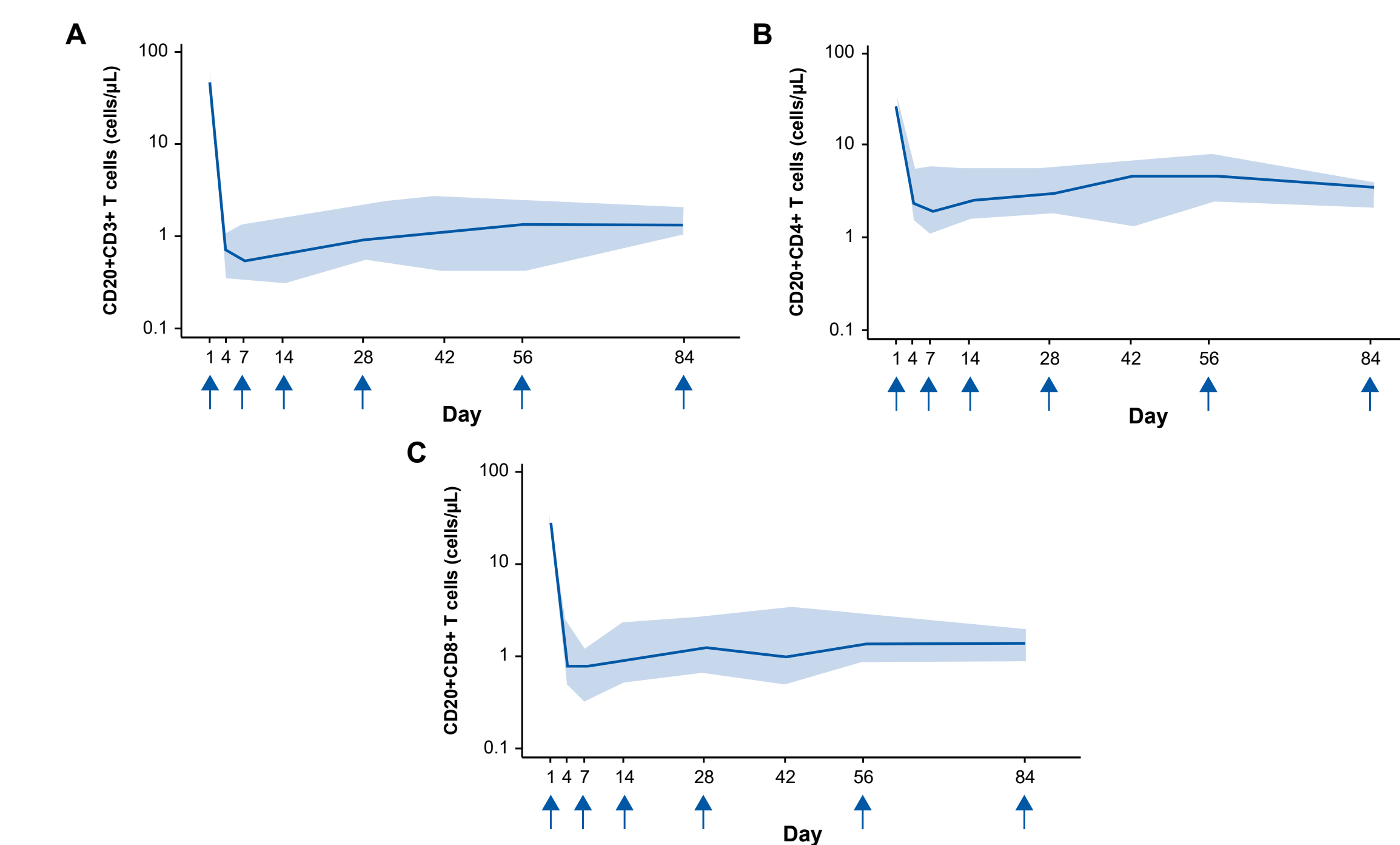


The analysis considered data until 30 days after the last injection. The shaded band marks the interquartile range of observations at each time point marked on the X-axis

CD20+ T-cell Subsets [CD20+CD3+ T cells, CD20+CD4+ T cells, and CD20+CD8+ T cells]

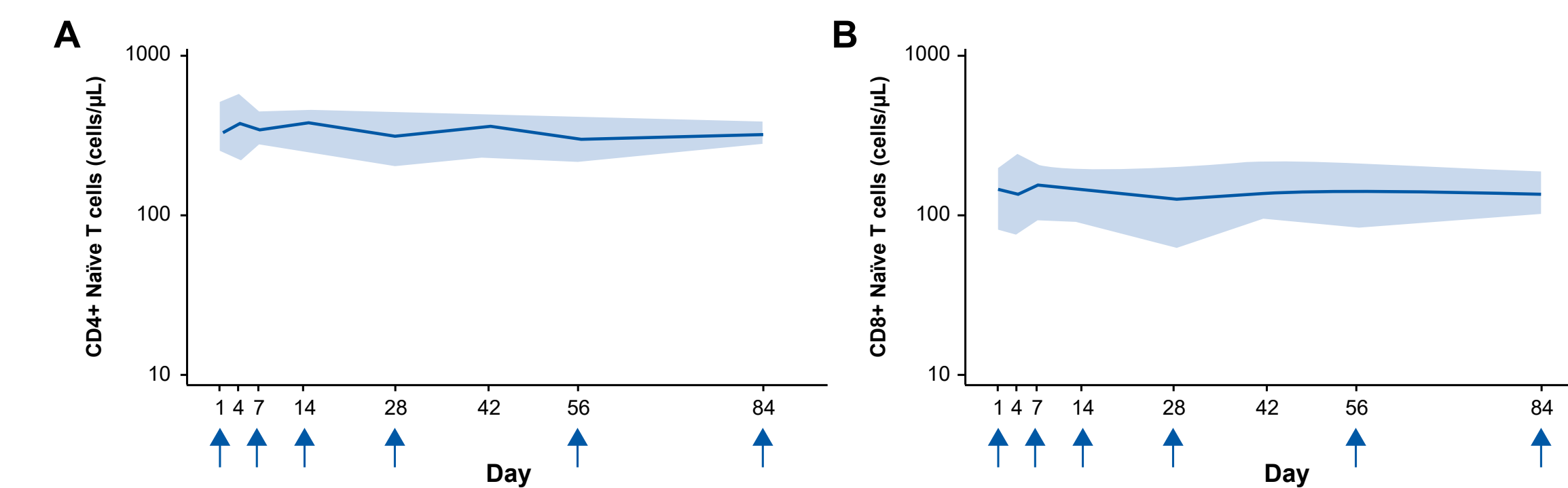
- CD20+CD3+ T cells were rapidly depleted with median count of <0.7 cells/μL at Day 4 through Day 7, and there was slight increase to 1.4 cells/μL by Day 84 (Figure 4A)
- Ofatumumab rapidly depleted CD20+CD4+ T cells (median count: 2.4 cells/μL) and CD20+CD8+ (median count: 0.8 cells/μL) at Day 4 (Figure 4B and 4C)
- However, both CD4+ and CD8+ naïve T-cells were largely unaffected with ofatumumab treatment (Figure 5A and 5B)

Figure 4. Median number of (A) CD20+CD3+ T cells (n=77), (B) CD20+CD4+ T cells (n=75), and (C) CD20+CD8+ T cells (n=73) over 12 weeks



The analysis considered data until 30 days after the last injection. The shaded band marks the interquartile range of observations at each time point marked on the X-axis

Figure 5. Median number of (A) CD4+ naïve T cells and (B) CD8+ naïve T cells over 12 weeks (n=79)



The analysis considered data until 30 days after the last injection. The shaded band marks the interquartile range of observations at each time point marked on the X-axis

Disclosures

The study was supported by Novartis Pharma AG, Switzerland.

Heinz Wiendl has received honoraria for acting as a member of Scientific Advisory Boards, Biogen, Evgen, Genzyme, MedDay Pharmaceuticals, Merck Serono, Novartis, Roche Pharma AG, and Sanofi-Aventis as well as speaker honoraria and travel support from Alexion, Biogen, Cognomed, F. Hoffmann-La Roche Ltd., Gemeinnützige Hertie-Stiftung, Merck Serono, Novartis, Roche Pharma AG, Genzyme, TEVA, and WebMD Global. Prof. Wiendl is acting as a paid consultant for Abbvie, Actelion, Biogen, IGES, Johnson & Johnson, Novartis, Roche, Sanofi-Aventis, and the Swiss Multiple Sclerosis Society. His research is funded by the German Ministry for Education and Research (BMBF), Deutsche Forschungsgemeinschaft (DFG), Else Kröner Fresenius Foundation, Fresenius Foundation, the European Union, Hertie Foundation, NRW Ministry of Education and Research, Interdisciplinary Center for Clinical Studies (IZKF) Muenster and RE Children's Foundation, Biogen, GlaxoSmithKline GmbH, Roche Pharma AG, Sanofi-Genzyme.

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Alexandra Goodyear was an employee of Novartis at the time of the presentation preparation.

Inga Ludwig, Morten Bagger, Harald Kropshofer, Martin Merschhemke, and Gisbert Weckbecker are employees of Novartis.

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Presenter email address: wiendl@uni-muenster.de

Text: Q4325f

To: 8NOVA (86682) US Only
+18324604729 North, Central and South Americas; Caribbean; China
+447860024038 UK, Europe & Russia
+46737494608 Sweden, Europe

Summary and Conclusions

- Ofatumumab 20 mg s.c. led to rapid and sustained depletion of both total CD20+ B cells and CD20+ T cells in RMS patients in the APLIOS study
- The differential impact on specific B- and T-cell subsets observed in this study is consistent with the efficacy and safety profile of ofatumumab derived from the ASCLEPIOS trials
- Depletion of memory and naïve B cells was rapid and sustained with ofatumumab
 - Memory B cells are known to be the key components in the MS pathology⁶ and increase in the frequency of these cells coincides with increased levels of the proinflammatory cytokines such as GM-CSF, IL-6, and TNF-α⁷
- Rapid depletion of specific CD20+ T-cell subsets (CD20+CD3+CD8+ T cells), well-known to exhibit an activated phenotype, was consistent with the previous findings in the ofatumumab-treated cynomolgus monkeys⁹
 - Based on the recent literature, there is an increase in CD20+ T cells in the blood and CSF of MS patients⁸
 - The T-cell subsets CD20+CD3+, CD20+CD4+, and CD20+CD8+ have strong ability to produce different inflammatory cytokines such as IL-17, TNF-α, and IFN-γ in the MS pathology⁸
 - Increase in myelin-specific CD8+ T cells in MS patients exhibits a memory phenotype and expresses CD20+ T cells⁹

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