EPR3102

Early Effect of Ofatumumab on B-cell Counts and MRI Activity in Relapsing Multiple Sclerosis Patients: Results From the APLIOS Study

Heinz Wiendl[1], Edward Fox[2], Alexandra Goodyear[3], Inga Ludwig[4], Morten Bagger[4], Dieter A. Häring[4], Harald Kropshofer[4], Martin Merschhemke[4], Amit Bar-Or[5]

ePresentation Session: MS AND RELATED DISORDERS
May 25, 2020

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

ePresentation at the annual meeting of the European Academy of Neurology, 2020

Scan to download a copy of this presentation

Disclosures

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.

Edward Fox has received consulting fees and carried out contracted research, speaker's bureau and advisory work for Biogen, Celgene, Chugai, EMD Serono, Genentech/Roche, MedDay, Novartis, Sanofi, Genzyme, Teva, and TG Therapeutics.

Amit Bar-Or has participated as a speaker in meetings sponsored by and received consulting fees and/or grant support from: Janssen/Actelion; Atara Biotherapeutics, Biogen Idec, Celgene/Receptos, Roche/Genentech, Medimmune, Merck/EMD Serono, Novartis, Sanofi-Genzyme.

Alexandra Goodyear was an employee of Novartis at the time of the presentation preparation. **Inga Ludwig**, **Morten Bagger**, **Dieter A. Häring**, **Harald Kropshofer**, and **Martin Merschhemke** are employees of Novartis.

Funding source: This study is supported by Novartis Pharma AG, Basel, Switzerland.

Acknowledgement: Editorial support was provided by **Arshjyoti Singh** and **Anuja Shah** (employees of Novartis Healthcare Pvt. Ltd., Hyderabad, India). The final responsibility for the content lies with the authors.

Background, Objective and Methods

- Ofatumumab, the first fully human anti-CD20 monoclonal antibody,[2] depletes CD20+ B and CD20+ T cells in the blood and lymphoid tissues through CDC and ADCC[3]
- In the Phase 3 ASCLEPIOS I and II trials, ofatumumab 20 mg s.c. (0.4 mL) dosing regimen suppressed 94–98% of Gd+ T1 lesions versus teriflunomide 14 mg oral once-daily in patients with RMS[4]
- The Phase 2 APLIOS study met its primary objective by demonstrating PK bioequivalence between an autoinjector pen (SensoReady®) and a prefilled syringe when ofatumumab 20 mg s.c. was administered at abdomen site[5]
- In APLIOS, frequent study assessments evaluated the early effect of ofatumumab treatment on B-cell counts and monthly MRI activity in patients with RMS

Methods

Following assessments[a] were made

CD20+ B-cell counts

- CD19+ B-cell counts over 12 weeks
- Proportion of patients achieving B-cell counts <10 cells/μL over 12 weeks

Gd+ T1 lesion counts

- Number of Gd+ T1 lesions at Weeks 4, 8, and 12
- Proportion of patients free of Gd+ T1 lesions at Weeks 4, 8, and 12

Safety profile

- Adverse events and serious adverse events

Objective

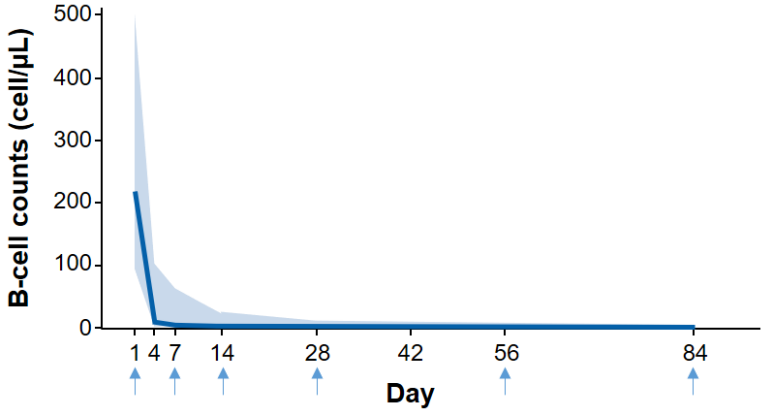
To evaluate the onset of B-cell depletion and suppression of MRI activity with ofatumumab 20 mg s.c. in patients with RMS from the APLIOS study

[a]All data were analysed using descriptive statistics. ADCC, antibody-dependent cell-mediated cytotoxicity; CDC, complement-dependent cytotoxicity; Gd+ gadolinium-enhancing; MRI, magnetic resonance imaging; MS, multiple sclerosis; PK, pharmacokinetic; RMS, relapsing multiple sclerosis; s.c, subcutaneous

1. Dalakas M, et al. *Nat Clin Pract Neurol*. 2008;4:557–567. 2. Bar-Or A, et al, *Neurology*. 2018;90(20):e1805-e1814. 3. Pacheco-Fernandez T, et al. Presented at the *AAN*. 2018;S52.003. 4. Hauser SL, et al. Presented at the *ECTRIMS*. 2019; S17.OP336. 5. Bar-Or A, et al. Presented at the *ACTRIMS*. 2020; PO#LB300.

Results: Early Onset and Consistent Maintenance of B-Cell Depletion With Ofatumumab Treatment

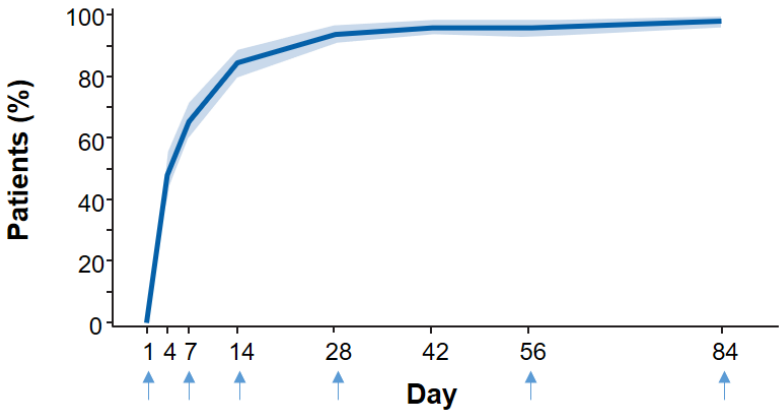
Median number of B cells over 12 weeks with ofatumumab 20 mg (N=284), total study population



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 84

↑Dose administration. Safety set. The analysis considered data until 30 days after the last injection. The shaded band marks the 5th–95th percentile range of observations

Proportion of patients with B cells <10 cells/µL over 12 weeks with ofatumumab 20 mg (N=284), total study population

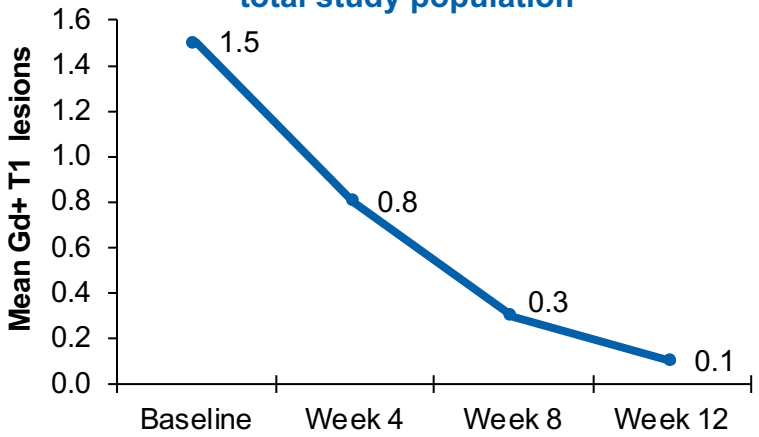


Approximately 85% of patients achieved B-cell counts <10 cells/µL by Day 14, and 94% by Day 28, which was maintained in 98.1% of patients through to Day 84

↑Dose administration. Safety set. The analysis considered data until 30 days after the last injection. The shaded band marks the 95% confidence interval calculated using the Clopper-Pearson method at each time point marked on the X-axis

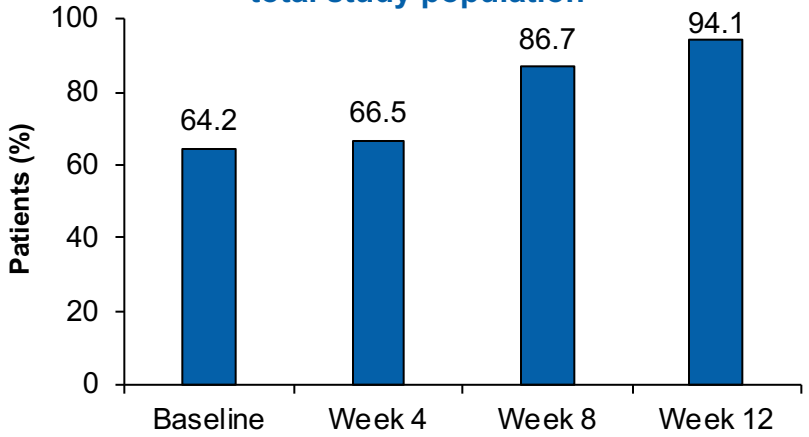
Results: Early Effect of Ofatumumab on Gd+ T1 Lesions

Number of Gd+ T1 lesions over 12 weeks with ofatumumab 20 mg (N=284), total study population



The dosing regimen of ofatumumab rapidly reduced the mean number of Gd+ T1 lesions from baseline over 12 weeks

Proportion of patients free of Gd+ T1 lesions over 12 weeks with ofatumumab 20 mg (N=284), total study population



The proportion of patients free of Gd+ T1 lesions increased over 12 weeks with ofatumumab treatment

Safety set
Gd+ gadolinium-enhancing

Results: Safety

Overall safety

- Proportion of patients with any AE during the study was 57%
- Majority of AEs were of Grade 1/2; overall incidence of Grade 3 AEs was low (7 patients, 2.5%). No Grade 4 AE was observed

IRRs

- Predominantly observed with the 1st injection
- All IRR cases were mild to moderate, except for one patient who had Grade 3 IRR with the 1st injection
- No IRR event was serious or led to study drug discontinuation
  - Systemic IRRs: Primarily occurred with the 1st injection (25%), and the incidence decreased with subsequent injections
    - Most commonly reported symptoms: headache, chills, and fever
  - Site IRRs: Occurred with the 1st injection (6%) and decreased with subsequent injections

Overall safety

Patients, n (%)	All patients (N=284)
AEs	162 (57.0)
SAEs	6 (2.1)
Drug-related AEs	114 (40.1)
AEs leading to drug discontinuation	1 (0.4)
AEs leading to drug interruptions	3 (1.1)

- No deaths occurred during the study

AEs, adverse events; IRRs, injection-related reactions; SAEs, serious AEs

Conclusions

Ofatumumab 20 mg s.c. dosing regimen over 12 weeks in the APLIOS study showed

- A rapid, close to complete and sustained B-cell depletion (median B-cell count: 1 cell/µL)
- No B-cell reconstitution in between monthly doses
- Profound and undelayed reduction of Gd+ T1 lesions in RMS patients, consistent with the effects observed in the pooled Phase 3 ASCLEPIOS I/II patient population[1]
- A safety profile that is well tolerated and in line with the results of the larger Phase 3 ASCLEPIOS I and II trials[1]

Thank you for your attention

Gd+ gadolinium-enhancing; RMS, relapsing multiple sclerosis; s.c., subcutaneous

1. Hauser SL, et al. Presented at the *ECTRIMS.* 2019; S17.OP336.