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

LB129

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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 site[5]
  - Systemic exposure to ofatumumab was similar across the injection sites (abdomen or thigh)[5]

Objective

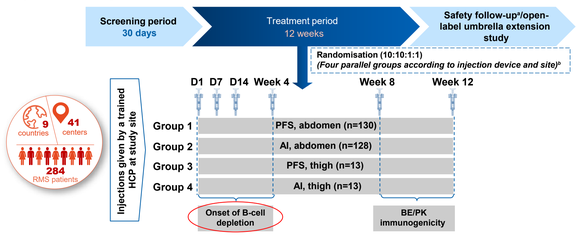
- To evaluate the effect of ofatumumab 20 mg s.c. dosing regimen on B- and T-cell subsets in RMS patients from the APLIOS study

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



[a]9 months or until the B cells returned to their baseline value or to LLN; [b]Randomisation was stratified by body weight (<60 kg, 60–90 kg, and >90 kg); ↑ *dose administration*

AI, Autoinjector; AUC_{tau}; 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

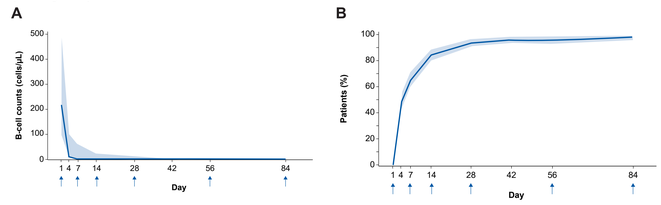
Parameter	All patients (N=284)
Age (years)	37.3±8.92
Sex, female, n (%)	199 (70.1%)
Race, white, n (%)	275 (96.8)
Weight (kg)	73.7±18.38
MS duration since first symptom (years)	9.3±7.75
No. of relapses in the year before the study	1.3±0.72
EDSS score	3.0±1.30
No. of Gd+ T1 lesions	1.5±4.97
B-cell counts (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 84[5] (**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 84[5] (**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)



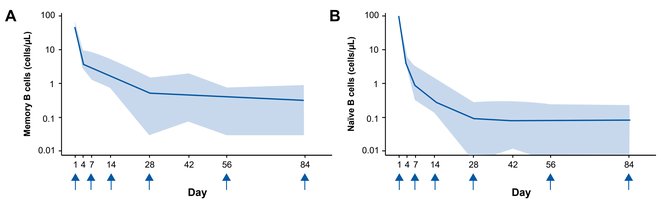
↑ Dose administration. Safety set. The analysis considered data until 30 days after the last injection. The shaded band marks the 5th–95th percentile range of observations

↑ 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

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)

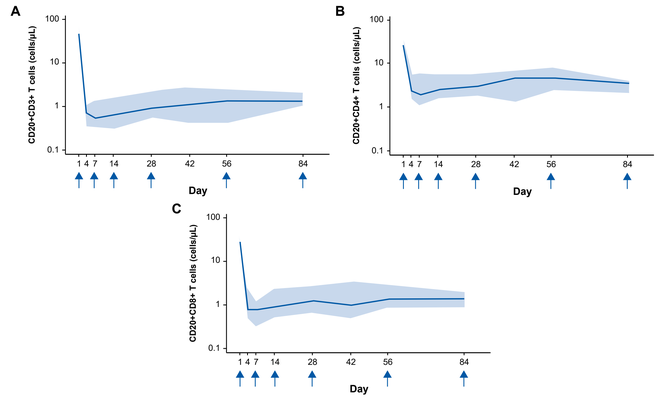


The analysis considered data until 30 days after the last injection. The shaded band marks the interquartile range of observations at each time point marked on the X-axis

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

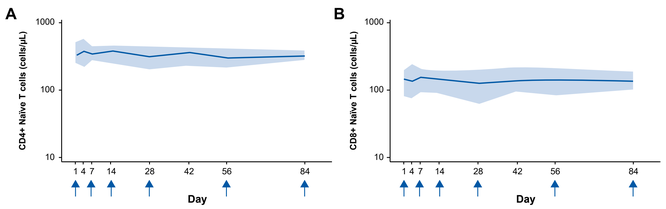
- CD20+CD3+ T cells were rapidly depleted with median count of <0.7 cells/µL at Day 4 through Day 7, and there was slight increase to 1.4 cells/µL by Day 84 (**Figure 4A**)
- Ofatumumab rapidly depleted CD20+CD4+ T cells (median count: 2.4 cells/µL) and CD20+CD8+ (median count: 0.8 cells/µL) at Day 4 (**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

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 pathology[6] and increase in the frequency of these cells coincides with increased levels of the proinflammatory cytokines such as GM-CSF, IL-6, and TNF-α[7]
- 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 monkeys[3]
  - Based on the recent literature, there is an increase in CD20+ T cells in the blood and CSF of MS patients[8]
  - 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 pathology[8]
  - Increase in myelin-specific CD8+ T cells in MS patients exhibits a memory phenotype and expresses CD20+ T cells[9]

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