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

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Background

- B cells play a major role in the pathogenesis of multiple sclerosis (MS)[1]
- Ofatumumab, the first fully human anti-CD20 monoclonal antibody,[2] depletes CD20+ B and CD20+ T cells in the blood and lymphoid tissues through complement-dependent cytotoxicity and antibody-dependent cell-mediated cytotoxicity[3]
- In the Phase 3 ASCLEPIOS I and II trials, the ofatumumab 20 mg subcutaneous s.c. (0.4 ml) dosing regimen suppressed 94%–98% of gadolinium-enhancing (Gd+) lesions versus once-daily oral teriflunomide 14 mg in patients with relapsing multiple sclerosis (RMS)[4]
- APLIOS, a 12-week, open-label, randomized, Phase 2 study, met its primary objective by demonstrating pharmacokinetic bioequivalence between an autoinjector pen (SensoReady®) and 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]
- In APLIOS, frequent study assessments evaluated the early onset of ofatumumab treatment effect on B-cell counts and monthly magnetic resonance imaging (MRI) activity in patients with RMS

Objectives

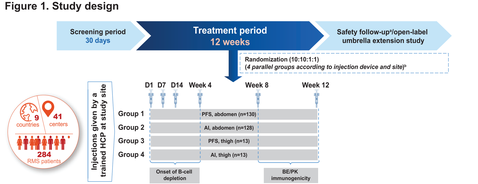
- To evaluate the onset of B-cell depletion and suppression of MRI activity with ofatumumab 20 mg s.c. in patients with RMS

Methods

Study design

- APLIOS was a 12-week, randomized, 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 were randomized (10:10:1:1) into 4 groups according to the injection device and site: autoinjector (AI) pen (n=128) and prefilled syringe (PFS; n=130) to the abdomen, and AI pen (n=13) and PFS (n=13) to the thigh
  - Randomization was stratified by bodyweight (<60 kg, 60–90 kg, and >90 kg) to ensure a balance between the randomized groups
- 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)

Figure 1. Study design



*Duration of 9 months or until the B cells returned to their baseline value or to LLN; ‡Randomization was stratified by body weight (<60 kg, 60–90 kg, and >90 kg). † dose administration

AI, autoinjector; BE, bioequivalence; D, day; HCP, healthcare professional; LLN, lower limit of normal; PFS, prefilled syringe; PK, pharmacokinetic

Study population

✔ Key inclusion criteria	✖ Key exclusion criteria
• Aged 18 to 55 years, with a diagnosis of RMS (Revised McDonald 2010)[7] • Relapsing form of MS: RRMS or SPMS with disease activity (Lublin 2014)[8] • EDSS score of 0 to 5.5 • Documented one of the following – ≥2 relapses in the 2 years before screening – ≥1 relapse in the year before screening – A positive T1 Gd+ scan during the year before randomization • Neurologically stable within 1 month prior to randomization	• Patients with PPMS or SPMS without disease activity • Patients meeting criteria for neuromyelitis optica • Disease duration of >10 years with an EDSS score of ≤2.0 • Patients with an active chronic disease of the immune system other than MS or immunodeficiency syndrome • Patients with neurological findings consistent with (or confirmed) progressive multifocal leukoencephalopathy

EDSS, Expanded Disability Status Scale, Gd+, gadolinium-enhancing; MS, multiple sclerosis; PPMS, primary progressive multiple sclerosis; RMS, relapsing multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis

Study assessments and statistical analysis

- Blood samples were collected at baseline and on Day 1, Day 4, Day 7, Day 14, Week 4, Week 6, Week 8, and Week 12 for assessments of CD19+ B-cell counts
- CD19+ 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
- The number of Gd+ lesions at Weeks 4, 8, and 12, and the proportion of patients free of Gd+ lesions at Weeks 4, 8, and 12 were determined and summarized using descriptive statistics
- Adverse events (AEs) and serious AEs (SAEs) were recorded to assess the safety profile

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

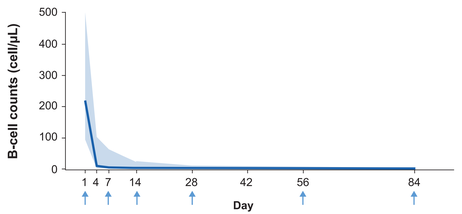
Characteristic	All patients (N=284)
Age (years)	37.3±8.92
Sex, female, n (%)	199 (70.1)
Race, white, n (%)	275 (96.8)
Weight (kg)	73.7±18.38
BMI (kg/m²)	25.5±6.13
MS duration since the first symptom (years)	9.3±7.75
No. of relapses in the year before the study	1.3±0.72
No. of relapses in the 2 years before the study	1.0±1.58
EDSS score	3.0±1.30
No. of Gd+ 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
BMI, body mass index; EDSS, Expanded Disability Status Scale; Gd+ gadolinium-enhancing; MS, multiple sclerosis; Q, quartile

B-cell counts

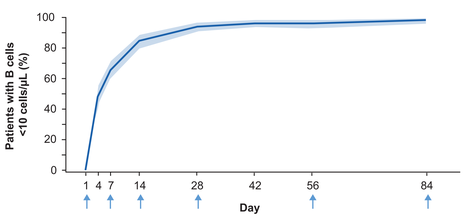
- The baseline median B-cell count was 214 cells/μL in the total study population
- The initial doses of ofatumumab rapidly depleted B cells, with median B-cell counts of 2 cells/μL by Day 14 and sustained at ≤1 cell/μL up to Day 84 (**Figure 2A**)
- Approximately 85% of patients achieved B-cell counts <10 cells/μL by Day 14, and 94% by Day 28, which was maintained in 98.1% of patients through to Day 84 (**Figure 2B**)

Figure 2A. Median number of B cells over 12 weeks with ofatumumab 20 mg (N=284), 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

Figure 2B. Proportion of patients with B cells <10 cells/μL over time, total study population (safety set)

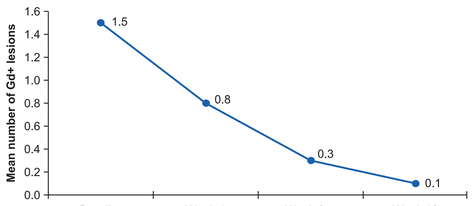


↑ Dose administration. Safety set. The analysis considered data until 30 days after the last injection. The shaded band marks the 95% confidence interval calculated using the Clopper-Pearson method at each time point marked on the X-axis

Gd+ lesions

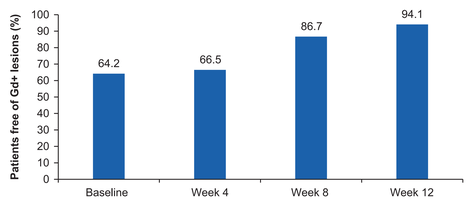
- The dosing regimen of ofatumumab rapidly reduced the mean number of Gd+ lesions from baseline over 12 weeks (**Figure 3A**)
- The proportion of patients free of Gd+ lesions increased over 12 weeks with ofatumumab treatment (**Figure 3B**)

Figure 3A. Number of Gd+ lesions over 12 weeks with ofatumumab 20 mg (N=284), total study population (safety set)



Gd+, gadolinium-enhancing

Figure 3B. Proportion of patients free of Gd+ lesions over 12 weeks with ofatumumab 20 mg (N=284), total study population (safety set)



Gd+, gadolinium-enhancing

Safety

- The proportion of patients with any AE was 57% during the study. The overall incidences of SAEs (2.1%), AEs leading to study drug discontinuation (0.4%) and AEs leading to study drug interruption (1.1%) were low
- The majority of AEs were of Grade 1/2. The overall incidence of Grade 3 AEs was low (7 patients, 2.5%). No Grade 4 AE was observed during the study
- Injection-related reactions (IRRs) were predominantly observed with the first injection in all treatment groups
  - All IRR cases were mild to moderate, except for one patient who had a Grade 3 IRR with the first injection
  - No IRR event was serious or led to study drug discontinuation
- Systemic IRRs primarily occurred with the first injection (25%), and the incidence decreased with subsequent injections similarly across the treatment groups. The most commonly reported injection systemic symptoms were headache, chills, and fever
- Site IRRs occurred with the first injection (6%) and the incidence decreased with subsequent injections
- No deaths occurred during the study

Conclusions

The 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+ lesions in RMS patients, consistent with the effects observed in the pooled Phase 3 ASCLEPIOS I/II patient population[6]
- A safety profile that is well tolerated and in line with the results of the larger Phase 3 ASCLEPIOS I and II trials[6]

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Disclosures

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