Onset Of B-cell Depletion and Suppression of MRI Activity with Ofatumumab Treatment in Relapsing Multiple Sclerosis: The APLIOS Study

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Poster Session: P8.1-001

Background

Methods

Results

Conclusions

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Disclosures

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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]
- 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[3]
- The Phase 2 APLIOS study met its primary objective by demonstrating pharmacokinetic bioequivalence between an autoinjector pen (SensoReady®) and a prefilled syringe when ofatumumab 20 mg s.c. was administered at abdomen site[4]
  - Systemic exposure to ofatumumab was similar across the injection sites (abdomen or thigh)[4]
- In APLIOS, frequent study assessments evaluated the early effect of ofatumumab treatment on B-cell counts and monthly MRI activity in patients with RMS

Objective

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

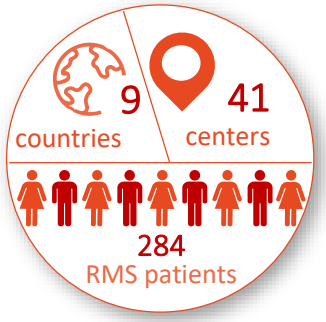
Gd+ gadolinium-enhancing; MRI, magnetic resonance imaging; RMS, relapsing multiple sclerosis; s.c, subcutaneous

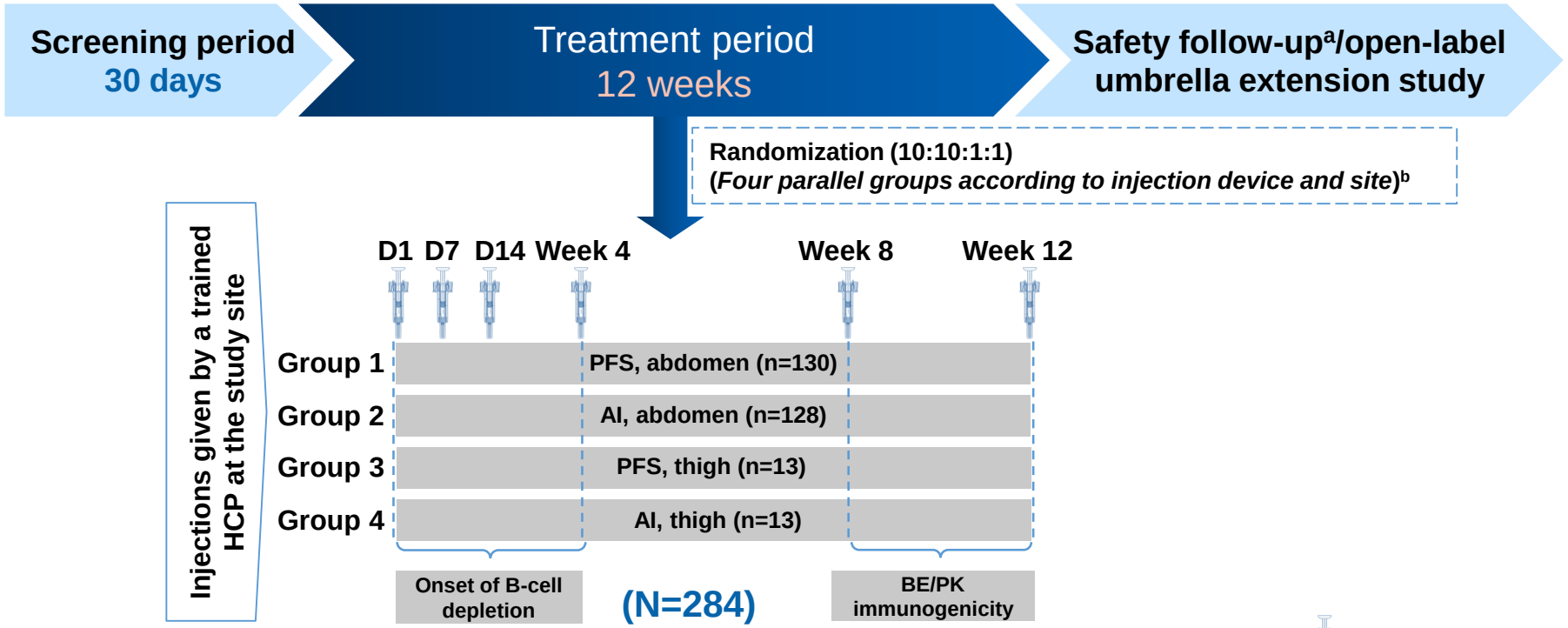
1. Bar-Or A, et al, *Neurology*. 2018;90(20):e1805-e1814. 2. Pacheco-Fernandez T, et al. Presented at the *AAN.* 2018;S52.003. 3. Hauser SL, et al. Presented at the *ECTRIMS.* 2019; S17.OP336. 4. Bar-Or A, et al. Presented at the *ACTRIMS* 2020; PO#LB300.

Methods

Study design

Randomized, open-label, multicenter, parallel group, Phase 2 BE study





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

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*)

AI, Autoinjector; AUC_{tau}; BE, bioequivalence; D, day; HCP, healthcare professional; LLN, lower limit normal; PK, pharmacokinetics; PFS, prefilled syringe; RMS, relapsing multiple sclerosis; s.c., subcutaneous

Methods

Study population

Inclusion criteria

- Aged 18 to 55 years with a diagnosis of MS (Revised McDonald 2010)[1]
- Relapsing form of MS: RRMS or SPMS with disease activity (Lublin 2014)[2]
- 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

Exclusion criteria

- Patients with PPMS or SPMS without disease activity
- Patients meeting criteria for neuromyelitis optica
- Disease duration of >10 years with an EDSS an 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

1. Polman CH, et al. *Ann Neurol*. 2011;69:292–302. 2. Lublin FD, et al. *Neurology*. 2014;83:278–286.

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

Methods

Study outcomes and statistical analysis

Outcomes	Assessments
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+ lesions at Weeks 4, 8, and 12
Safety profile	• Adverse events and serious adverse events

- All data were analyzed using descriptive statistics.

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Results

Patient population were representative of typical RMS population

Patient demographics and baseline characteristics	
	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/m^2)	25.5±6.13
MS duration since 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+ T1 lesions	**1.5±4.97**
B-cell counts (cell/µL), median (Q1, Q3)	**214 (154, 286)**
Treatment-naïve patients, n (%)	**90 (31.7)**

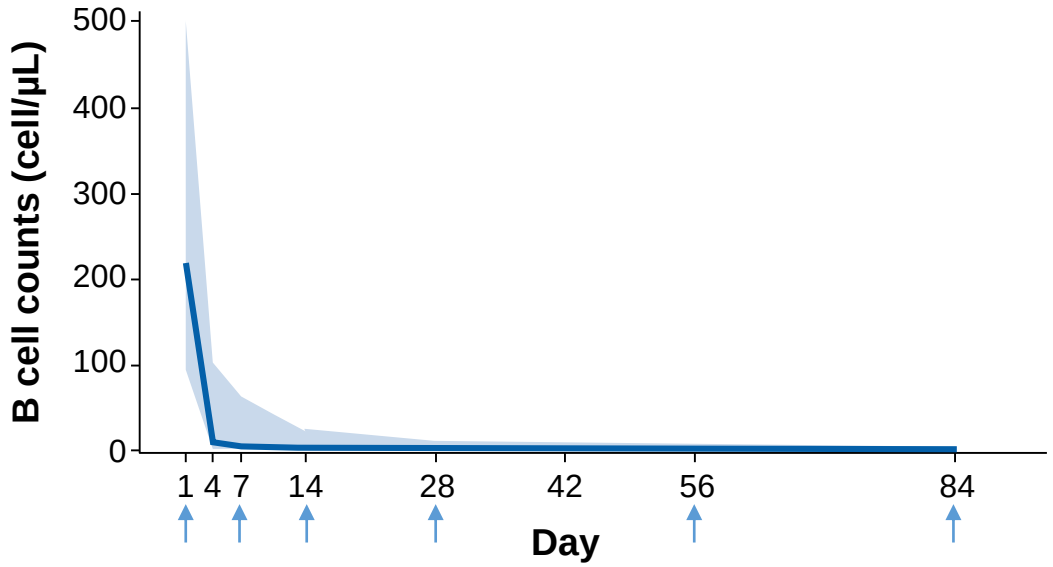
Data are expressed as mean±standard deviation, unless stated otherwise

BMI, body mass index; EDSS, Expanded Disability Status Scale; Gd+ gadolinium-enhancing; MS, multiple sclerosis; RMS, relapsing MS; Q, quartile

Results

Early onset and consistent maintenance of B-cell depletion with ofatumumab treatment

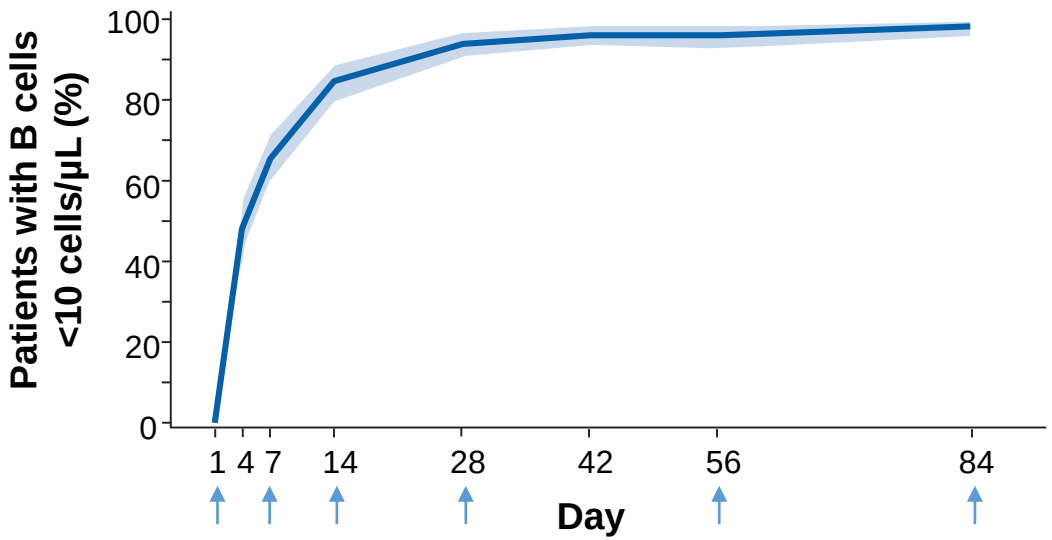
Median number of B-cells over 12 weeks with ofatumumab 20 mg (N=284), total study population



Loading 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



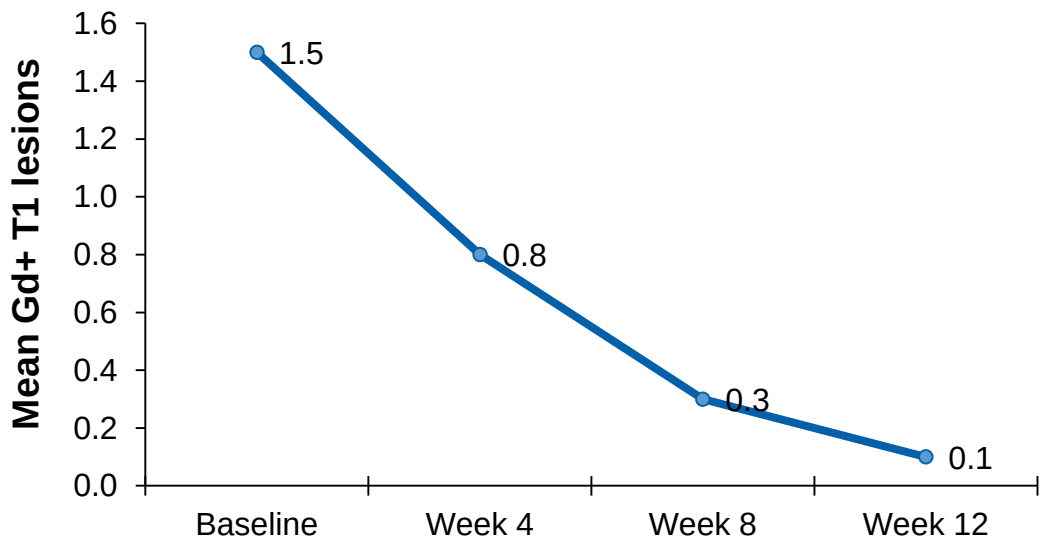
Approximately 85% of patients achieved B-cell counts <10 cells/µL by Day 14, and 94% by Day 28, which was maintained in 98.1% of patients through Day 84

† 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 axis

Results

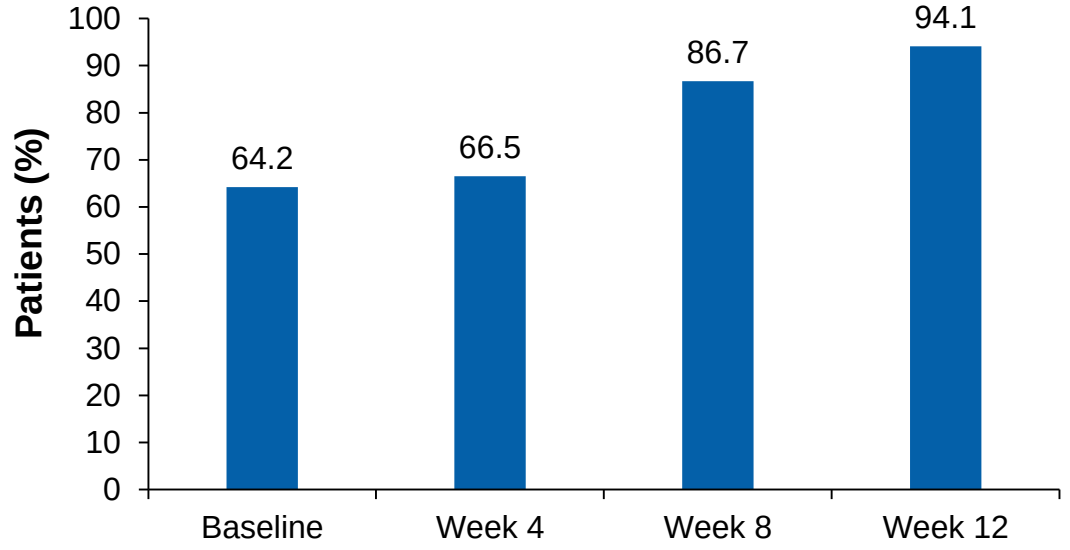
Early effect of ofatumumab on Gd+ T1 lesions

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



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



Proportion of patients free from Gd+ T1 lesions increased over 12 weeks with ofatumumab treatment

Safety set.
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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

AE, adverse event; IRR, 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+ lesions in RMS patients, consistent with the effects observed in the pooled Phase 3 ASCLEPIOS I and 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]

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

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

Thank you