Sustained Efficacy of Ofatumumab in Relapsing Multiple Sclerosis Patients: Results from Extended Treatment in the Phase 2 APOLITOS Study

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Introduction

- Ofatumumab is a fully human anti-CD20 monoclonal antibody, administered as a monthly 20 mg s.c injection for the treatment of RMS[1,2]
- In the 24-week core APOLITOS study, ofatumumab demonstrated superior efficacy versus placebo in Japanese and non-Japanese (Russian) patients:[3]
  - Reduced the cumulative number of Gd+ T1 lesions by 93.6%
  - Reduced the annualized relapse rate by 58.0%
  - Safety profile was consistent with the Phase 3 ASCLEPIOS I/II trials[2,3]

Objective

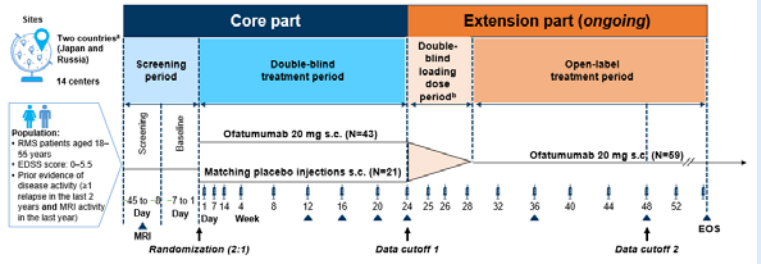
- To evaluate the long-term efficacy and safety of ofatumumab treatment through 48 weeks of core and extension parts of the APOLITOS Phase 2 study in Japanese and non-Japanese RMS patients

Methods

Study design

- Patients who completed the randomized (2:1), double-blind, 24W core APOLITOS study entered the open-label extension (data cutoff: W48)
- Patients initially randomized to placebo switched to ofatumumab (placebo-ofatumumab group) in the extension and those patients on ofatumumab continued treatment for at least 24 weeks
- 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 W4 onwards (subsequent doses) **(Figure 1)**

Figure 1: APOLITOS Study Design



[a]The randomization was stratified by region (Japan or non-Japan) and baseline Gd+ T1 lesion status (0 or ≥1). [b]Patients randomized to placebo in the double-blind treatment period received ofatumumab 20 mg s.c. at Weeks 24, 25, and 26 as the loading dose regimen. Patients randomized to ofatumumab in the double-blind treatment period received ofatumumab 20 mg s.c. at Week 24 and the matching placebo injections s.c. at Weeks 25 and 26. In all patients, the extension part started with the Week 24 injection. Data cutoffs 1 and 2 are defined as the last patient completing all the assessments for Weeks 24 and 48, respectively; EDSS, Expanded Disability Status Scale; EOS, end of study; FU, follow-up; Gd+, gadolinium enhancing; MRI, magnetic resonance imaging; MS, multiple sclerosis; RMS, relapsing multiple sclerosis s.c., subcutaneous; W, Week

1. KESIMPTA® (ofatumumab) Prescribing Information. https://www.novartis.us/sites/www.novartis.us/files/kesimpta.pdf. Last updated: August 2020; Accessed: September 16, 2020; 2. Hauser SL, et al. *N Engl J Med*. 2020;383:546–57. 3. Kira J. et al. *ACTRIMS-ECTRIMS* 2020, P0209.

Methods (Contd.)

Study outcomes

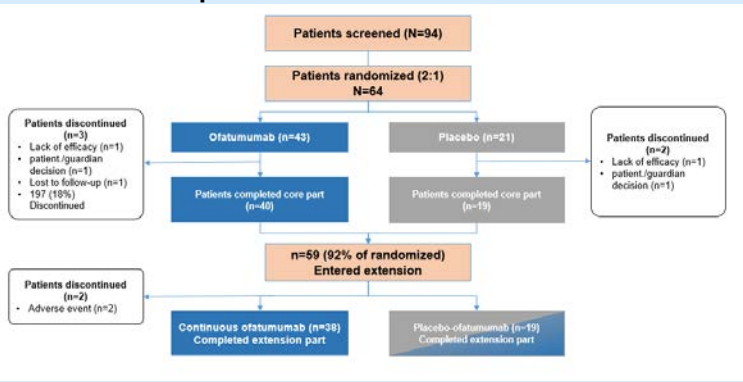
- Gd+ T1 lesions, T2 lesions, relapses, and safety parameters up to 48 weeks

Results: Patient disposition

Patient disposition

- Of the 64 patients randomized, 59 patients (ofatumumab [n=40] and placebo [n=19]) completed the double-blind core phase and continued in the extension part; 57 (97%) patients completed the extension part **(Figure 2)**

Figure 2: Patient disposition: Core+Extension



Results: Patient demographics

Patient demographics and baseline characteristics:

- Study population was representative of typical RMS population **(Table 1)**

Table 1: Patient demographics and baseline characteristics

Characteristics[a]	Core part (24 weeks)			Extension part (up to 48 weeks)
	Ofatumumab 20 mg (N=43)	Placebo (N=21)	Overall (N=64)	Overall (N=59)
Age (years)	35.0±9.49	35.5±8.93	35.2±9.24	34.9±9.40
Sex, female, n (%)	36 (83.7)	19 (90.5)	55 (85.9)	51 (86.4)
Race, n (%)				
Asian	21 (48.8)	11 (52.4)	32 (50.0)	30 (50.8)
White	22 (51.2)	10 (47.6)	32 (50.0)	29 (49.2)
Weight (kg)	58.31±11.84	64.87±9.84	60.47±11.57	60.0±10.75
Duration of MS since first symptoms (years)	7.92±8.63	7.99±6.83	7.95±8.03	7.6±7.56
Previously treated with DMTs, n (%)	29 (67.4)	15 (71.4)	44 (68.8)	40 (67.8)
Number of relapses in the last 12 months	1.6±0.90	1.2±0.70	1.5±0.85	1.5±0.86
EDSS score[a]	2.20±1.04	2.24±1.29	2.21±1.12	2.25±1.10
T2 lesion volume (cm^3)	11.5±10.92	11.9±11.79	11.6±11.12	12.0±11.48
Number of Gd+ lesions	1.3±2.62	1.0±1.47	1.2±2.29	1.3±2.35

[a]Data are expressed as mean±standard deviation unless stated otherwise; [b]Baseline EDSS was used and defined as the last EDSS assessment prior to the first dose of study treatment. ARR, annualized relapse rate; DMTs, disease-modifying therapies; EDSS, Expanded Disability Status Scale; Gd+, gadolinium enhancing; MRI, magnetic resonance imaging; MS, multiple sclerosis; RMS, relapsing multiple sclerosis

Results: Lesion activity

- **Ofatumumab reduced the number of Gd+ T1 lesions up to W48 (Figure 3)**
  - In the continuous ofatumumab group, the mean number of Gd+ T1 lesions per scan up to W24 was low (0.106) and further abrogated to 0.027 after W24 up to W48
  - In the placebo-ofatumumab group, the mean number of Gd+ T1 lesions per scan up to W24 was high (1.150), with a marked reduction to 0.025 after switching to ofatumumab
- Consistent effect on Gd+ T1 lesion reduction was observed with ofatumumab across geographical regions (Japan/Non-Japan [Russian])
- **Ofatumumab reduced the number of n/neT2 lesions up to W48 (Figure 4)**
  - In the continuous ofatumumab group, the annualized rate of neT2 lesions decreased from 4.810 (between baseline and W24) to 0.230 (between W24 and W48)
  - In the placebo-ofatumumab group, the annualized rate of neT2 lesions reduced from 12.080 (between baseline to W24) to 0.813 (between W24 to W48)

Figure 3: Number of Gd+ T1 lesions per scan over 48 weeks

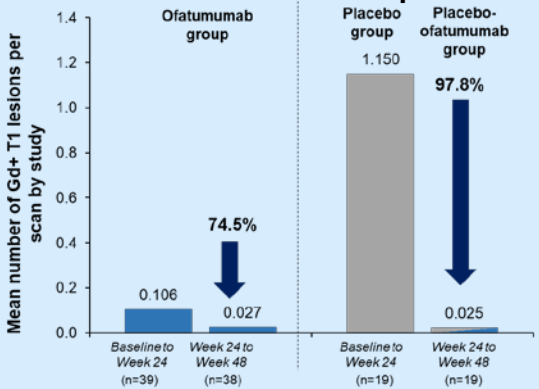
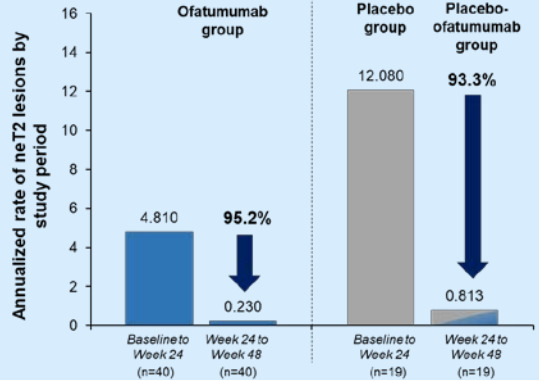


Figure 4: Annualized rate of n/neT2 lesions over 48 weeks

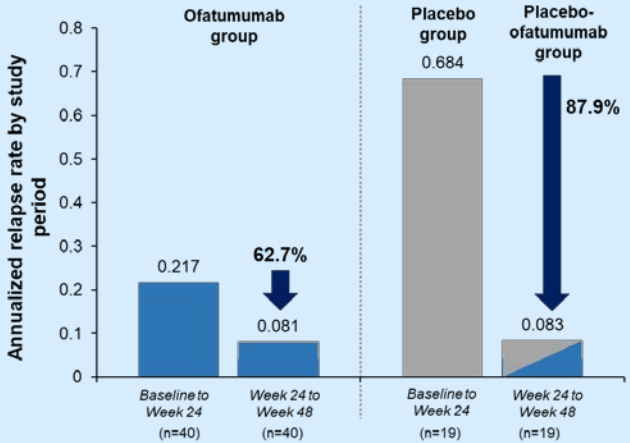


The mean number of Gd+ T1 lesions were determined using a negative binomial regression model with log-link that included treatment, region (Japan or non-Japan), and number of Gd+ lesions at baseline (0 or ≥1) as factors. All post-baseline scans up to and including Week 24 were included. The natural log of the number of MRI scans with evaluable Gd+ lesion counts was used as the offset to obtain the lesion rate per scan. Gd+ lesion counts from scans collected within 14 days after termination of steroid therapy were excluded from the analysis. Gd+, gadolinium enhancing; MR!, magnetic resonance imaging; n/neT2, new or newly enlarging T2 lesions; W, Week

Results: Annualized relapse rate

- **Ofatumumab reduced the ARR up to W48 (Figure 5)**
  - In the continuous ofatumumab group, the time-based ARR up to W24 was 0.217 and further decreased to 0.081 after W24 and up to W48
  - In the placebo-ofatumumab group, the time-based ARR up to W24 was 0.684 and decreased to 0.083 (relative reduction of 87.9%) after switching from placebo to ofatumumab at W24

Figure 5: Annualized relapse rate over 48 weeks



Safety Results:

- Patients were exposed to ofatumumab treatment for 44.7 patient-years in the "ofatumumab group" and for 12.9 patient-years in the "placebo-ofatumumab group"
- Across the study, IRRs were the most common AEs **(Table 2)**
  - All IRRs were mild to moderate in severity (Grade 1 or 2) and predominantly reported with the first injection and decreased with subsequent injections
  - No IRRs were serious or resulted in discontinuation or interruption of ofatumumab treatment
- No deaths, opportunistic infections, or malignancies occurred during the study
- The AE profiles for Japanese and non-Japanese (Russian) patients (data not shown) were consistent with those observed for the overall population

Table 2: Safety profile

Patients, n (%)	Ofatumumab group (N=40)	Placebo-ofatumumab group (N=19)	All patients (N=59)
Patients with at least one AE	33 (82.5)	11 (57.9)	44 (74.6)
Treatment-emergent AEs (≥8% in either group)[a]			
Injection-related reaction[b]	10 (25.0)	4 (21.0)	14 (23.7)
Nasopharyngitis	9 (22.5)	4 (21.1)	13 (22.0)
Oral herpes	6 (15.0)	0	6 (10.2)
Tension headache	5 (12.5)	0	5 (8.5)
Rash	4 (10.0)	0	4 (6.8)
Patients with SAEs	2 (5.0)	0	2 (3.4)
Cardiac failure acute	1 (2.5)	0	1 (1.7)
CIDP[c]	1 (2.5)	0	1 (1.7)

[a]A patient with multiple AEs is counted only once in the "at least one AE" row; a patient with multiple AEs with the same preferred term is counted only once for that preferred term. [b]Injection systemic reactions were coded as a MedDRA preferred term of "injection-related reaction" and injection site reactions as "injection site reaction". The original safety analysis included AEs reported post-dose at the Week 24 visit when patients in the placebo group received the first injection of ofatumumab. When excluding these events reported at Week 24, the n (%) of injection-related/site reaction has been reported here. [c]One ofatumumab-treated patient was diagnosed with serious CIDP after completing the double-blind treatment. AE, adverse event; ARR, annualized relapse rate; CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; IRR, injection-related reaction; SAE, serious AE; W, Week

Conclusions

- Ofatumumab demonstrated superior efficacy versus placebo in an RMS population with recent disease activity in Japanese and non-Japanese (Russian) patients
  - Continued treatment with ofatumumab across 48 weeks was associated with sustained radiological and clinical efficacy. Switching from placebo to ofatumumab after 24 weeks led to rapid radiological and clinical benefit
  - No new safety signals were detected. The safety profile of ofatumumab was consistent with that observed in the pivotal Phase 3 ASCLEPIOS I/II trials[1]

[1]Hauser SL, et al. *N Engl J Med*. 2020;383:546–557.

Disclosures

Takahiko Saida was a coordinating investigator, received funding, held board membership, spoke at scientific meetings, prepared manuscripts, and has had consulting agreements with Biogen, Eisai, Mitsubishi Tanabe, Nihon, Novartis, Ono, Sanofi, and Teijin. Jin Nakahara received honoraria from Biogen, Mitsubishi Tanabe, Novartis, and Takeda and served as a paid scientific advisor to Biogen, Novartis, and Takeda. Denis V. Sazonov received honoraria form BIOCAD and Biogen. Jun-ichi Kira is supported by grants from JSPS KAKENHI (Grant No. 19H01045) and Health and Labour Sciences Research Grants on Intractable Diseases [H29-Nanchitou (Nan)-Ippan-043] and received consultancy fees, speaking fees, and/or honoraria from Novartis, Mitsubishi Tanabe, Boehringer Ingelheim, Teijin, Takeda, Otsuka Pharmaceutical, Astellas, Pfizer Japan, and Eisai. Takayoshi Kurosawa, Isao Tsumiyama, Roman Willi, Martin Zalesak, Ratnakar Pingili, Dieter A. Häring, Krishnan Ramanathan, and Wendy Su are employees of Novartis.

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