Efficacy and safety of ofatumumab versus placebo in relapsing multiple sclerosis patients in Japan and Russia: results from the Phase 2 APOLITOS study

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Background and objective

- Ofatumumab, an FDA-approved fully human anti-CD20 monoclonal antibody, with a 20 mg s.c. monthly dosing regimen, is indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults[1]
- Ofatumumab demonstrated superior efficacy versus teriflunomide 14 mg oral once daily and a favorable safety profile in RMS patients in the Global (Ex-Japan) Phase 3 ASCLEPIOS I/II trials[2,3]
  - Reduction in the annualized relapse rate by 50.5% (p<0.001) in ASCLEPIOS I and by 58.5% (p<0.001) in ASCLEPIOS II
  - Reduction in 3-month confirmed disability worsening (CDW) by 34.4% (p=0.002) and in 6-month CDW by 32.5% (p=0.012) in the pre-specified pooled analysis
  - Reduction in the number of gadolinium enhancing T1 lesions by 97.5% (p<0.001) in ASCLEPIOS I and by 93.8% (p<0.001) in ASCLEPIOS II
  - No unexpected safety signals and no imbalance in the rates of infections or malignancies (low in both arms)
- The Phase 2 APOLITOS study was designed to support the registration of ofatumumab for the treatment of RMS in Japan in conjunction with the ASCLEPIOS I/II trials

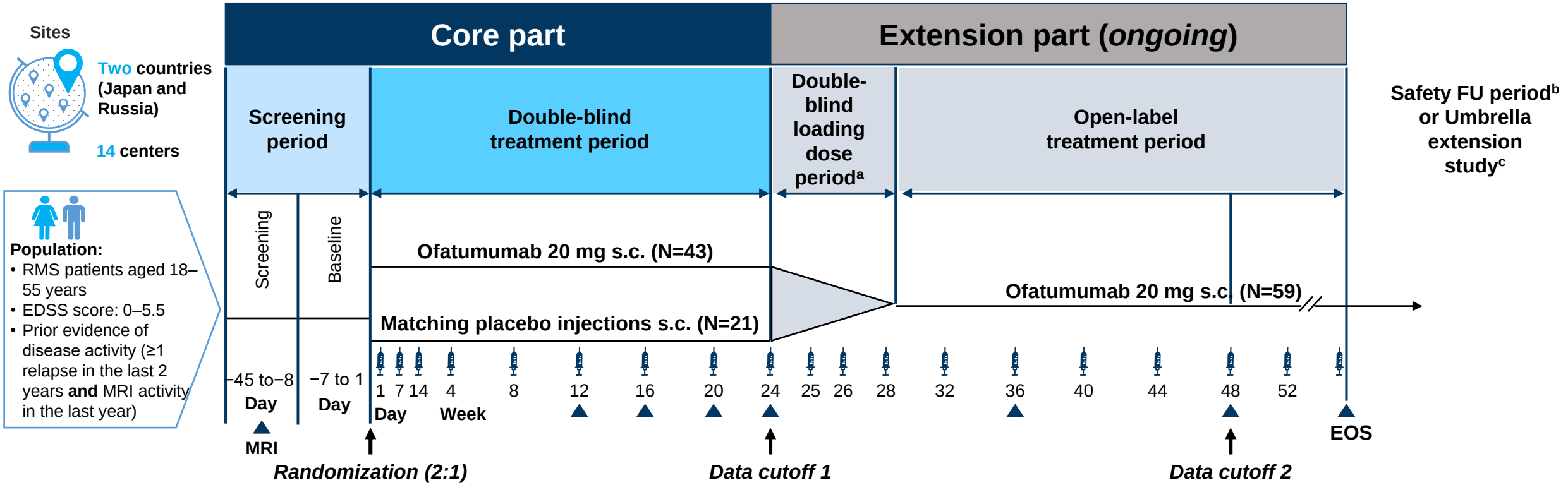
Objective	**To evaluate the efficacy and safety of ofatumumab versus placebo in RMS patients and assess consistency of treatment effect in Japanese and non-Japanese patients**

RMS, relapsing multiple sclerosis; s.c., subcutaneous

1. KESIMPTA® (ofatumumab) Prescribing Information. https://www.novartis.us/sites/www.novartis.us/files/kesimpta.pdf (accessed Aug 24, 2020); 2. Hauser SL, et al. Presented at the *ECTRIMS*. 2019; S17.OP336; 3. Hauser SL, et al. *N Engl J Med*. 2020;383:546–57.

Study design

24-week, randomized, double-blind, placebo-controlled, parallel-group, multicenter core study followed by an open-label extension up to Week 48



- **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)**
- **Of the 64 patients randomized, 59 patients (ofatumumab [N=40] and placebo [N=19]) completed the double-blind phase and continued in the extension part**

The randomization was stratified by region (Japan or non-Japan) and baseline Gd+ T1 lesion status (0 or ≥1). [a]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. [b]Patients who prematurely discontinued the study drug or patients who did not enter the Umbrella extension study entered the safety FU period following their EOS visits. [c]The Umbrella extension study is being conducted under a separate protocol. 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; RMS, relapsing multiple sclerosis; s.c., subcutaneous

Study endpoints

Primary endpoint

- Reduction in cumulative number of Gd+ T1 lesions across MRI scans at Weeks 12, 16, 20, and 24 in patients with RMS

Secondary endpoints

- Reduction in the cumulative number of Gd+ T1 lesions across regions (Japan versus non-Japan)
- Reduction in ARR and time to first relapse
- Safety and tolerability

ARR, annualized relapse rate; Gd+, gadolinium enhancing; MRI, magnetic resonance imaging; RMS, relapsing multiple sclerosis

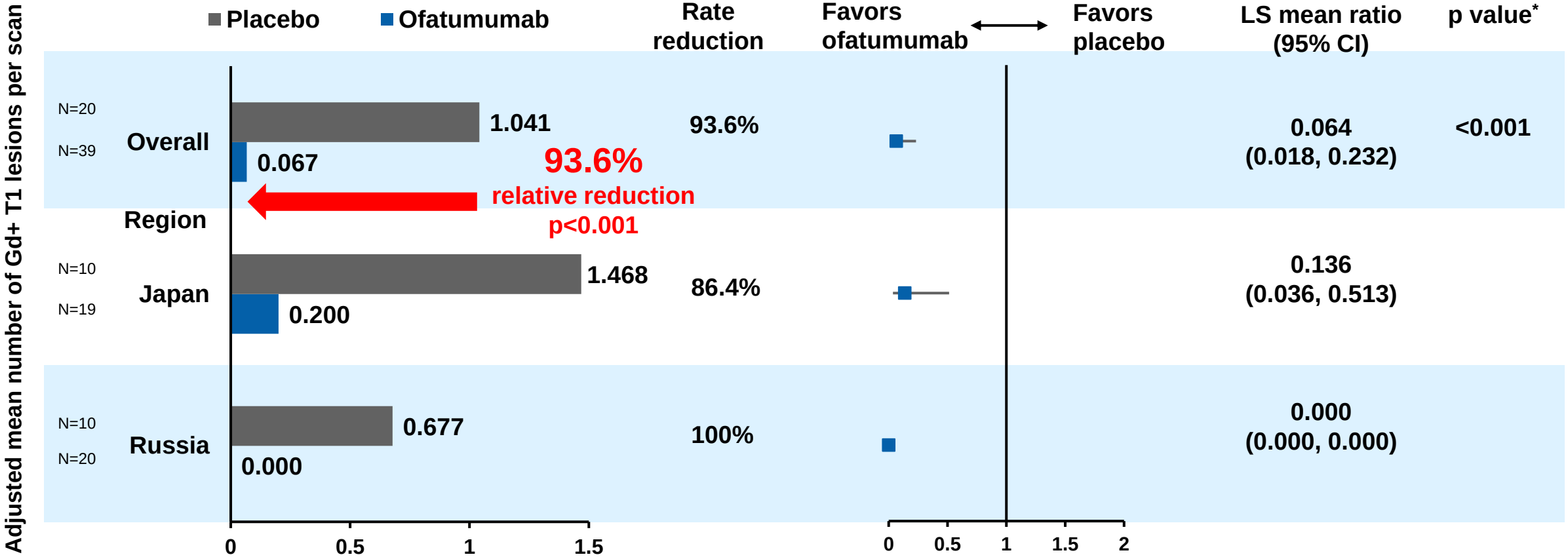
Demographics and baseline characteristics

Characteristics	Ofatumumab 20mg (N=43)	Placebo (N=21)	All (N=64)
Age (years)	35.0±9.49	35.5±8.93	35.2±9.24
Sex, female	36 (83.7)	19 (90.5)	55 (85.9)
Race			
Asian	21 (48.8)	11 (52.4)	32 (50.0)
White	22 (51.2)	10 (47.6)	32 (50.0)
Weight (kg)	58.31±11.84	64.87±9.84	60.47±11.57
Duration of MS since first symptoms (years)	7.92±8.63	7.99±6.83	7.95±8.03
Previously treated with DMTs	29 (67.4)	15 (71.4)	44 (68.8)
Number of relapses in the last 12 months	1.6±0.90	1.2±0.70	1.5±0.85
EDSS score[a]	2.20±1.04	2.24±1.29	2.21±1.12
T2 lesion volume (cm^3)	11.5±10.92	11.9±11.79	11.6±11.12
Number of Gd+ lesions	1.3±2.62	1.0±1.47	1.2±2.29

Most patients had high baseline disease activity and received prior DMTs

Data are expressed as mean±standard deviation or n (%). [a]Baseline EDSS was used and defined as the last EDSS assessment prior to the first dose of study treatment.
DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; Gd+, gadolinium enhancing; MS, multiple sclerosis

Primary endpoint: ofatumumab significantly reduced the number of Gd+ T1 lesions versus placebo by Week 24



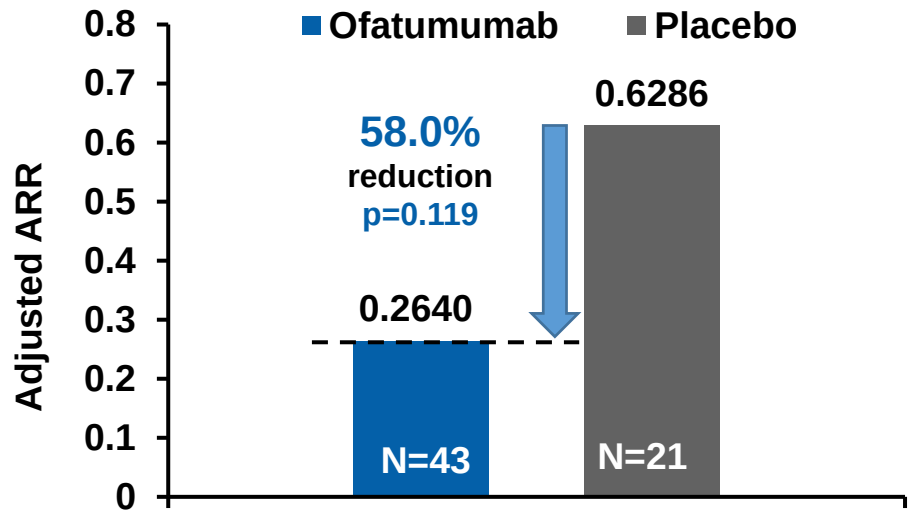
- **Ofatumumab significantly reduced number of Gd+ T1 lesions versus placebo by 93.6% overall (primary endpoint), and the rate ratio was less than 1 in both Japan and Russia, indicating a consistent outcome across regions (secondary endpoint)**

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. *Indicates statistical significance at the 0.05 level.

CI, confidence interval; Gd+, gadolinium enhancing; LS, least square; MRI, magnetic resonance imaging

Secondary endpoint: Ofatumumab was numerically superior to placebo in reducing ARR

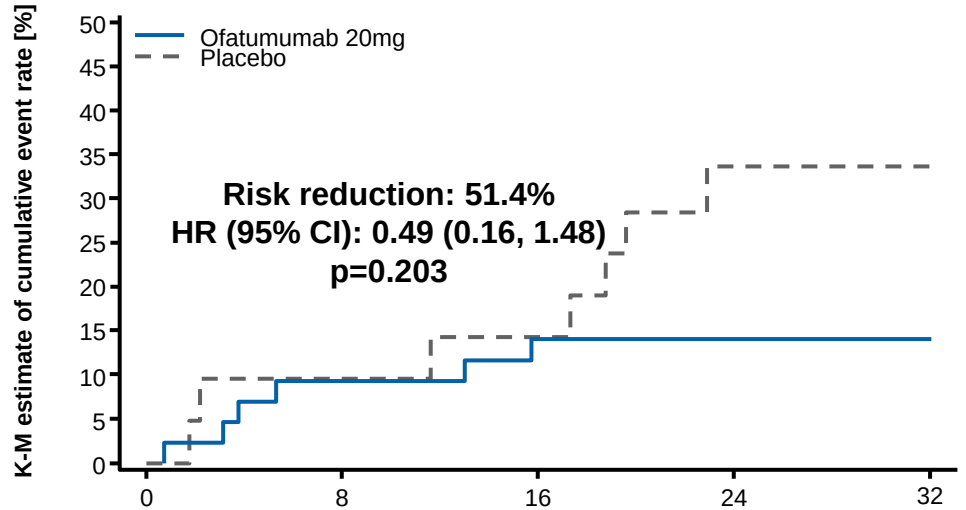
ARR by Week 24



ARR ratio (95% CI): 0.420 (0.141, 1.250)

Ofatumumab reduced the ARR versus placebo by 58.0%

Percentage of patients with confirmed relapse during the double-blind treatment period (Week 24)



Number of patients at risk

Ofatumumab 20mg	43	39	37	22	0
Placebo	21	19	18	8	0

Ofatumumab reduced the risk of time to first relapse by 51.4% versus placebo

Confirmed relapses are relapses that are accompanied by a clinically relevant change in the EDSS. Adjusted ARR was obtained by fitting a negative binomial regression model with log-link to the number of relapses, adjusted for treatment and region as factors. The natural log of the time in study was used as an offset to the ARR. At week 48, the ARR (time-based) was observed to be 0.081 with Ofatumumab which is consistent with the Phase 3 studies.

ARR, annualized relapse rate; CI, confidence interval; EDSS, Expanded Disability Status Scale; HR, hazard ratio; K-M, Kaplan-Meier

Safety and tolerability

- Patients were exposed to ofatumumab treatment for 22.4 patient-years and placebo for 10.9 patient-years
- No patient in either of the treatment groups discontinued or interrupted the 24-week study treatment
- The incidence of treatment-emergent AEs was lower with ofatumumab (27.9%) versus placebo (38.1%)
- Injection-related reactions were the most common AEs
- No deaths, opportunistic infections, or malignancies occurred during the study

	Ofatumumab 20 mg (N=43)	Placebo (N=21)
Patients with at least one AE	30 (69.8)	17 (81.0)
Treatment-emergent AEs (≥7% in either group)[a]		
Injection-related reaction[b]	9 (20.9)	4 (19.0)
Nasopharyngitis	6 (14.0)	3 (14.3)
Oral herpes	4 (9.3)	0
Tension headache	4 (9.3)	3 (14.3)
Back pain	3 (7.0)	1 (4.8)
Injection site reaction[b]	1 (2.3)	2 (9.5)
Patients with SAEs	1 (2.3)	0
CIDP[c]	1 (2.3)	0

[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; CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; SAE, serious AE

Conclusions

- Ofatumumab demonstrated superior efficacy versus placebo in an RMS population with recent disease activity in Japanese and non-Japanese patients:
  - Reduced the cumulative number of Gd+ T1 lesions by 93.6%
  - Reduced the annualized relapse rate by 58.0%
- The reduction in the cumulative number of Gd+ T1 lesions was consistent in Japanese and non-Japanese RMS patients
- No new safety signals were detected. The safety profile was consistent with that observed in the Phase 3 ASCLEPIOS I/II trials[1,2]

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Gd+, gadolinium enhancing; n.s., non-significant; RMS, relapsing multiple sclerosis

1. Hauser SL, et al. Presented at the ECTRIMS. 2019; S17.OP336; 2. Hauser SL, et al. N Engl J Med. 2020;383:546–57.