Efficacy and Safety of Ofatumumab Versus Teriflunomide in Patients with Relapsing Multiple Sclerosis: Phase 3 ASCLEPIOS I and II Trials

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Platform session-DMT03

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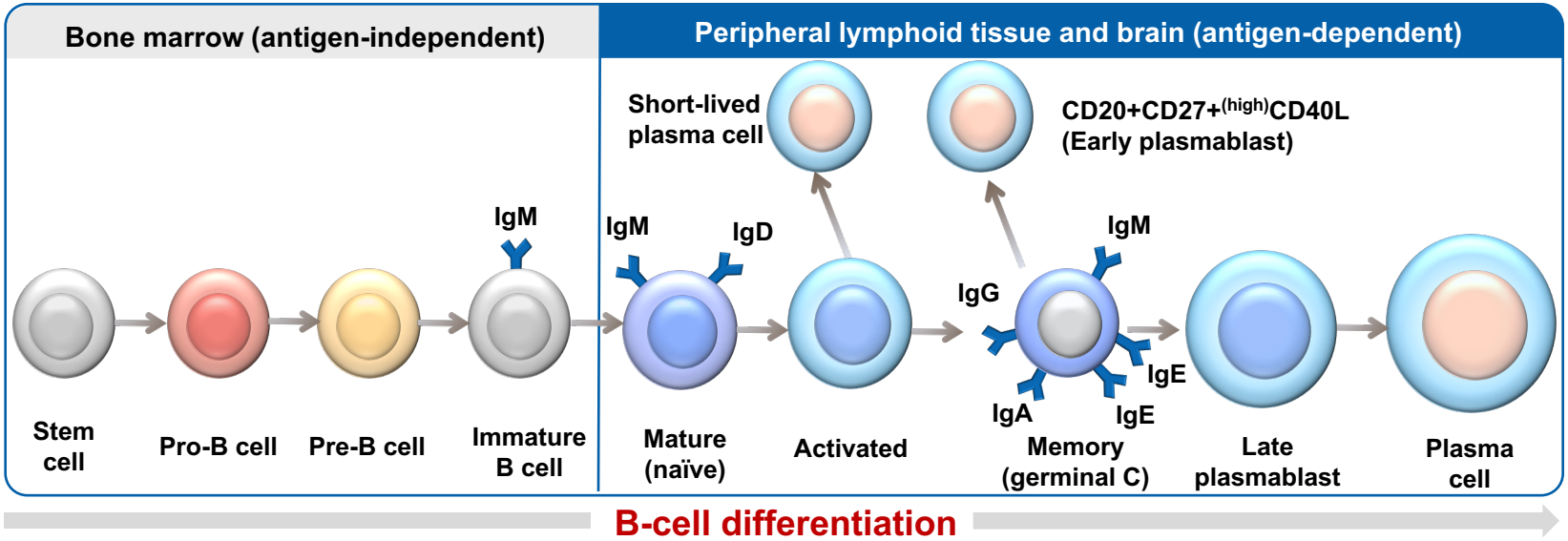
Anti-CD20 Therapy May Preserve Capacity of B-cell Reconstitution and Pre-existing Humoral Immunity

CD20 expression in B-cell lineage



Ofatumumab binds to CD20, resulting in B-cell depletion and reduced B- and T-cell interactions, which may reduce inflammation in the CNS

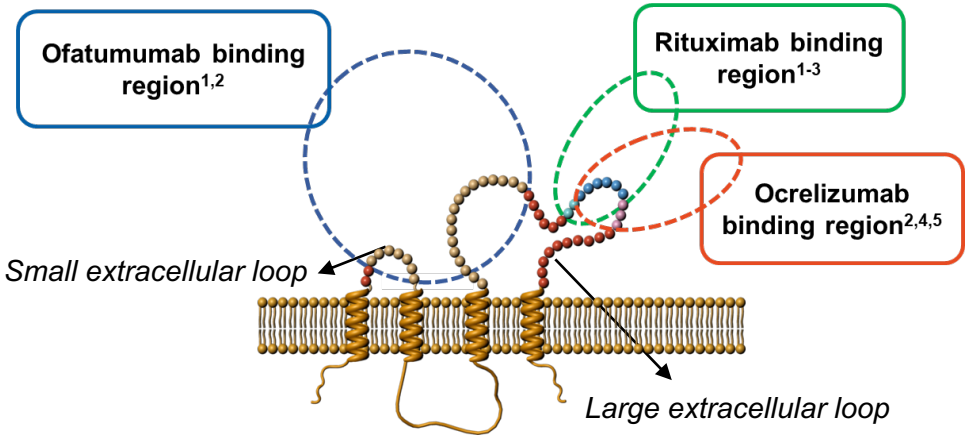
CNS, central nervous system; Ig, immunoglobulin

Figure adapted from Dalakas M. *Nat Clin Pract Neurol.* 2008;4:557–567. Hauser S, et al. *ECTRIMS* 2015. P.90.

Ofatumumab

Anti-CD20 therapy in MS

- Ofatumumab is the first fully human anti-CD20 monoclonal antibody, administered with a monthly 20 mg s.c. dosing regimen[1]
- Phase 2b MIRROR study: ≥90% reduction in Gd+ T1 lesions versus placebo at Week 12 for all cumulative ofatumumab doses of ≥30 mg over 12 weeks[7]



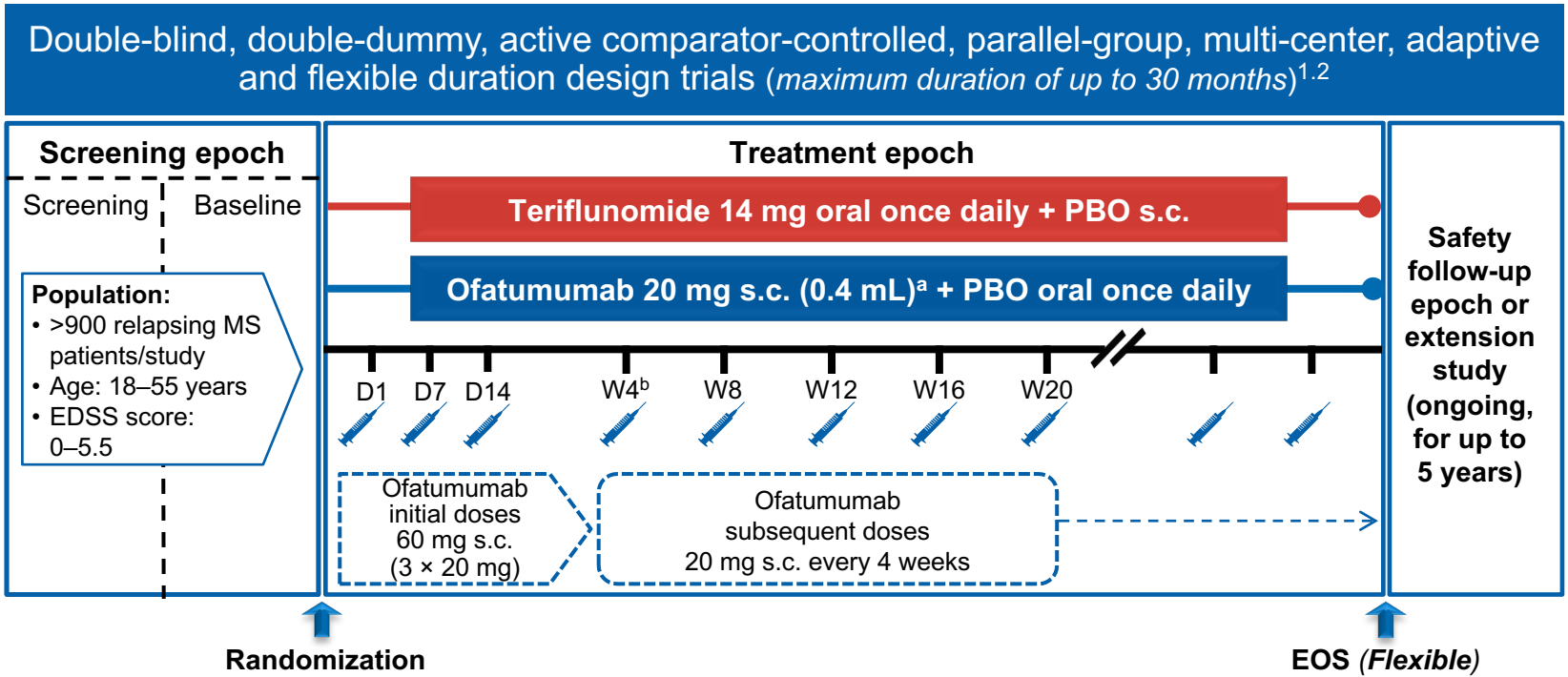
Ofatumumab binds to an epitope that consists of two distinct non-contiguous amino acid sequences,[1,5] has a low off-rate,[6] and potent and sustained effector activity[1]

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

[1]Smith P, et al. Presented at *ECTRIMS* 2016;P1143. [2]Teeling JL, et al. *J Immunol*. 2006;177:362–371. [3]Ruuls SR, et al. *Biotechnol J*. 2008;3:1157–1171. [4]Genovese MC, et al. *Arthritis Rheum*. 2008;58:2652–2661. [5]Klein C, et al. *MAbs*. 2013;5:22–33. [6]Pacheco-Fernandez T, et al. *AAN* 2018;S52.003. [7]Bar-Or A, et al. *Neurology*. 2018;90:e1805–e1814.

ASCLEPIOS I and II: Study Design

Identical study designs, conducted in parallel



[a]20 mg of ofatumumab was administered in an injection volume of 0.4 mL; [b]Week 4 (Month 1) and every 4 weeks thereafter. D, day; EDSS, Expanded Disability Status Scale; EOS, end of study; MS, multiple sclerosis; PBO, placebo; s.c., subcutaneous; W, week

1. Hauser SL, et al. Presented at *ECTRIMS*.2019. S17.OP336; 2. Kappos L, et al. Presented at *AAN* 2020.

ASCLEPIOS I and II: Study Objective and Key Endpoints

Objective: To evaluate the efficacy and safety of ofatumumab compared with teriflunomide in patients with relapsing multiple sclerosis

Study endpoints[1,2]		
Primary endpoint *(within each study)*	• Annualized relapse rate *(number of confirmed multiple sclerosis relapses in a year)*	
Key secondary endpoints	**Pre-specified pooled analysis** • 3-month confirmed disability worsening • 6-month confirmed disability worsening • 6-month confirmed disability improvement	**By individual study** • Gadolinium-enhancing T1 lesions • New or enlarging T2 lesions • Serum neurofilament light chain levels • Brain volume loss

1. Hauser SL, et al. Presented at *ECTRIMS*.2019. S17.OP336; 2. Kappos L, et al. Presented at *AAN* 2020.

ASCLEPIOS I and II: Study Population

Key inclusion criteria[1,2]

- Male or female patients aged 18 to 55 years
- Diagnosis of MS according to the 2010 Revised McDonald criteria[3]
- Relapsing form of MS: RRMS or SPMS with disease activity as defined by Lublin et al. 2014[4]
- EDSS score of 0 to 5.5
- One of the following documented:
  - ≥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

Key exclusion criteria[1,2]

- 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 or confirmed with PML
- Patients at risk of developing or history of syphilis, tuberculosis or hepatitis
- Patients who received any live/live-attenuated vaccines in the 2 months prior to randomization

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

1. Hauser SL, et al. Presented at *ECTRIMS*.2019. S17.OP336; 2. Kappos L, et al. Presented at *AAN* 2020; 3. Kappos L et al, Presented at *ECTRIMS* 2018. P965. 4. Lublin FD, et al. *Neurology*. 2014;83:278–286.

ASCLEPIOS I and II: Independent Global Studies

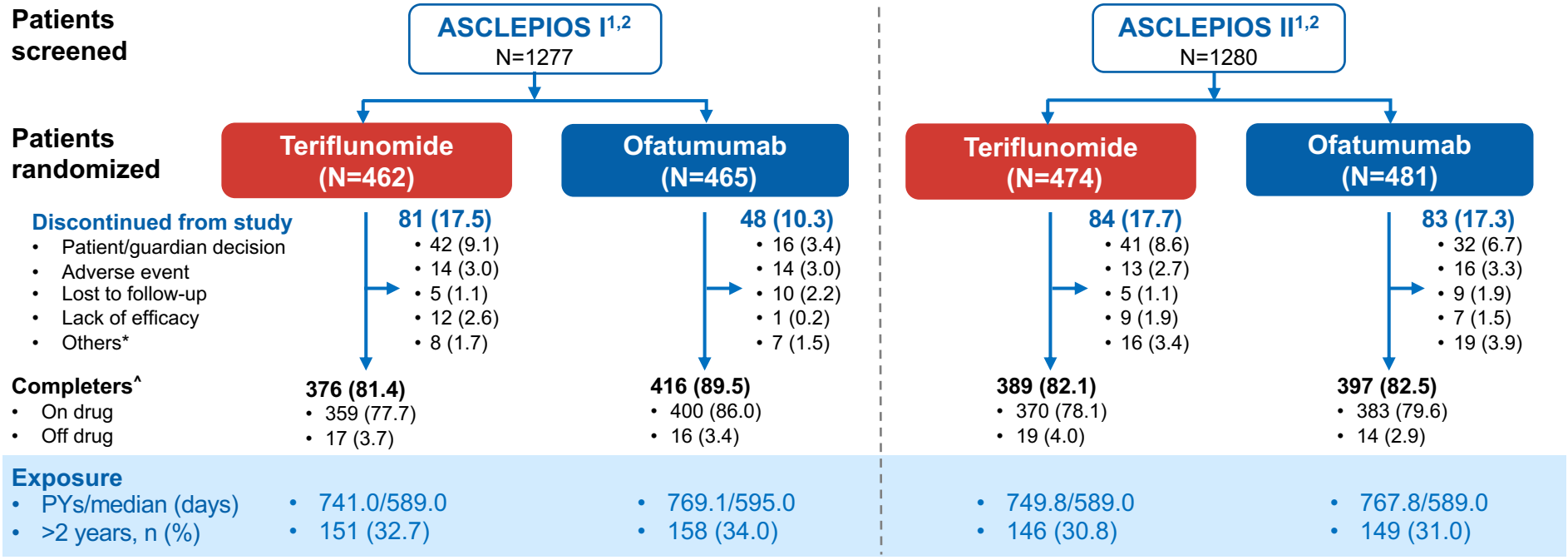
- First patient first treatment: October 5, 2016
- Last patient first treatment: March 1, 2018

Geographic region[1,2], n (%)	ASCLEPIOS I	ASCLEPIOS II
Eastern Europe	325 (35.1)	233 (24.4)
Western Europe	170 (18.3)	246 (25.8)
US/Canada	208 (22.4)	213 (22.3)
Others	224 (24.2)	263 (27.5)
Total	**927**	**955**

Countries with the highest enrollment included the United States, Russia, Poland, Czech Republic, Croatia, Germany, Spain and India

1. Hauser SL, et al. Presented at *ECTRIMS*.2019. S17.OP336; 2. Kappos L, et al. Presented at *AAN* 2020.

ASCLEPIOS I and II: Patient Disposition and Exposure Data



Data are represented as n (%). *Others include physician decision, protocol deviation, new therapy for study indication, non-compliance with study treatment, pregnancy and technical problems. On study drug: Patients who took the study drug until the treatment epoch completion. Off study drug: Patients who completed the treatment epoch but discontinued the study drug prematurely. ^Six patients in ASCLEPIOS I and two in ASCLEPIOS II were considered ongoing at the time of the data cut-off date. PYs, patient-years; 1. Hauser SL, et al. Presented at *ECTRIMS*.2019. S17.OP336; 2. Kappos L, et al. Presented at *AAN* 2020.

Demographics and Baseline Characteristics

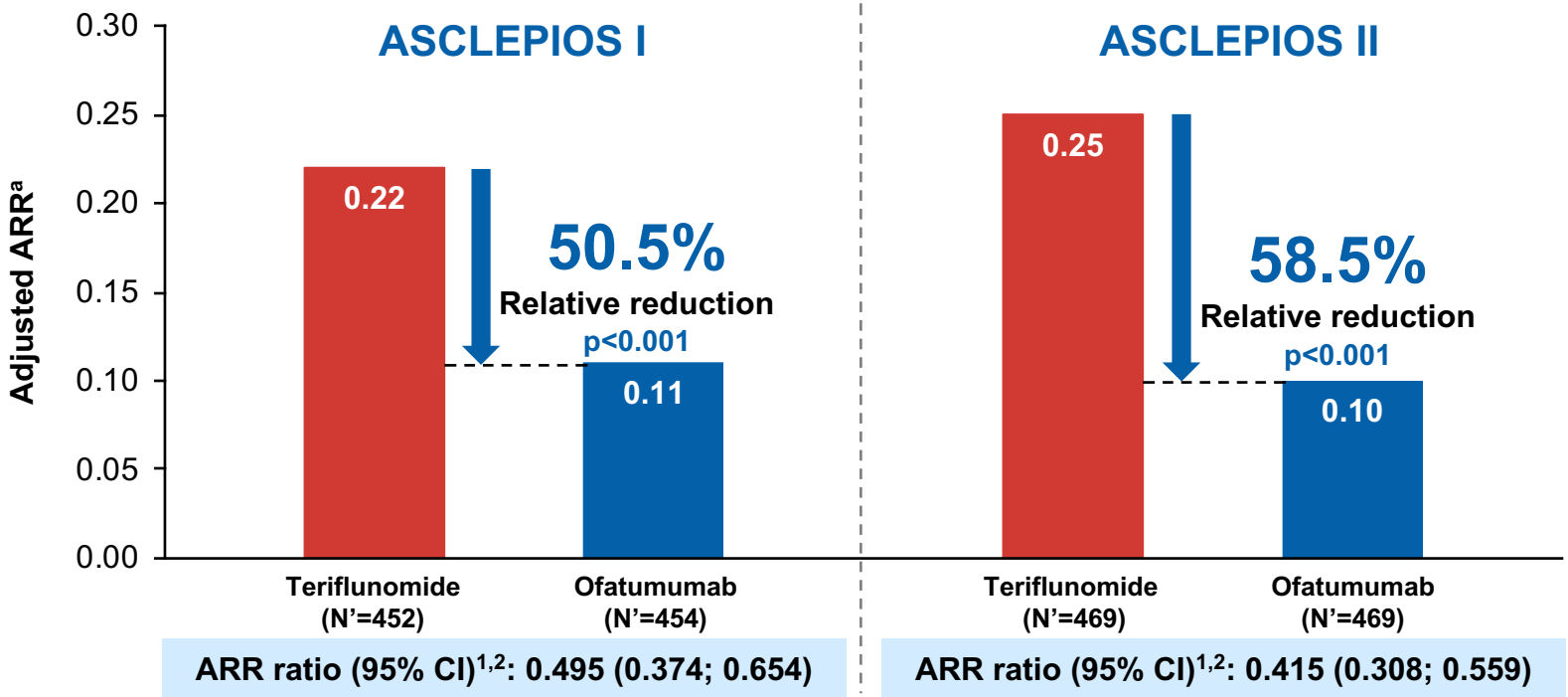
ASCLEPIOS I and II populations are consistent and poolable

Characteristics[1,2]	ASCLEPIOS I (N=927)		ASCLEPIOS II (N=955)	
Mean±standard deviation or n (%)	Teriflunomide (N=462)	Ofatumumab (N=465)	Teriflunomide (N=474)	Ofatumumab (N=481)
Age (years)	37.8±9.0	38.9±8.8	38.2±9.5	38.0±9.3
Sex, female	317 (68.6)	318 (68.4)	319 (67.3)	319 (66.3)
Weight (kg)	75.47±20.0	74.84±19.9	73.97±17.9	73.62±19.0
Duration of MS since first symptoms (years)	8.18±7.2	8.36±6.8	8.19±7.4	8.2±7.4
Previously treated with DMTs	280 (60.6)	274 (58.9)	293 (61.8)	286 (59.5)
Number of relapses in the last 12 months	1.3±0.69	1.2±0.63	1.3±0.73	1.3±0.74
EDSS score	2.94±1.4	2.97±1.4	2.86±1.4	2.90±1.3
T2 lesion volume (cm^3)	13.1±14.6	13.2±13.3	12.0±13.0	14.3±14.2
Patients free of Gd+ T1 lesions	293 (63.4)	291 (62.6)	291 (61.4)	270 (56.1)
Number of Gd+ T1 lesions	1.2±2.6	1.7±4.9	1.5±4.1	1.6±4.1

Full analysis set. DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; MS, multiple sclerosis

1. Hauser SL, et al. Presented at *ECTRIMS*.2019. S17.OP336; 2. Kappos L, et al. Presented at *AAN* 2020.

Ofatumumab Demonstrated Significant Reduction in ARR

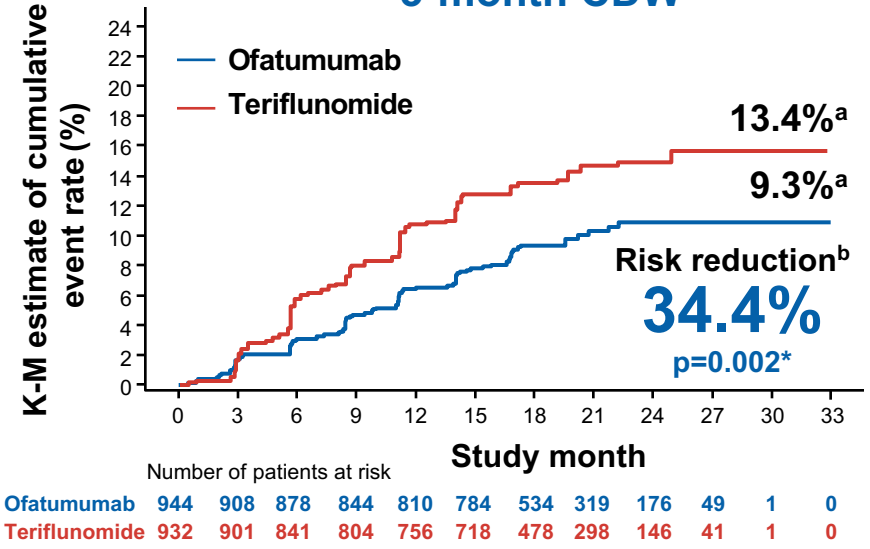


Full analysis set. Primary endpoint. [a]Negative binomial regression model.
ARR, annualized relapse rate; CI, confidence interval; N', total number of patients included in the analysis
1. Hauser SL, et al. Presented at *ECTRIMS*.2019. S17.OP336; 2. Kappos L, et al. Presented at *AAN* 2020. .

Ofatumumab Showed Significant Reductions in 3- and 6-month CDW

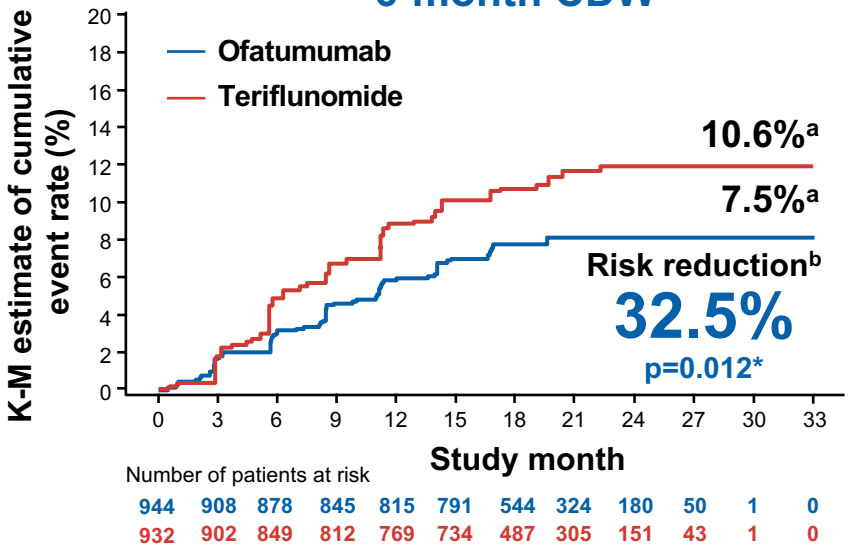
Pre-specified pooled analysis

3-month CDW



Hazard ratio (95% CI)[1,2]: 0.656 (0.499; 0.862)

6-month CDW



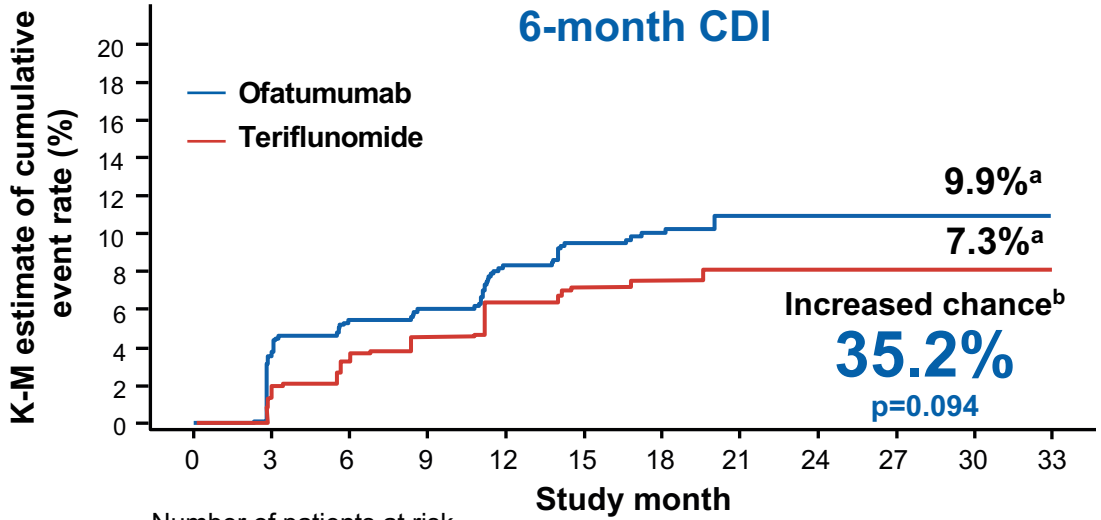
Hazard ratio (95% CI)[1,2]: 0.675 (0.498; 0.916)

Full analysis set. Secondary endpoints. *Indicates statistical significance (two-sided) at the 0.04875 level. [a]Proportion of patients with 3- or 6-month CDW, [b]Cox regression model. CDW, confirmed disability worsening; CI, confidence interval; K-M, Kaplan–Meier

1. Hauser SL, et al. Presented at *ECTRIMS*.2019. S17.OP336; 2. Kappos L, et al. Presented at *AAN* 2020.

Ofatumumab Demonstrated a Favorable Trend to Achieve 6-month CDI

Pre-specified pooled analysis

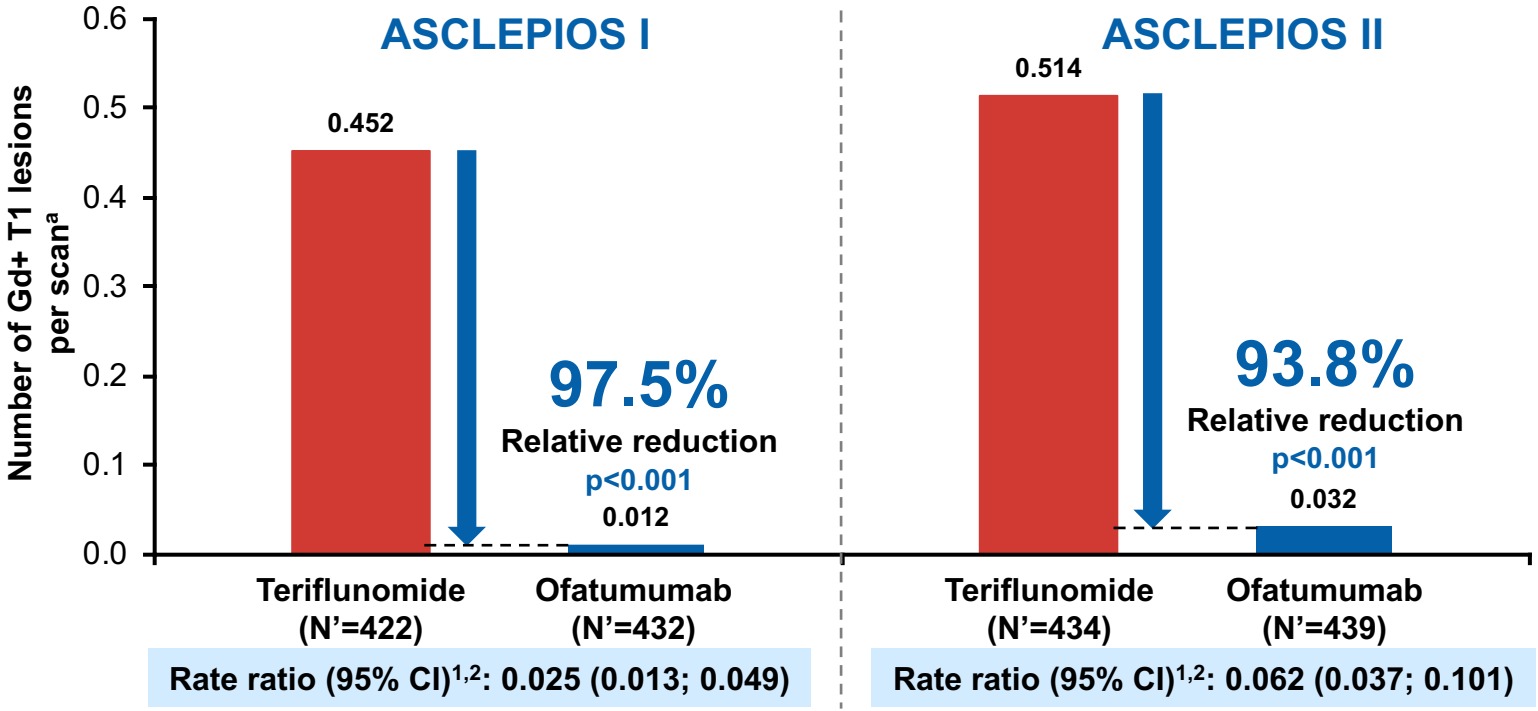


Hazard ratio (95% CI)[1,2]: 1.352 (0.950; 1.924)

Full analysis set. Secondary endpoint.. [a]Proportion of patients with 6-month CDI, [b]Cox regression model.
CDI, confirmed disability improvement; K-M, Kaplan–Meier

1. Hauser SL, et al. Presented at *ECTRIMS*.2019. S17.OP336; 2. Kappos L, et al. Presented at *AAN* 2020.

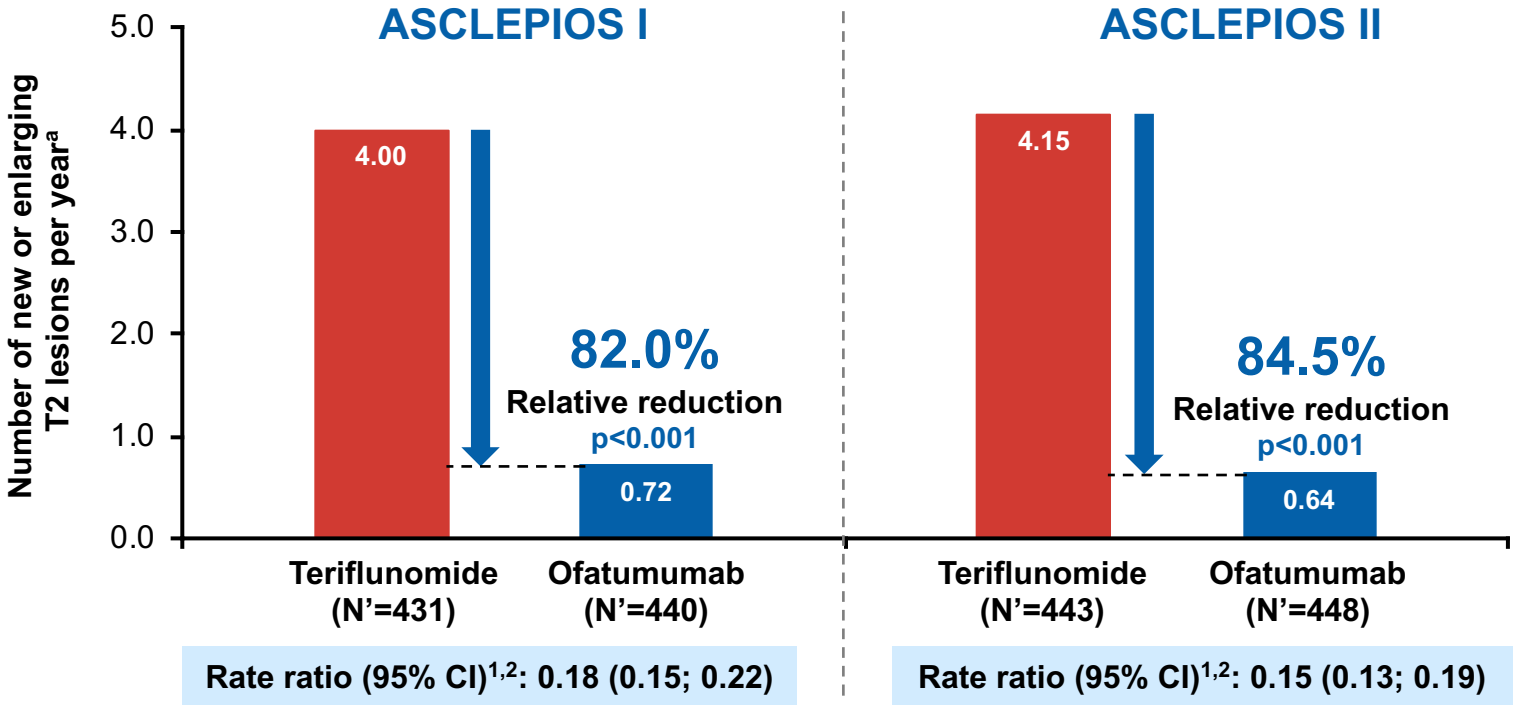
Ofatumumab Showed Significant Reductions in the Number of Gd+ T1 Lesions per scan



Full analysis set. Secondary endpoint. End of study. [a]Negative binomial regression model of the cumulative number of Gd+ lesions on the M12 and M24 scan, with an offset for the number of available scans. CI, confidence interval; Gd+, gadolinium-enhancing; N', total number of patients included in the analysis

1. Hauser SL, et al. Presented at *ECTRIMS*.2019. S17.OP336; 2. Kappos L, et al. Presented at *AAN* 2020.

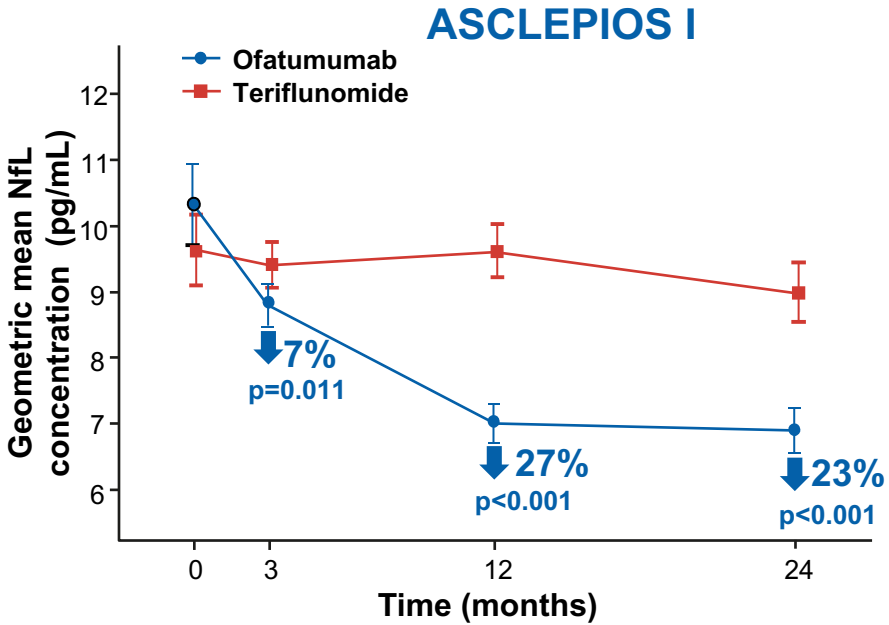
Ofatumumab Showed Significant Reductions in the Number of New or Enlarging T2 Lesions per year



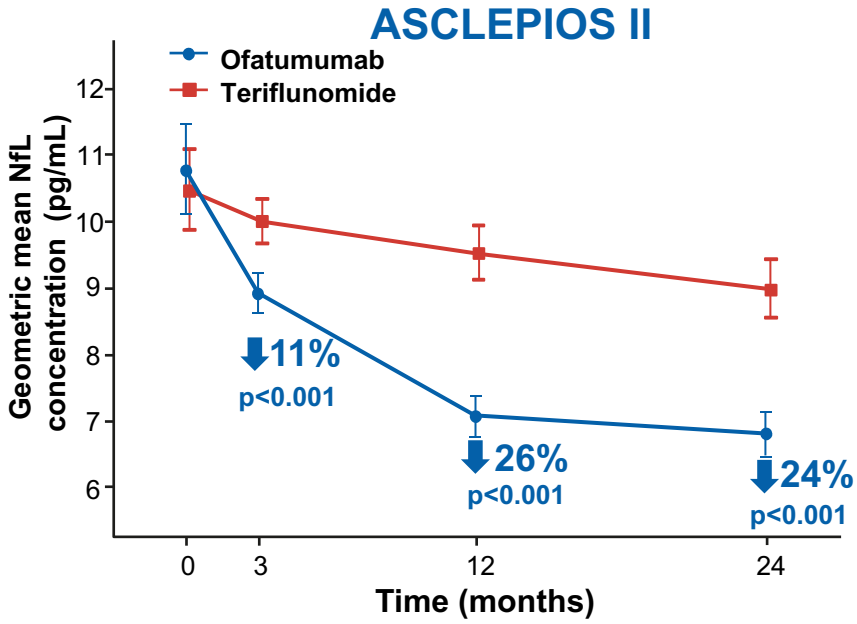
Full analysis set. Secondary endpoint. End of study. [a]Negative binomial regression model of the number of new or enlarging T2 lesions on the last scan relative to the screening scan, with an offset for the time in years between these two scans.

CI, confidence interval; N', total number of patients included in the analysis; 1. Hauser SL, et al. Presented at *ECTRIMS*.2019. S17.OP336; 2. Kappos L, et al. Presented at *AAN* 2020.

Ofatumumab Showed Significant and Consistent Reductions in Serum NfL levels From the First Assessment at Month 3



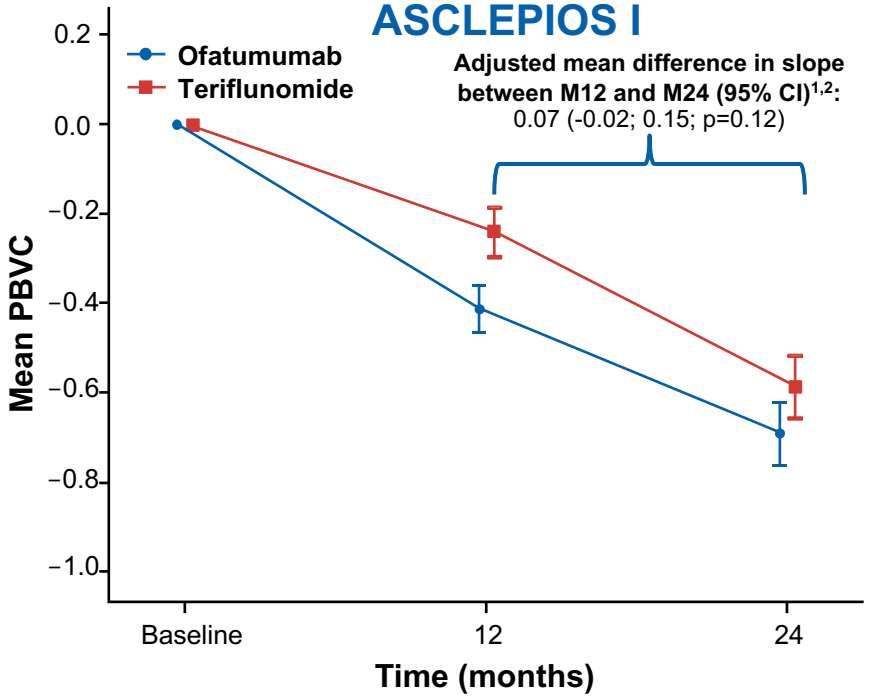
Geometric mean ratio at Month 3 (95% CI)[1,2]:
0.93 (0.89; 0.98) p=0.011

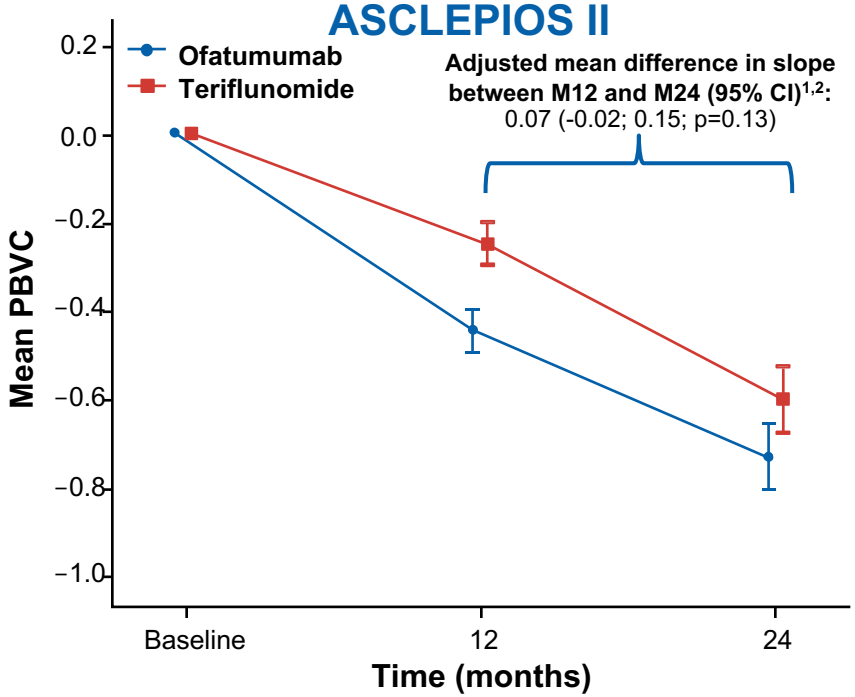


Geometric mean ratio at Month 3 (95% CI)[1,2]:
0.89 (0.85; 0.93) p<0.001

Full analysis set. Secondary endpoint. Repeated measures model. CI, confidence interval; NfL, neurofilament light chain
1. Hauser SL, et al. Presented at *ECTRIMS*.2019. S17.OP336; 2. Kappos L, et al. Presented at *AAN* 2020.

No Difference in the Slope of Brain Volume Change From Baseline Between Treatments





Whole brain volume was analyzed using the Jacobian integration model.
Full analysis set. Secondary endpoint. Random coefficient model. CI, confidence interval; M, month; PBVC, percent brain volume change

1. Hauser SL, et al. Presented at *ECTRIMS*.2019. S17.OP336; 2. Kappos L, et al. Presented at *AAN* 2020.

Comparison of AEs Between Groups; No Unexpected Safety Findings

Safety events[1,2], n (%)	Teriflunomide (N=936)	Ofatumumab (N=946)
Any adverse events (AEs)	**788 (84.2)**	**791 (83.6)**
Any serious AEs	**74 (7.9)**	**86 (9.1)**
Most common AEs *(≥5% in any treatment group, by preferred term)*		
Injection-related reaction[a]	143 (15.3)	195 (20.6)
Nasopharyngitis	156 (16.7)	170 (18.0)
Headache	116 (12.4)	126 (13.3)
Injection-site reaction	52 (5.6)	103 (10.9)
Upper respiratory tract infection	120 (12.8)	97 (10.3)
Urinary tract infection	78 (8.3)	97 (10.3)
Back pain	58 (6.2)	72 (7.6)
Fatigue	72 (7.7)	71 (7.5)
Influenza	59 (6.3)	62 (6.6)
Nausea	64 (6.8)	61 (6.4)
Blood immunoglobulin M decreased	21 (2.2)	56 (5.9)
Alopecia	138 (14.7)	54 (5.7)
Arthralgia	44 (4.7)	49 (5.2)
Diarrhea	111 (11.9)	49 (5.2)
Pain in extremity	66 (7.1)	46 (4.9)
Depression	48 (5.1)	45 (4.8)
Hypertension	55 (5.9)	35 (3.7)
Paresthesia	52 (5.6)	27 (2.9)

[a]These are injection-systemic reactions; 1. Hauser SL, et al. Presented at *ECTRIMS*.2019. S17.OP336; 2. Kappos L, et al. Presented at *AAN* 2020.

Serious Adverse Events Were Low in both groups

Safety events[1,2], n (%)	Teriflunomide (N=936)	Ofatumumab (N=946)
Any serious AEs	**74 (7.9)**	**86 (9.1)**
Most common SAEs *(≥1% in any treatment group)*		
Primary system organ class		
Infections and infestations	17 (1.8)	24 (2.5)
Injury, poisoning and procedural complications	9 (1.0)	13 (1.4)
Nervous system disorders	15 (1.6)	7 (0.7)
Psychiatric disorders	2 (0.2)	10 (1.1)
MedDRA Query/Preferred term		
Malignancies (AEs and SAEs)	4 (0.4)[a]	5 (0.5)

- During the ASCLEPIOS I and II studies, one death occurred
  - Teriflunomide: fatal aortic hemorrhage

[a]One case of basal cell carcinoma was not listed as a serious AE
AEs, adverse events; SAEs, serious adverse events; 1. Hauser SL, et al. Presented at *ECTRIMS*.2019. S17.OP336; 2. Kappos L, et al. Presented at *AAN* 2020.

Summary and Conclusion

In a typical active RMS population ofatumumab as compared to teriflunomide —

- Reduced ARR by 50.5%–58.5%
- Reduced MRI activity: Gd+ lesions by 93.8%–97.5%; new/enlarging T2 lesions by 82%–84.5%
- Reduced 3-month CDW by 34.4% and 6-month CDW by 32.5% (pooled data)
- Lowered levels of NfL by month 3 (first time-point tested) and at all subsequent visits
- Demonstrated no unexpected safety signals. There was no imbalance in the rates of infections or malignancies (low in both arms)

Ofatumumab, with a monthly 20 mg s.c.* dosing regimen, demonstrated high efficacy and no unexpected safety concerns

*20 mg of ofatumumab was administered in an injection volume of 0.4 mL.
CDW, confirmed disability worsening; MRI, magnetic resonance imaging; NfL, neurofilament light chain; RMS, relapsing multiple sclerosis
s.c., subcutaneous; 1. Hauser SL, et al. Presented at *ECTRIMS*.2019. S17.OP336; 2. Kappos L, et al. Presented at *AAN* 2020.

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