Benefit-risk of Ofatumumab in Treatment-naïve Early Relapsing Multiple Sclerosis Patients

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Background and objective

- Ofatumumab, an FDA-approved fully human anti-CD20 monoclonal antibody with a monthly 20 mg s.c. dosing regimen, is indicated for the treatment of relapsing forms of multiple sclerosis, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults[1]
- Current treatment guidelines recommend that initiation of DMT should be considered in MS patients at the time of diagnosis[2,3]
- Despite availability of many DMTs for the treatment of RMS, there remains an unmet need for highly efficacious therapies that have a favorable safety profile and are easy to use

Objective

To evaluate the benefit-risk profile of ofatumumab in patients with early RMS in the Phase 3 ASCLEPIOS I/II trials

DMT, disease-modifying therapy; FDA, food and drug administration; MS, multiple sclerosis; 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. Montalban X et al. *Mult Scler*; 2018;24; 96–120; 3. Rae-Grant A et al. *Neurology*; 2018;90:778-800

Methods: Patient population and study outcomes

Subgroup analysis: ASCLEPIOS I and II trials

- The subgroup analysis included data from newly diagnosed (within 3 years before screening), treatment-naïve (no prior DMT use) patients who received following treatments as a first-line therapy for up to 30 months:
  - ofatumumab 20 mg s.c. (initial doses: Days 1, 7, and 14) every 4 weeks from Week 4 OR
  - teriflunomide 14 mg oral once daily
- This analysis in early MS patients comprised 32.7% (615/1882) of the total pooled ASCLEPIOS population

Study outcomes	
Efficacy	• Annualized relapse rate *(number of confirmed multiple sclerosis relapses in a year)* • 3-month confirmed disability worsening[#] • 6-month confirmed disability worsening[#] • Gadolinium-enhancing T1 lesions • New or enlarging T2 lesions • No evidence of disease activity
Safety	• Treatment-emergent adverse events • Serious adverse events

[#]A 3-month confirmed disability worsening was defined as an increase from baseline in EDSS sustained for at least 3 months. [#]Analogously, a 6-month confirmed disability worsening was defined as an increase from baseline in EDSS sustained for at least 6 months. DMT, disease-modifying therapy; MS, multiple sclerosis; s.c., subcutaneous

Patient demographics and baseline characteristics

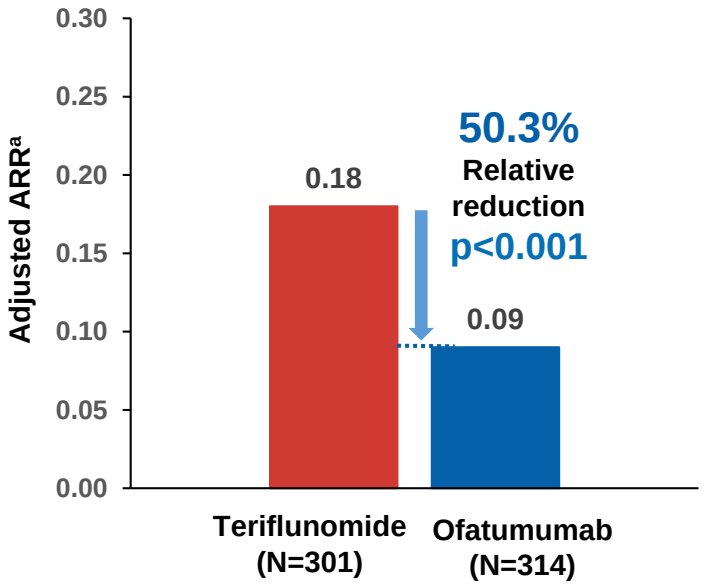
Characteristics	Teriflunomide (N=301)	Ofatumumab (N=314)	All patients (N=615)
Age, years	35.7±9.03	36.8±9.40	36.3±9.23
Sex, Female, n (%)	195 (64.8)	217 (69.1)	412 (67.0)
Weight, kg	76.4±19.70	74.2±18.91	75.3±19.32
Duration of MS since diagnosis, years median (min–max)	0.36 (0.1–2.9)	0.35 (0.1–2.9)	0.35 (0.1–2.9)
Number of relapses in the last 12 months	1.4±0.72	1.3±0.70	1.4±0.71
EDSS score	2.3±1.20	2.3±1.20	2.3±1.20
T2 lesion volume, cm^3	8.3±8.83	10.1±12.23	9.2±10.72
Patients free of Gd+ T1 lesions, n (%)	171 (56.8)	173 (55.1)	344 (55.9)
Number of Gd+ T1 lesions	1.4±2.79	1.8±4.35	1.6±3.66

Baseline characteristics of the newly diagnosed, treatment-naïve subgroup were typical of early MS patients and were generally balanced between treatment groups

Data are presented as mean±SD, unless stated otherwise; EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; min, minimum; max, maximum; MS, multiple sclerosis; SD, standard deviation

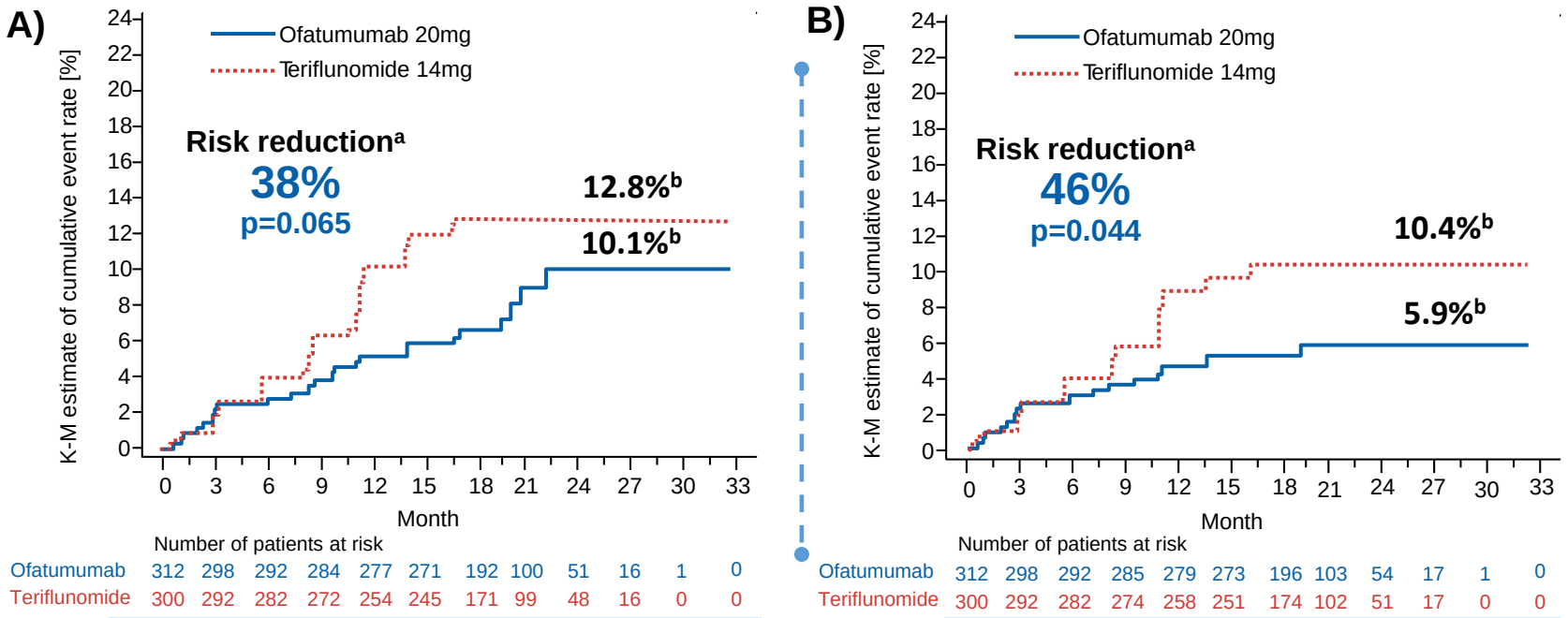
Effect of ofatumumab on clinical outcomes

ARR



ARR ratio (95% CI): 0.50 (0.33; 0.74)

Time to A) 3mCDW[#] and B) 6mCDW[#]



Hazard ratio (95% CI): 0.62 (0.37; 1.03)

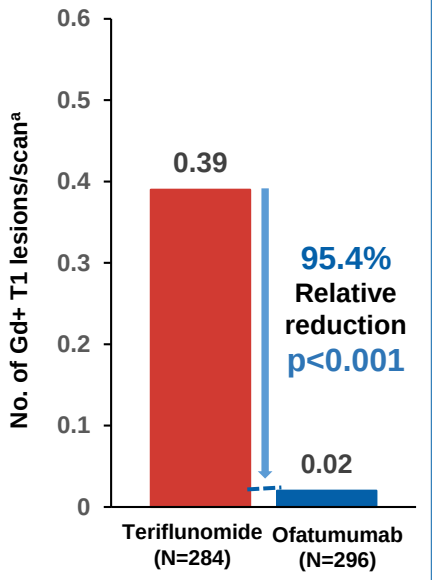
Hazard ratio (95% CI): 0.54 (0.30; 0.98)

- **Ofatumumab significantly reduced ARR by 50.3% versus teriflunomide**
- **Ofatumumab reduced 3mCDW risk by 38% and 6mCDW risk by 46% versus teriflunomide**

Full analysis set; [a]Cox regression model; [b]Proportion of patients with 3- or 6-month CDW; 3m/6mCDW, 3-month and 6-month confirmed disability worsening; [#]A 3-month confirmed disability worsening was defined as an increase from base EDSS sustained for at least 3 months. [#]Analogously, a 6-month confirmed disability worsening was defined as an increase from baseline in EDSS sustained for at least 6 months. ARR, annualized relapse rate; CI, confidence interval; EDSS, Expanded Disability Status Scale; K-M, Kaplan-meier

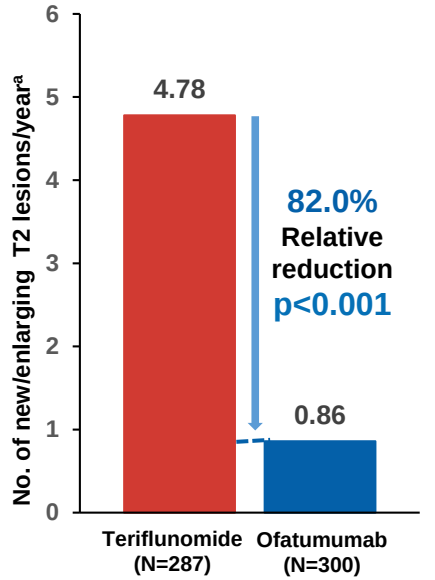
Effect of ofatumumab on MRI activity and NEDA-3

Gd+ lesions/scan



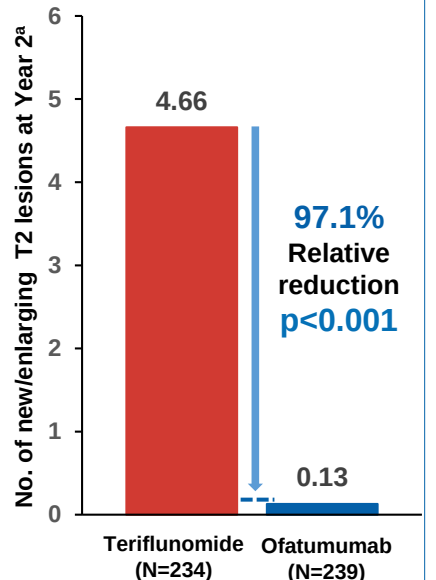
Rate ratio (95% CI): 0.05 (0.02; 0.10)

T2 lesions/year



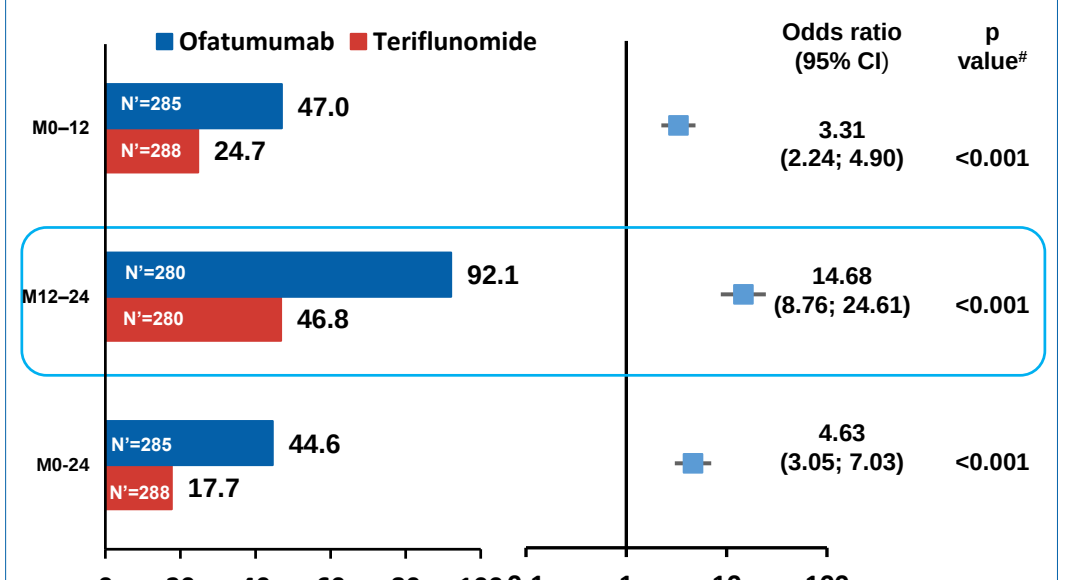
Rate ratio (95% CI): 0.18 (0.14; 0.24)

T2 lesions at Year 2



Rate ratio (95% CI): 0.03 (0.02; 0.05)

NEDA-3



- **Ofatumumab significantly reduced Gd+ T1 lesions per scan by 95.4%, T2 lesions per year by 82.0%, and T2 lesions at Year 2 by 97.1%, respectively compared to teriflunomide**
- **The odds of achieving NEDA-3 with ofatumumab versus teriflunomide was >3-fold higher at first year and >14-fold higher at the second year of treatment**

[a]Negative binomial regression model of the cumulative number of Gd+ lesions and number of new or enlarging T2 lesions; #Indicates statistical significance (two-sided) at 0.05 level; CI, confidence interval; Gd+, gadolinium-enhancing; M, M
MRI, magnetic resonance imaging; N, total number of patients included in the analysis N', total number of patients in the treatment group with response variable defined; NEDA-3, no evidence of disease activity

Safety profile

ASCLEPIOS I and II: Early MS subgroup and overall population

Safety events, n (%)	Newly diagnosed, treatment-naïve		Overall	
	Teriflunomide (N=301)	Ofatumumab (N=314)	Teriflunomide (N=936)	Ofatumumab (N=946)
AEs	**259 (86.0)**	**266 (84.7)**	**788 (84.2)**	**791 (83.6)**
Patients with AE leading to discontinuation	**7 (2.3)**	**19 (6.1)**	**49 (5.2)**	**54 (5.7)**
Most common AEs *(≥5% any group)*				
Nasopharyngitis	70 (23.3)	78 (24.8)	156 (16.7)	170 (18.0)
Injection-related reaction[#]	45 (15.0)	63 (20.1)	143 (15.3)	195 (20.6)
Alopecia	50 (16.6)	16 (5.1)	138 (14.7)	54 (5.7)
Upper respiratory tract infection	49 (16.3)	40 (12.7)	120 (12.8)	97 (10.3)
Headache	47 (15.6)	45 (14.3)	116 (12.4)	126 (13.3)
Fatigue	30 (10.0)	28 (8.9)	72 (7.7)	71 (7.5)
Infections	**170 (56.5)**	**176 (56.1)**	**493 (52.7)**	**488 (51.6)**
Risk of malignancy	**1 (0.3)[a]**	**2 (0.6)[a]**	**4 (0.4)[b]**	**5 (0.5)**
SAEs	**16 (5.3)**	**22 (7.0)**	**74 (7.9)**	**86 (9.1)**
Infections	**2 (0.7)**	**6 (1.9)**	**17 (1.8)**	**24 (2.5)**

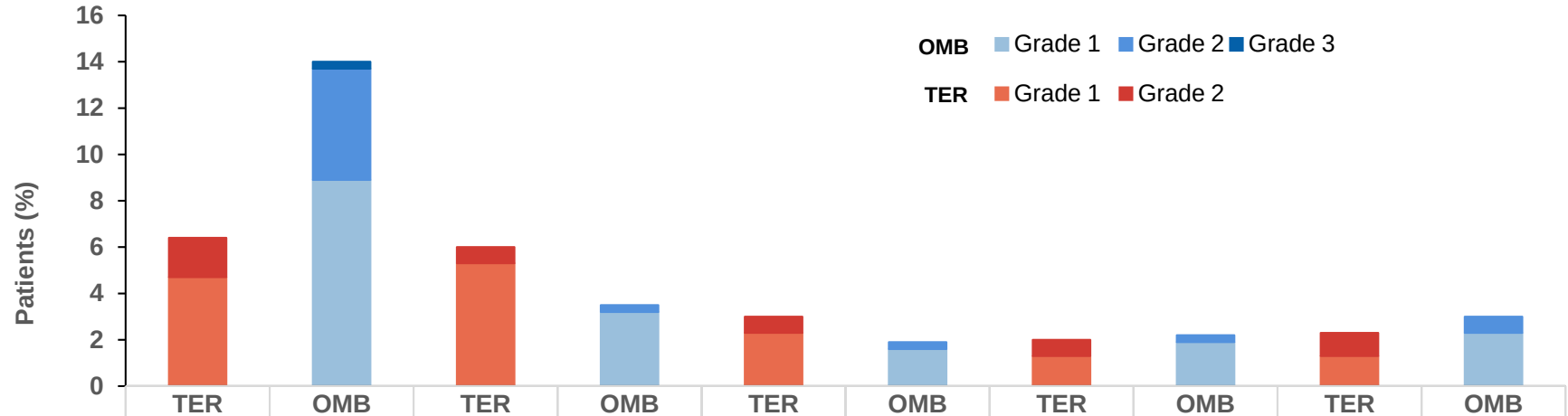
- **Incidence of AEs were balanced between the treatment groups; patients with SAEs were lower in treatment-naïve group than overall study population, but similar between teriflunomide and ofatumumab**
- **No opportunistic infections such as PML and hepatitis B reactivation were reported and no imbalance in infections or malignancies observed**
- **Compliance with ofatumumab in early, treatment-naïve patients was high (98.8%) and consistent with the total ASCLEPIOS population (98.3%)**

[#]These are injection-systemic reactions; [a]Basal cell carcinoma; [b]One case of basal cell carcinoma was not listed as a serious AE
AEs, adverse events; PML, progressive multifocal leukoencephalopathy; MS, multiple sclerosis; SAEs, serious adverse events;

Systemic injection reactions: 99.8% were mild-to-moderate

IRRs in the early cohort

Systemic injection reactions, by injection



Injection number		1		2		3		4		5	
		TER	OMB	TER	OMB	TER	OMB	TER	OMB	TER	OMB
Grade 3		0	0.3	0	0	0	0	0	0	0	0
Grade 2		1.7	4.8	0.7	0.3	0.7	0.3	0.7	0.3	1	0.7
Grade 1		4.7	8.9	5.3	3.2	2.3	1.6	1.3	1.9	1.3	2.3

- **Systemic injection reactions were only imbalanced between ofatumumab and teriflunomide (with placebo injections) at the first injection given at the study site**
- **After the 4th injection, >70% RMS patients self-injected at home**

IRRS, injection related reactions; OMB, ofatumumab; RMS, relapsing multiple sclerosis; TER, teriflunomide

Conclusions

- Ofatumumab is the first FDA-approved high efficacy injectable DMT that can be self-administered at home, as demonstrated in the Phase 3 ASCLEPIOS trials
- Ofatumumab showed superior efficacy versus teriflunomide in newly diagnosed, treatment-naïve patients producing low absolute relapse rates, very low MRI lesion activity and prolonged time to disability worsening, consistent with the overall ASCLEPIOS study population
- Ofatumumab significantly increased the chances of patients achieving NEDA-3, both in the first and second year of treatment, versus teriflunomide
- The safety profile of ofatumumab in newly-diagnosed, treatment-naïve subgroup was consistent with the overall ASCLEPIOS study population, with no unexpected safety signals

DMT, disease-modifying therapy; FDA, food and drug administration; MRI, magnetic resonance imaging

Thank you