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Improvement in Cognitive Processing Speed With Ofatumumab in Patients With Relapsing Multiple Sclerosis

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SUMMARY

1 **The effect of ofatumumab vs teriflunomide on SDMT performance was assessed in a pooled population of patients with RMS from the double-blind, double-dummy, randomized, phase 3 ASCLEPIOS I/II trials**

2 **Improvement in SDMT performance from baseline was significantly more pronounced with ofatumumab vs teriflunomide in the overall population and in the subgroup of patients recently diagnosed with MS. Significant benefits in favor of ofatumumab were also observed for the proportion of patients with sustained clinically meaningful cognitive improvement**

3 **Observed trends for greater benefits of OMB in those without cognitive impairment at baseline and in those recently diagnosed with MS provide further support for initiating a high-efficacy therapy early in the disease course to preserve cognitive function**

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INTRODUCTION

- Cognitive impairment (CI) presents in 40% to 70% of patients with multiple sclerosis (MS) and can start early in the disease course[1,2]
- CI has profoundly negative effects on patients' quality of life,[3] particularly employment[4]
- Several studies also suggest that CI, particularly cognitive processing speed (CPS), can predict disease progression in MS[5]
- The Symbol Digit Modalities Test (SDMT), primarily a measure of CPS, is considered the gold standard monitoring tool and outcome measure for clinical trials in MS and is an effective screening tool for CI in clinical settings[6-8]
  - Early baseline screening with the SDMT (or similarly validated test) is recommended when patients are clinically stable[6,7]
  - A subsequent score change of ≥4 points or a ≥10% change in SDMT score is considered clinically meaningful[7,9]
- In the phase 3 ASCLEPIOS I/II trials, ofatumumab (OMB) significantly reduced inflammatory disease activity and relapses and delayed disability worsening vs teriflunomide (TER) in patients with relapsing MS (RMS)[10]

OBJECTIVE

- To examine the effect of OMB vs TER on CPS, assessed using SDMT performance in patients with RMS

METHODS

STUDY DESIGN

- This analysis pooled data from the ASCLEPIOS I and II trials (NCT02792218 and NCT02792231, respectively)[10]
- ASCLEPIOS I/II were phase 3, randomized, double-blind, double-dummy, active-controlled trials with identical study designs in patients with RMS
- Patients were randomized to receive subcutaneous injections of OMB 20 mg every 4 weeks (following initial loading doses of three 20-mg subcutaneous doses per week in the first 14 days) or oral TER 14 mg once daily for up to 30 months
- The SDMT was administered according to standardized instructions by the investigator or another qualified health care professional experienced with the administration of the SDMT at baseline and Months 6, 12, 18, and 24
- Patient populations and assessments are described in **Table 1**

Table 1. Patient Populations and Assessments

Analyses based on pooled data from the ASCLEPIOS I/II double-blind, double-dummy, randomized, phase 3 trials in patients with RMS			
Patient population	**Description**	**Analyses**	
		Assessments	**Assessed by**
Overall population	Includes all patients from ASCLEPIOS I/II who were randomized to OMB (N=946) or TER (N=936)	Change in SDMT score from baseline to Month 24 (**pre-specified**)	Mixed model for repeated measures
		Proportion of patients with ≥4-point sustained improvement on SDMT* (post hoc analysis)	Categorical analysis (worsened, stable, or improved)
Recently diagnosed	Subgroup of patients who were diagnosed in the 36 months before screening and subsequently randomized to OMB (n=443) or TER (n=454)	Time to first 6mCCI (≥4-point improvement on SDMT) (post hoc analysis)	KM analysis
Patients with and without CI at baseline	With CI (SDMT ≤43)	Time to first 6mCCI (≥4-point improvement on SDMT) (post hoc analysis)	KM analysis
	Without CI (SDMT >43)		

6mCCI, 6-month confirmed cognitive improvement; CI, cognitive impairment; KM, Kaplan-Meier; OMB, ofatumumab; RMS, relapsing multiple sclerosis; SDMT, Symbol Digit Modalities Test; TER, teriflunomide
*The SDMT will be administered according to standardized instructions by the investigator or another qualified health care professional experienced with the administration of the SDMT

RESULTS

DEMOGRAPHICS AND BASELINE CHARACTERISTICS

- Of the 1882 patients in the overall ASCLEPIOS population, 897 were recently diagnosed with RMS (within the last 3 years) (**Table 2**)

Table 2. Patient Demographics and Baseline Characteristics

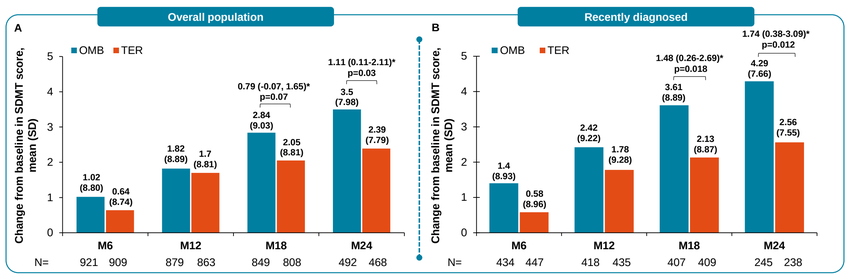
	ASCLEPIOS I/II			
	Overall population		Recently diagnosed	
Characteristic	**OMB (N=946)**	**TER (N=936)**	**OMB (n=443)**	**TER (n=454)**
Age, years, mean (SD)	38.4 (9.0)	38.0 (9.2)	36.3 (9.4)	35.6 (9.0)
Female, n (%)	637 (67.3)	636 (67.9)	309 (69.8)	292 (64.3)
Type of MS, n (%)				
RRMS	890 (94.1)	884 (94.4)	439 (99.1)	444 (97.8)
SPMS	56 (5.9)	52 (5.6)	4 (0.9)	10 (2.2)
Time since diagnosis, years, mean (SD)	5.68 (6.21)	5.56 (6.10)	0.85 (0.7)	0.92 (0.8)
Relapses in previous 12 months, mean (SD)	1.2 (0.7)	1.3 (0.7)	1.3 (0.7)	1.4 (0.7)
Relapses in previous 12-24 months, mean (SD)	0.8 (1.0)	0.9 (1.1)	0.7 (0.9)	0.7 (1.0)
EDSS score at baseline, mean (SD)	2.9 (1.4)	2.9 (1.4)	2.4 (1.2)	2.4 (1.2)
SDMT score at baseline, mean (SD)	48.4 (14.2)	49.0 (14.0)	52.1 (13.6)	52.5 (13.2)
Number of Gd+ T1 lesions, mean (SD)	1.7 (4.5)	1.3 (3.4)	1.7 (4.4)	1.3 (2.8)
Total volume of T2 lesions, cm³, mean (SD)	13.7 (13.8)	12.6 (13.8)	10.0 (11.6)	8.5 (8.6)
NfL concentration, pg/mL, mean (SD)	13.98 (15.9)	12.54 (11.9)	14.5 (17.1)	12.7 (13.0)
Normalized brain volume, cm³, mean (SD)	1439.8 (78.9)	1444.0 (77.8)	1470.6 (70.3)	1470.5 (67.8)

EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; MS, multiple sclerosis; NfL, neurofilament light chain; OFA, ofatumumab; RRMS, relapsing-remitting multiple sclerosis; SD, standard deviation; SDMT, Symbol Digit Modalities Test; SPMS, secondary progressive multiple sclerosis; TER, teriflunomide

CHANGE FROM BASELINE IN SDMT SCORE

- OMB was associated with significantly more pronounced improvement in SDMT score vs TER from baseline to Month 24 in both the overall and recently diagnosed patient populations (**Figure 1**)
- The difference in SDMT scores vs TER was more pronounced in the recently diagnosed subgroup (**Figure 1**)

Figure 1. Change From Baseline in SDMT Score

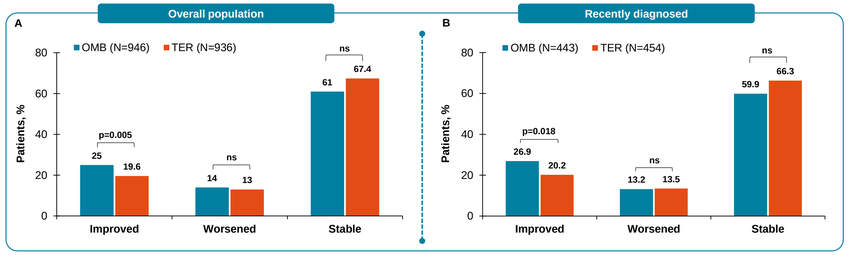


CI, confidence interval; M, Month; OMB, ofatumumab; SD, standard deviation; SDMT, Symbol Digit Modalities Test; TER, teriflunomide
*Adjusted mean difference (95% CI)

SUSTAINED CLINICALLY MEANINGFUL CHANGE ON SDMT

- Significantly more patients experienced sustained clinically meaningful cognitive improvement (≥4 points) with OFA vs TER until the end of the study (**Figure 2**)

Figure 2. Proportion of Patients With Sustained Clinically Meaningful Change on SDMT

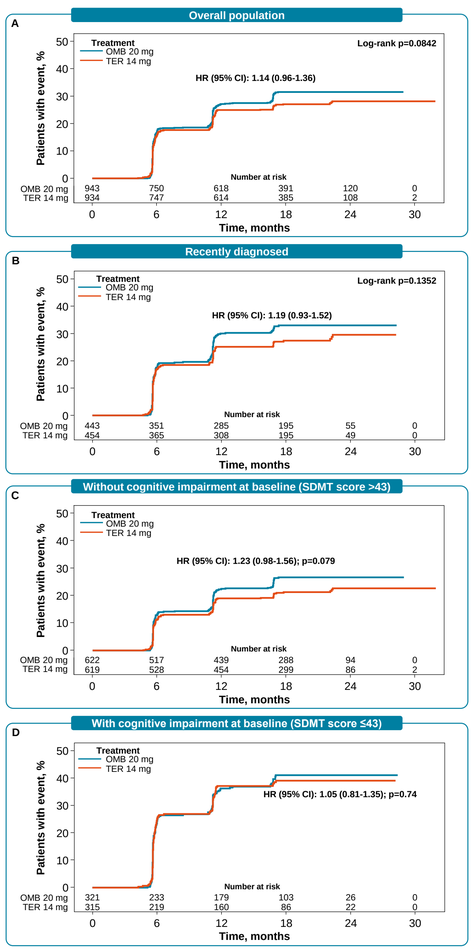


6mCCD, 6-month confirmed cognitive decline; 6mCCI, 6-month confirmed cognitive improvement; EOS, end of study; ns, nonsignificant; OMB, ofatumumab; TER, teriflunomide
Cognitive status during the study (classified as improved, stable, or worsened): Patients were classified as improved if 6mCCI was sustained until EOS was met (regardless of whether 6mCCD status was met at an earlier visit window); or classified as stable if 6mCCD was not met and 6mCCI was sustained until EOS was not met; or classified as worsened if 6mCCD was met and 6mCCI was sustained until EOS was not met. p-value was obtained from a chi-square test

TIME TO FIRST 6-MONTH CONFIRMED CLINICALLY MEANINGFUL COGNITIVE IMPROVEMENT ON SDMT

- In the overall population and recently diagnosed patients, those receiving OMB had a numerically higher chance of a clinically meaningful improvement (≥4 points) in CPS, which became apparent from Month 12 onward (**Figure 3A-B**)
- In patients without CI at baseline, a strong trend favoring an increase in the chance of 6-month confirmed cognitive improvement with OMB vs TER was observed (**Figure 3C**)
- In patients with CI at baseline, no difference between treatment groups was observed (**Figure 3D**)

Figure 3. Time to First 6-Month Confirmed Clinically Meaningful Cognitive Improvement on SDMT



CI, confidence interval; HR, hazard ratio; OMB ofatumumab; SDMT, Symbol Digit Modalities Test; TER, teriflunomide
An SDMT score change of ≥4 points represents a clinically meaningful improvement

REFERENCES: 1. Benedict RHB et al. *Lancet Neurol*. 2020;19(10):860-871. **2.** Al-Falaki TA et al. *Egypt J Neurol Psychiatr Neurosurg*. 2021;57:127. **3.** Meca-Lallana V et al. *Neurol Sci*. 2021;42(12):5183-5193. **4.** Morrow SA et al. *Clin Neuropsychol*. 2010;24(7):1131-1145. **5.** Zipoli V et al. *Mult Scler*. 2010;16(1):62-67. **6.** Kalb R et al. *Mult Scler*. 2018;24(13):1665-1680. **7.** Benedict RHB et al; Multiple Sclerosis Outcome Assessments Consortium. *Mult Scler*. 2017;23(5):721-733. **8.** Langdon DW et al. *Mult Scler*. 2012;18(6):891-898. **9.** Strober I et al; Multiple Sclerosis Outcome Assessments Consortium (MSOAC). *Mult Scler*. 2019;25(13):1781-1790. **10.** Hauser SL et al; ASCLEPIOS I and ASCLEPIOS II Trial Groups. *N Engl J Med*. 2020;383(6):546-557.

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