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

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Gary Cutter is employed by the University of Alabama at Birmingham and President of Pythagoras, Inc. a private consulting company located in Birmingham AL.

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Background

- Cognitive impairment (CI) presents in 40–70% patients with MS and can start early in the disease course[1,2]
- CI has a profound negative effect on patients' quality of life[3], and on employment in particular[4]
- Several studies also suggest 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, outcome measure for clinical trials in MS, and as an effective screen 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 and II trials, ofatumumab significantly reduced inflammatory disease activity, relapses and delayed disability worsening versus teriflunomide in patients with RMS[10]

Objective

To assess the effect of ofatumumab versus teriflunomide on SDMT performance in RMS patients

*CI, cognitive impairment; CPS, cognitive processing speed; HCP, health care practitioners; plwMS, people living with multiple sclerosis; RMS, relapsing multiple sclerosis; SDMT, Symbol Digit Modalities Test

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Patient populations and analyses

Analyses based on data from the ASCLEPIOS I and II double-blind, double-dummy, randomized Phase 3 trials in RMS patients					
	Patient populations			Analyses	
Group	Description	N		Assessments	Assessed by
		OMB	TER		
Overall population	Includes all patients from ASCLEPIOS I and II who were randomized to OMB or TER	946	936	Change in SDMT score baseline to Month 24 **(Pre-specified)** Proportion of patients with ≥4-point sustained improvement on SDMT[a] (Post-hoc analysis) Time-to-first 6mCCI (≥4-point improvement on SDMT) (Post-hoc analysis)	Mixed model for repeated measures by categorical analysis- (worsened, stable or improved) KM analysis
Recently diagnosed	Subgroup of patients who were diagnosed in the 36 months before screening and subsequently randomized to OMB or TER	443	454		
Patients with and without cognitive impairment at baseline	With cognitive impairment (SDMT ≤43)	296	281	Time-to-first 6mCCI (≥4-point improvement on SDMT) (Post-hoc analysis)	KM analysis
	Without cognitive impairment (SDMT >43)	634	636		

6mCCI, 6 month confirmed cognitive improvement; DMT, disease-modifying therapy; KM, kaplein meier; OMB, ofatumumab; SDMT, Symbol Digit Modalities Test; TER, teriflunomide

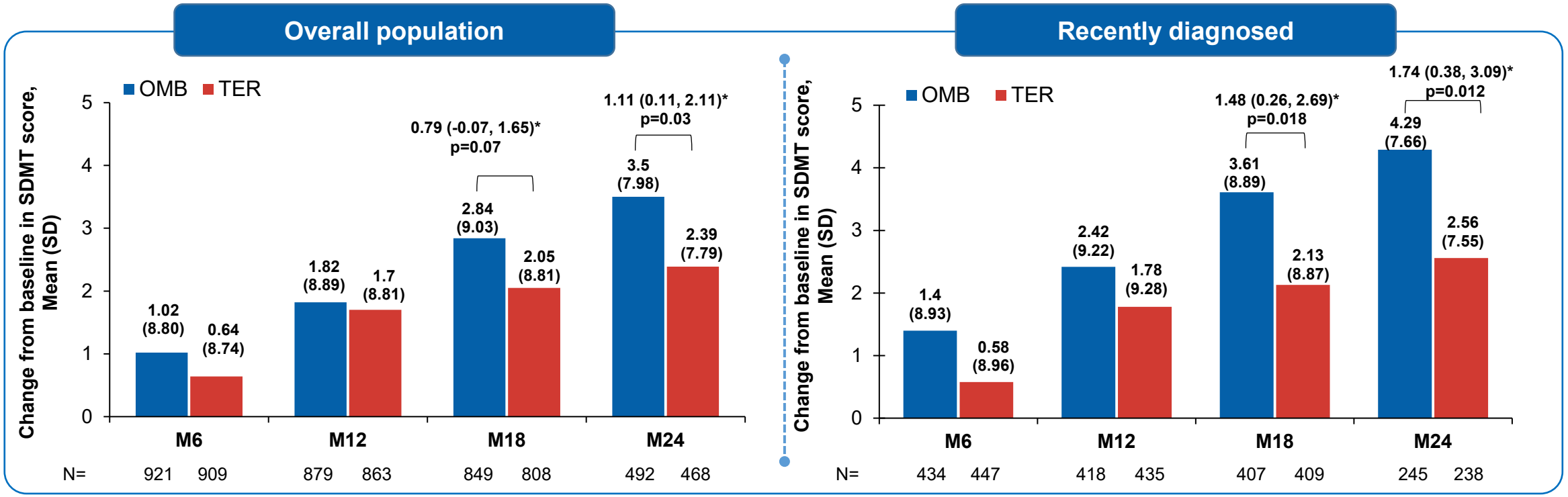
[a]The SDMT will be administered according to standardized instructions by the Investigator or another qualified health care professional experienced with the administration of the SDMT

Demographics and baseline characteristics

Characteristics	ASCLEPIOS I and II			
	Overall population		Recently diagnosed	
	Ofatumumab (N=946)	Teriflunomide (N=936)	Ofatumumab (N=443)	Teriflunomide (N=454)
Age, mean (SD), years	38.4 (9.0)	38.0 (9.2)	36.3 (9.4)	35.6 (9.0)
Women, 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, mean (SD), years	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)[c]	2.93 (1.35)	2.90 (1.37)	2.40 (1.2)	2.43 (1.2)
SDMT at baseline, mean (SD)	48.4 (14.2)	49.0 (14.03)	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, mean (SD), cm^3	13.72 (13.80)	12.55 (13.81)	10.01 (11.6)	8.46 (8.63)
NfL concentration, mean (SD), pg/mL	13.98 (15.86)	12.54 (11.94)	14.5 (17.1)	12.7 (13.0)
Normalized brain volume, mean (SD), cm^3	1439.8 (78.9)	1444.0 (77.8)	1470.6 (70.3)	1470.5 (67.8)

EDSS, Expanded Disability Status Scale; GD+, gadolinium enhancing; NfL, neurofilament light chain; RRMS, repalsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis

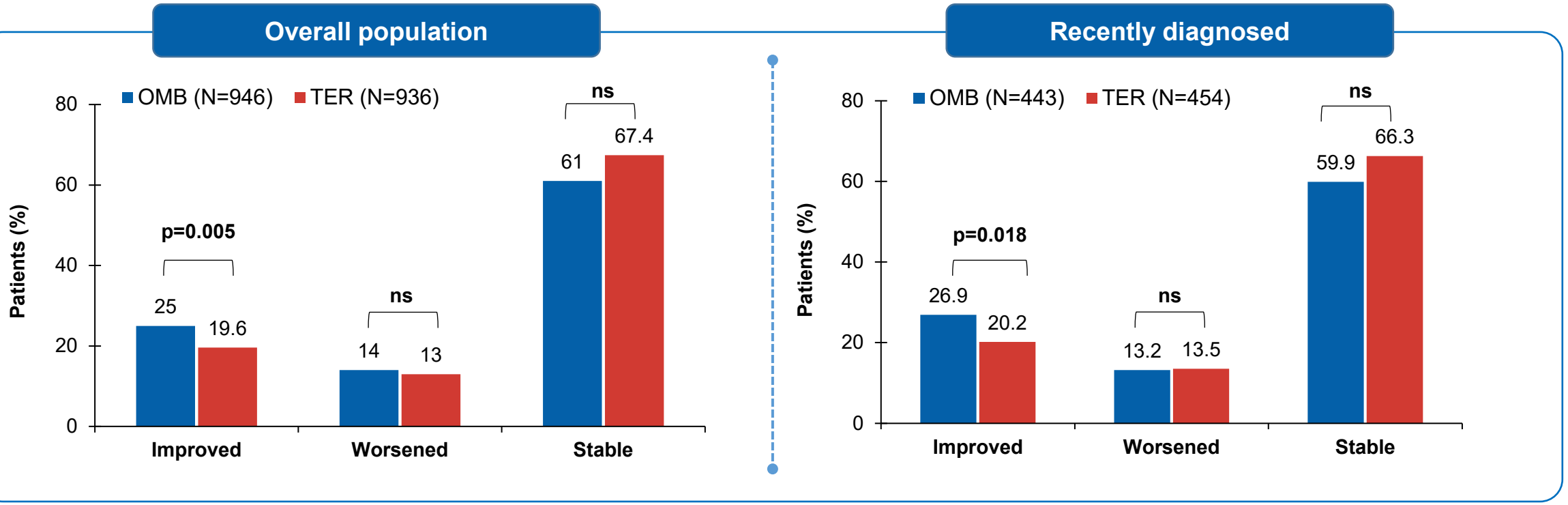
Change from baseline in SDMT score



- **Ofatumumab was associated with significantly more pronounced improvement on SDMT score versus teriflunomide from baseline to Month 24 in both the overall and recently diagnosed patient populations**
- **The difference in SDMT scores versus teriflunomide was more pronounced in the recently diagnosed subgroup**

*Adjusted mean difference (95% CI)
CI, confidence interval; M, month.;OMB, ofatumumab; RMS, relapsing multiple sclerosis; SDMT, Symbol Digit Modalities Test; TER, teriflunomide;

Proportion of patients with sustained clinically meaningful change (≥4 points) on SDMT

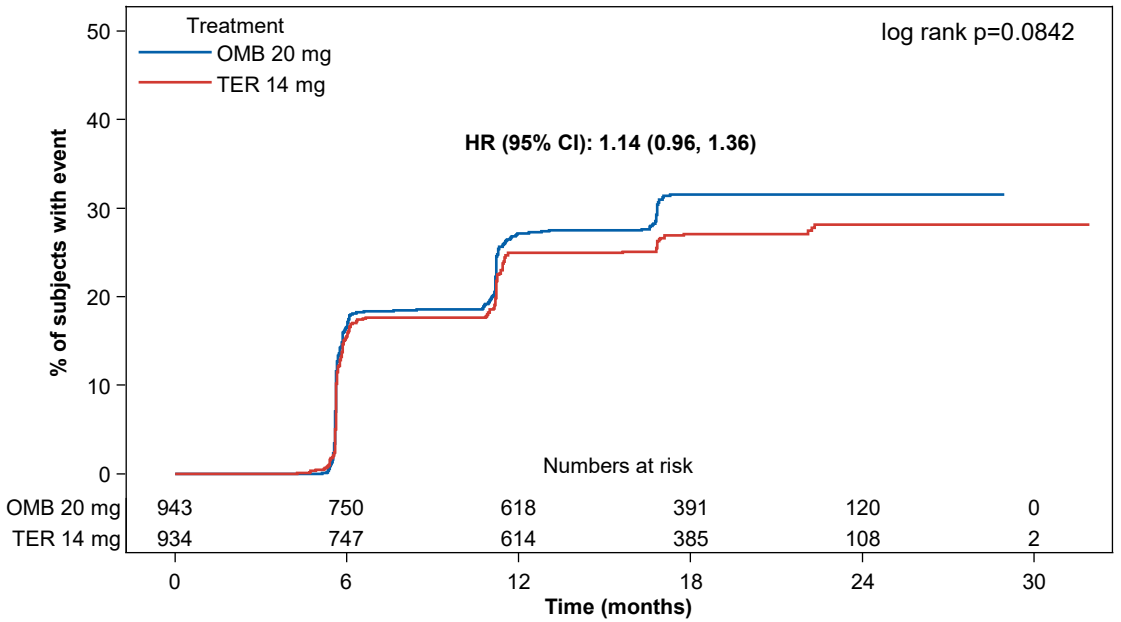


- **Significantly more patients experienced sustained* clinically meaningful cognitive improvement with ofatumumab versus teriflunomide until end of the study**

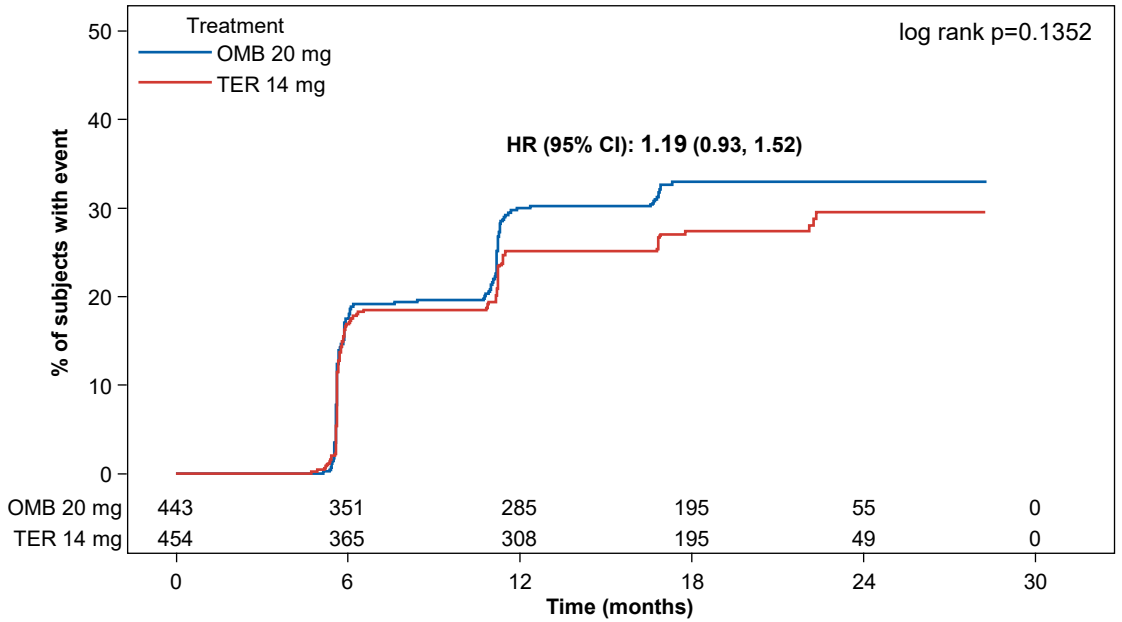
Cognitive status during the study (classified as improved, stable, or worsened): Patients will be classified as improved if 6mCCI sustained until EOS was met (regardless whether 6mCCD status was met at an earlier visit-window); or classified as stable if 6mCCD was not met & 6mCCI sustained until EOS was not met; or classified as worsened if 6mCCD was met & 6mCCI sustained until EOS was not met.
P-value is obtained from chi-square test.*≥ 4points change considered clinically meaningful
ns, non-significant; OMB, ofatumumab; TER, teriflunomide

Time-to-first 6-month confirmed clinically meaningful cognitive improvement (≥4 points) on SDMT

Overall population



Recently diagnosed

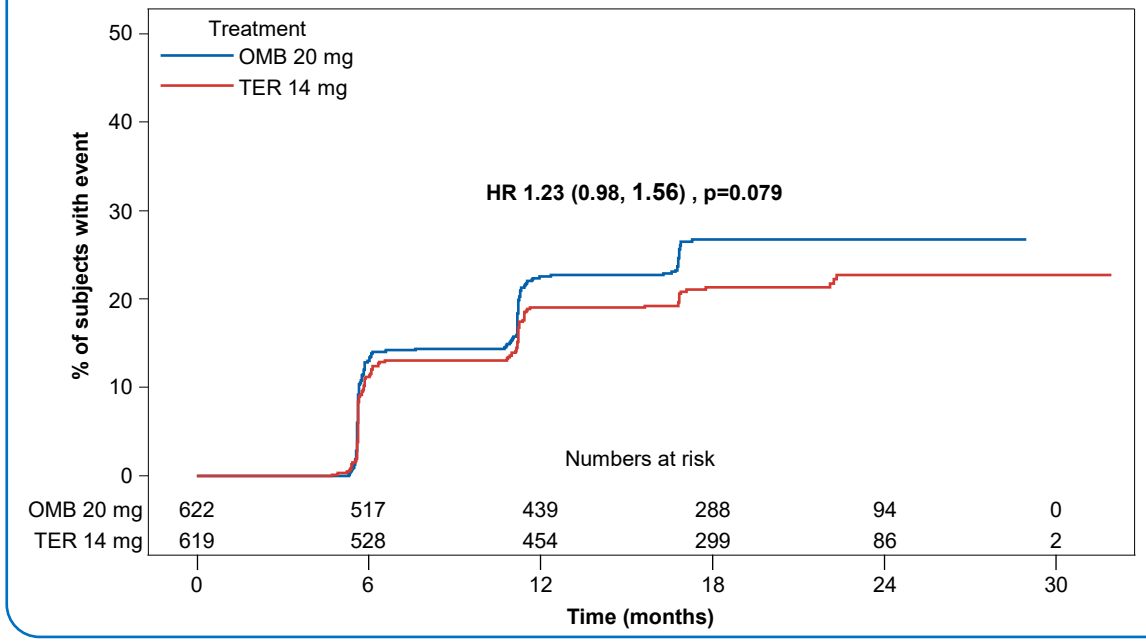


- **Patients receiving ofatumumab had a numerically higher chance of a clinically meaningful improvement in cognitive processing speed, which became apparent from Month 12 onwards (p=ns)**

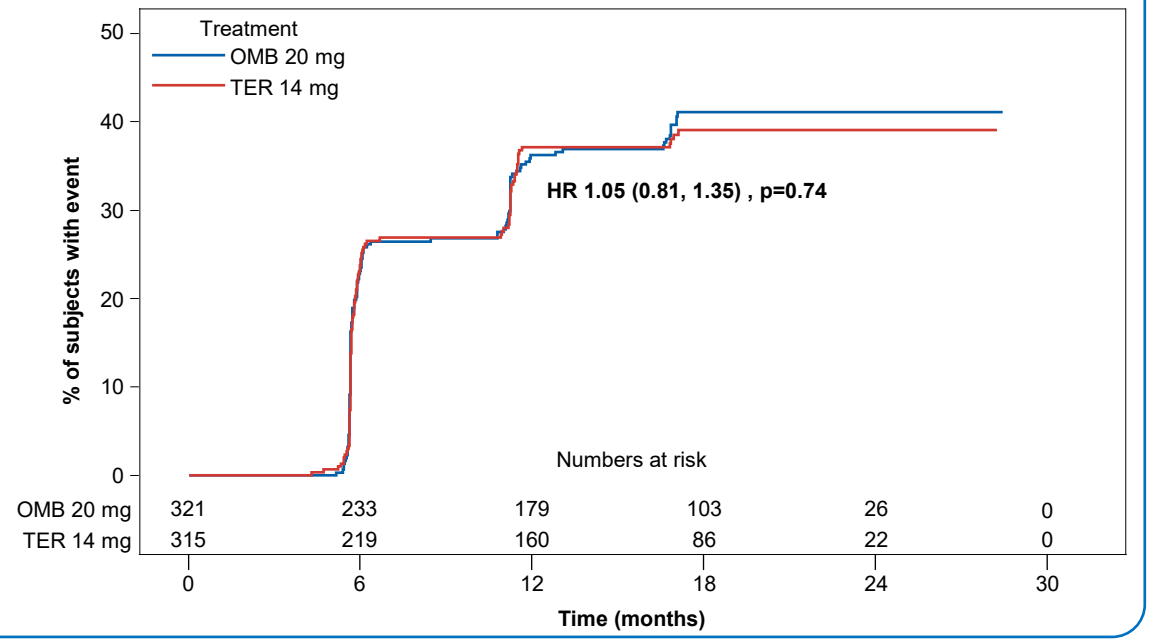
6mCCI, 6 month confirmed cognitive improvement; CI, confidence interval; HR, hazard ratio; ns, non-significant; OMB ofatumumab; SDMT, TER, teriflunomide

Time-to-first 6-month confirmed clinically meaningful cognitive improvement (≥4 points) on SDMT

Without cognitive impairment at baseline (SDMT >43)



With cognitive impairment at baseline (SDMT ≤43)



- **In patients without cognitive impairment at baseline, a strong trend favoring an increase in the chance of 6mCCI with ofatumumab versus teriflunomide was observed**

- **In patients with cognitive impairment at baseline, no difference between treatment groups was observed**

6mCCI, 6-month confirmed clinically meaningful cognitive improvement; BL, baseline; CI, cognitive impairment; HR, hazard ratio; SDMT, Symbol Digit Modalities Test

Conclusions

- In ASCLEPIOS I and II, the improvement in SDMT performance from baseline was significantly more pronounced with ofatumumab, versus 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 a sustained clinically meaningful cognitive improvement
- Observed trends for greater benefits of ofatumumab in those without cognitive impairment at baseline and in those recently diagnosed with MS provides further support for initiating a high-efficacy therapy (HET) early in the disease course to preserve cognitive function

Data on the ability of CPS, as measured by SDMT, to predict physical disability progression is being discussed at the congress by
Professor Gavin Giovannoni in Oral Presentation OS3005

CI, cognitive impairment; CPS, cognitive processing speed; DMTs, disease modifying therapies; RMS, relapsing multiple sclerosis