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Original article

Effect of Ozanimod on Symbol Digit Modalities Test Performance in Relapsing MS

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ABSTRACT

Background: Cognitive dysfunction, including slowed cognitive processing speed (CPS), is one of the most disabling symptoms of multiple sclerosis (MS). The Symbol Digit Modalities Test (SDMT) is a preferred measure of CPS for MS trials and routine screening. Based on encouraging SDMT results in the phase 3 SUNBEAM trial, these post hoc, exploratory analyses were conducted to further compare effects of the sphingosine 1-phosphate receptor modulator ozanimod versus intramuscular interferon β-1a on CPS in participants with relapsing multiple sclerosis (RMS).

Methods: In the phase 3, double-blind, double-dummy, SUNBEAM study, adults (aged 18–55 years) with RMS (N=1,346) were randomized to once-daily oral ozanimod 0.92 or 0.46 mg, or weekly intramuscular interferon β-1a 30 μg. The study continued until the last participant was treated for 12 months. CPS was measured as part of a secondary endpoint using the SDMT. Exploratory, post hoc analyses evaluated SDMT change and percentages of participants with clinically meaningful (≥4-point) SDMT improvement or worsening at months 6 and 12, and relationship between SDMT and brain volume on magnetic resonance imaging.

Results: Ozanimod improved SDMT scores compared with interferon β-1a at months 6 and 12. At month 12, least squares mean difference in SDMT z-scores for ozanimod 0.92 mg versus interferon β-1a was 0.102 (95% CI, 0.031–0.174, nominal $p = 0.0051$; standardized mean difference = 0.1376). A greater percentage of ozanimod 0.92 mg–treated participants had clinically meaningful improvements in SDMT scores versus interferon β-1a at month 6 (30.0% versus 22.2%) and month 12 (35.6% versus 27.9%). Of those with SDMT improvement at month 6, 66.4% of those treated with ozanimod 0.92 mg and 55.9% of those treated with interferon β-1a had sustained

Statistician: Hongjuan Liu, Bristol Myers Squibb, Princeton, New Jersey. **Nonstandard abbreviations:** CPS = cognitive processing speed; PwMS = persons with multiple sclerosis; SMD = standardized mean differences.

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improvement at month 12. Brain volume loss was similar for those with SDMT improvement versus worsening at month 12.

Conclusions: In these exploratory analyses, ozanimod had modestly beneficial effects on CPS in RMS participants. The effects of ozanimod on SDMT are being further evaluated in an ongoing 3-year clinical trial. SUNBEAM is registered on clinicaltrials.gov (NCT02294058) and the European Clinical Trials Database (EudraCT 2014-002320-27).

1. Introduction

Cognitive dysfunction, one of the most disabling symptoms of multiple sclerosis (MS), can include diminished cognitive processing speed (CPS), memory, learning, and executive ability (Benedict et al., 2017). Slowed CPS, generally the first cognitive deficit to emerge in persons with MS (PwMS) (Van Schependom et al., 2015), may underlie other cognitive dysfunctions (Costa et al., 2017). It is associated with decreased quality of life, interference with everyday tasks, depression, and unemployment (Barker-Collo, 2006; Clemens and Langdon, 2018; Eizaguirre et al., 2018). The Symbol Digit Modalities Test (SDMT) is a preferred measure of CPS for MS trials and routine screening (Drake et al., 2010; Strober et al., 2019; Kalb et al., 2018).

Ozanimod, an oral sphingosine 1-phosphate receptor 1 and 5 modulator, causes lymphocyte retention in lymphoid tissues (Scott et al., 2016). In phase 3 trials (RADIANCE, SUNBEAM), ozanimod resulted in lower annualized relapse rates (ARR), fewer gadolinium-enhancing (GdE) and new/enlarging T2 lesions on brain magnetic resonance imaging (MRI), and less loss of whole brain, cortical grey matter, and thalamic volume than intramuscular interferon β-1a 30 μg weekly in participants with relapsing MS (RMS) (Cohen et al., 2019; Comi et al., 2019). Ozanimod 0.92 mg is approved by regulatory agencies in multiple countries for the treatment of RMS.

SUNBEAM included SDMT in the Multiple Sclerosis Functional Composite (MSFC), a secondary endpoint. Difference versus interferon β-1a in mean change in MSFC score (average of component z-scores) from baseline to month 12 was 0.040 (95% CI −0.009–0.090, nominal $p = 0.1091$) for ozanimod 0.92 mg. Difference for mean change in SDMT z-score was 0.111 (0.039–0.182, nominal $p = 0.0024$) (Comi et al., 2019). Based on the encouraging SDMT results, we undertook additional post hoc, exploratory analyses to further evaluate ozanimod's effects on CPS in PwMS compared with interferon β-1a.

2. Methods

2.1. Study design and procedures

SUNBEAM was a randomized, double-blind, active-controlled, parallel-group, phase 3 study conducted in 20 countries from December 2014 through December 2016 (Comi et al., 2019). Participants with RMS were randomized (1:1:1) to once-daily oral ozanimod 0.92 mg (equivalent to ozanimod HCl 1 mg) or 0.46 mg (equivalent to ozanimod HCl 0.5 mg), or weekly intramuscular interferon β-1a 30 μg. To maintain blinding, participants in the ozanimod groups also received weekly placebo intramuscular injections, and participants in the interferon β-1a group received once-daily oral placebo tablets. Randomization was carried out according to a blocked algorithm stratified by country and baseline Expanded Disability Status Scale (EDSS) score (≤3.5 or >3.5).

Ozanimod was dose-escalated as follows: ozanimod 0.23 mg (equivalent to ozanimod HCl 0.25 mg) on days 1–4, 0.46 mg on days 5–7, and the assigned dose starting on day 8. Treatment continued until the last participant randomized was treated for 12 months. The MSFC, which included the written SDMT, was a secondary outcome performed at screening, baseline, month 6, month 12, end of treatment, and at the time of suspected relapse.

Brain MRI for assessment of brain volume and lesions was performed at screening, month 6, and month 12 using 1.5 or 3.0 Tesla scanners. Scans included 3 scout images (fast 3-plane localizer scan, true mid-line sagittal scan, and fast axial scan) followed by 7 sequences (PD-weighted, T2-weighted, MT-off, MT-on, T1-weighted, FLAIR, and GdE T1-weighted scans). Images were acquired using a standardized process and analyzed by a blinded central imaging facility (NeuroRx, Montréal, Quebec, Canada). Percentage change from baseline to month 12 in whole brain volume was a secondary endpoint; changes in cortical grey matter (CGM) and thalamic volumes were prespecified exploratory endpoints. Whole brain volume and CGM were measured using SienaX, which provides an automated analysis of brain volume normalized for head size. Thalamic volume was measured using ThalamicVolume software. Loss of whole brain volume, CGM volume, and thalamic volume was measured using paired Jacobian integration via JacobianAtrophy software (Nakamura et al., 2014).

2.2. Study population

SUNBEAM participants were aged 18 to 55 years inclusive with a diagnosis of MS by 2010 McDonald criteria (Polman et al., 2011), a clinical course and history of brain MRI lesions consistent with RMS, and baseline EDSS score of ≤5.0. Participants had to have ≥1 documented relapse within 12 months before screening, or ≥1 relapse in the 24 months before screening plus ≥1 GdE lesion on brain MRI in the 12 months before randomization but no relapses from 30 days before screening until randomization. Key exclusion criteria included primary progressive MS, illness duration >15 years with an EDSS score ≤2.0, presence of >20 GdE lesions at baseline, current signs of major depression or history of suicide attempts, and history of alcohol or drug abuse in the year before randomization. Persons with any condition (eg, neurological, ophthalmological) that would make implementation of study procedures or interpretation of the study results difficult, in the opinion of the treating investigator, were also excluded. Complete inclusion/exclusion criteria are available in the primary SUNBEAM publication appendix (Comi et al., 2019). The institutional review board/ethics committee at each site approved the study protocol, which conformed to Good Clinical Practice guidelines and Declaration of Helsinki principles. All participants provided informed consent before enrollment.

2.3. Assessment of CPS with SDMT

The same person, either the blinded evaluator or another designated team member trained in conducting MSFC assessments, administered the SDMT throughout the study. The SDMT pairs symbols with numerical digits, and participants must match the appropriate symbol to the paired digit using a key (Benedict et al., 2017). Scoring is based on the correct number of responses given within 90 seconds; higher scores indicate faster processing (Benedict et al., 2017). Normative scores in a (non-MS) general community population <40 years of age ranged from 50–58 for written responses and 59–66 for oral responses (Sheridan et al., 2006). Scores tend to decrease with age and are influenced by education and gender (Sheridan et al., 2006; Strober et al., 2020). Updated normative values for the oral SDMT range from 55–68 in men aged 18–54 years, and 60–70 in women in the same age range (Strober et al., 2020). A score change of ≥4 points is considered clinically meaningful (Benedict et al., 2017).

2.4. Analyses of cognitive outcomes

Post hoc analyses of cognitive outcomes compared ozanimod 0.92 mg with interferon β-1a 30 μg in the intent-to-treat (ITT) population (all randomized participants who received ≥1 dose of assigned study drug). All reported *p*-values are nominal and not controlled for type I error.

Least squares (LS) mean change in SDMT score and z-score from baseline to months 6 and 12 and between-treatment differences in LS means were estimated using a mixed model for repeated measures (MMRM), a method that implicitly imputes missing data (Siddiqui et al., 2009). The ITT study population served as the reference population for the z-scores. The model included change from baseline in SDMT score or z-score as the dependent variable, stratification factors (region [Eastern Europe versus rest of world] and baseline EDSS category [≤3.5 versus >3.5]), baseline SDMT score or z-score, age at baseline, brain volume at baseline, and the interaction between treatment and time point as fixed effects, and subject as a random effect. An unstructured covariance was used to model within-subject errors. This analysis differs from the previously reported analysis in which change in SDMT z-scores were reported descriptively, and comparisons of ozanimod versus interferon β-1a were made using an analysis of covariance (ANCOVA) model with adjustments for region, baseline EDSS score, and baseline SDMT z-score; data were imputed by the last observation carried forward (LOCF) method (Comi et al., 2019). Compared with the ANCOVA and LOCF approach, MMRM provides a less biased approach to minimizing type I error and handling missing data (Siddiqui et al., 2009). Standardized mean differences (SMD, also called Cohen's *d*) between ozanimod and interferon β-1a were calculated as a measure of effect size (Faraone, 2008). Per established interpretations, SMD 0.2 was considered small; 0.5, medium; and 0.8, large (Faraone, 2008).

SDMT response was analyzed categorically as percentage of participants at months 6 and 12 with clinically meaningful improvement (≥4-point increase), stability (<4-point [±] change), or worsening (≥4-point decrease) in SDMT scores relative to baseline. Rate ratios with 95% confidence intervals (CIs), and nominal *p*-values for comparison of ozanimod with interferon β-1a were calculated. Cohen's *d* was calculated based on the corresponding odds ratios and interpreted using the same cutoffs for small, medium, and large effect size as for the SMDs. Rate ratios of SDMT improvement relative to baseline with ozanimod 0.92 mg versus interferon β-1a were analyzed using a generalized estimating equation model adjusted by baseline SDMT score, age at baseline, brain volume at baseline, stratification factors, and the interaction between treatment and time point as fixed effects, assuming unstructured within-subject covariate structure. The generalized estimating equation model implicitly imputes missing data.

A shift table was produced for number and percentage of participants in each response category (improved/stable/worsened) at month 12 based on month 6 category. The improvement rate (≥4-point increase) maintained at months 6 and 12 was analyzed using a generalized estimating equation model adjusted by baseline SDMT score, age at baseline, and brain volume at baseline, stratification factors, and treatment. Rate ratios with 95% CIs, and nominal *p*-values for comparison of ozanimod with interferon β-1a were calculated for each shift, and Cohen's *d* effect sizes were calculated based on corresponding odds ratios.

Demographics and baseline disease characteristics were assessed among those with SDMT improvement (≥4-point increase) and worsening (≥4-point decrease) at month 12 in the interferon β-1a and ozanimod 0.92 mg groups. For each treatment group, the nominal *p* value and SMD were calculated for those with SDMT improvement versus worsening at month 12.

Percentage change from baseline (screening MRI) to month 6 and month 12 in whole brain volume, thalamic volume, and CGM volume were calculated using an ANCOVA model adjusted for stratification factors (region and baseline EDSS category), age at baseline, and baseline brain volume value of interest. Two analyses were performed, one to test ozanimod 0.92 mg versus interferon β-1a in those within SDMT improvement (≥4-point increase) and those within SDMT worsening (≥4-point decrease) at month 12, and the other to compare SDMT improvement versus SDMT worsening within each treatment group. SMD was calculated for each analysis, and effect size was interpreted as described above.

Table 1
LS mean changes from baseline in SDMT scores and z-scores for ozanimod and interferon β-1a based on mixed model for repeated measures regression modeling.[a]

	Interferon β-1a 30 μg	Ozanimod 0.92 mg
Month 6, N	446	444
LS mean (SE) change from baseline in SDMT score	−0.5 (0.48)	0.5 (0.47)
LS mean difference (95% CI) vs interferon β-1a	–	1.0 (0.08–1.93)
Nominal *p* value	–	0.0336
SMD vs interferon β-1a		0.10
LS mean (SE) change from baseline in SDMT z-score	−0.034 (0.036)	0.041 (0.035)
LS mean difference (95% CI) vs interferon β-1a	–	0.074 (0.006–0.143)
Nominal *p* value	–	0.0336
SMD vs interferon β-1a	–	0.10
Month 12, N	426	427
LS mean (SE) change from baseline in SDMT score	−0.1 (0.49)	1.3 (0.48)
LS mean difference (95% CI) vs interferon β-1a	–	1.4 (0.42–2.34)
Nominal *p* value	–	0.0051
SMD vs interferon β-1a	–	0.14
LS mean (SE) change from baseline in SDMT z-score	−0.009 (0.036)	0.093 (0.036)
LS mean difference (95% CI) vs interferon β-1a	–	0.102 (0.031–0.174)
Nominal *p* value	–	0.0051
SMD vs interferon β-1a	–	0.14

CI = confidence interval; EDSS = Expanded Disability Status Scale; LS = least squares; SDMT = Symbol Digit Modalities Test; SE = standard error; SMD = standardized mean difference (Cohen's *d*), in which 0.2 = small effect, 0.5 = medium effect, 0.8 = large effect (Faraone, 2008).

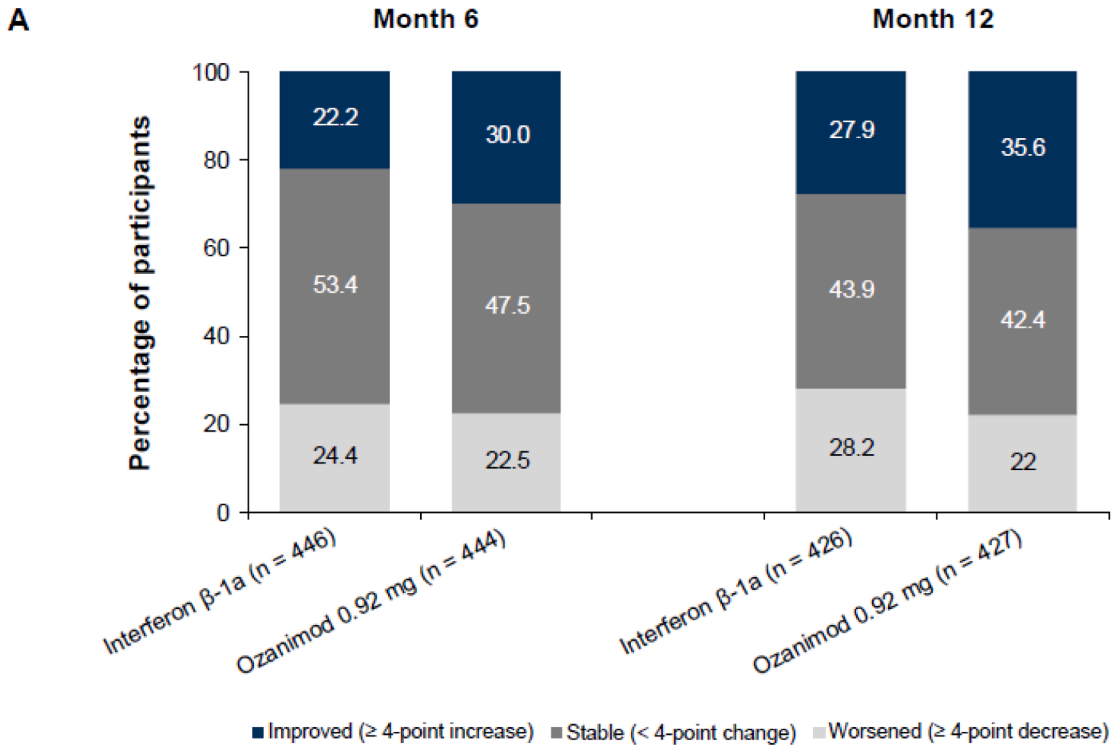
[a] Adjusted by baseline SDMT score (or z-score), region (Eastern Europe vs rest of world), baseline EDSS category (≤3.5 vs >3.5), age at baseline, brain volume at baseline, and interaction between treatment and time point as fixed effects, assuming unstructured within-subject covariate structure.

3. Results

3.1. Subject disposition and demographics

In SUNBEAM, 447 participants received ≥1 dose of ozanimod 0.92 mg and 448 received ≥1 dose of interferon β-1a; 418 (93.5%) and 412 (92.0%) of those participants, respectively, completed the study. Mean (standard deviation [SD]) duration of treatment exposure in these 2 groups, respectively, was 13.6 (2.7) and 13.5 (2.9) months.

As previously reported, baseline demographics and disease characteristics in the overall population were similar across treatment groups (Comi et al., 2019). Mean age was 34.8 years in the ozanimod 0.92 mg group and 35.9 years in the interferon β-1a group, 63.3% and 67.0% were female, 99.8% in each group were white, and 92.8% and 93.5% were from Eastern Europe. Mean time since first MS symptoms was 6.9 years and mean EDSS was 2.6 in both groups, and 28.6% of the ozanimod 0.92 mg group and 33.7% of the interferon β-1a group had previously used an MS disease-modifying therapy (DMT) (Comi et al., 2019). Baseline mean (SD) SDMT score was 47.7 (13.7) in the ozanimod 0.92 mg group and 47.1 (13.5) in the interferon β-1a group; SDMT z-scores were 0.045 (1.02) and 0.002 (1.00), respectively. At baseline, the ozanimod 0.92 mg group and interferon β-1a group had similar whole brain volume (mean 1456 and 1443 cm^3, respectively), thalamic volume



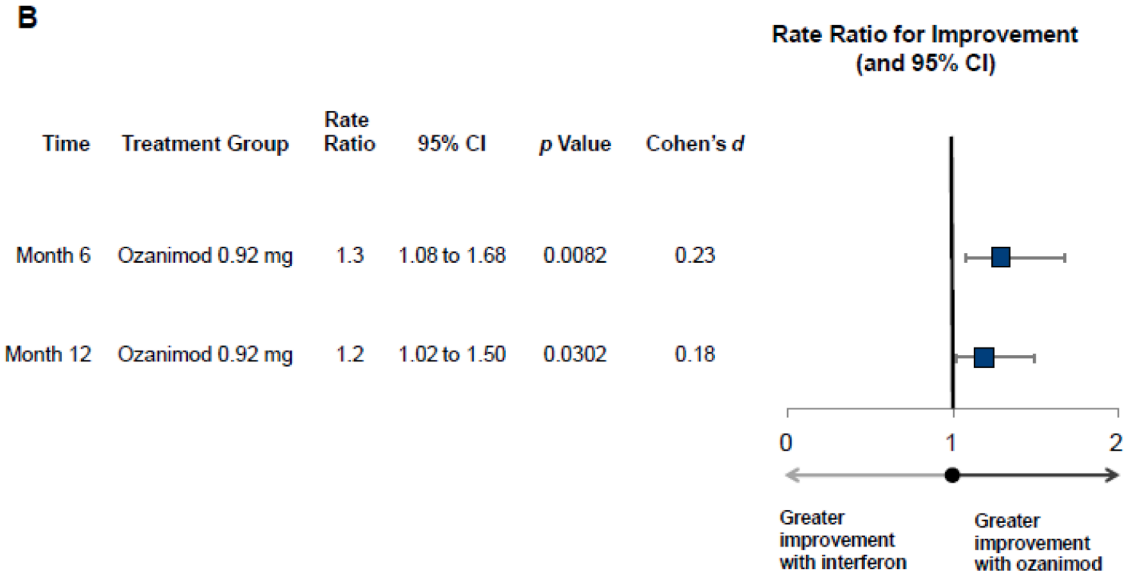


Fig. 1. (A) Categorical analysis of clinically meaningful change in SDMT. (B) SDMT clinically meaningful improvement relative to baseline with ozanimod 0.92 mg vs interferon β-1a (A) Percentage of participants treated with interferon β-1a or ozanimod who experienced clinically meaningful changes in SDMT scores at months 6 and 12. (B) Rate ratios (ozanimod vs interferon β-1a) for clinically meaningful SDMT improvement (≥ 4-point increase) relative to baseline at months 6 and 12 were analyzed based on a generalized estimating equation model adjusted by baseline SDMT score, stratification factors, age at baseline, brain volume at baseline, and treatment. Cohen's *d* effect size was calculated based on odds ratios; interpretation: 0.2 = small effect, 0.5 = medium effect, 0.8 = large effect (Faraone, 2008). CI = confidence interval; SDMT = Symbol Digit Modalities Test.

(mean 15.4 and 15.1 cm^3), and CGM volume (mean 527 and 521 cm^3).

3.2. LS mean change in SDMT score and z-scores

Ozanimod nominally significantly improved SDMT scores compared with interferon β-1a at months 6 and 12 (Table 1). At month 12, LS mean change from baseline in z-scores was 0.093 in the ozanimod 0.92 mg group and -0.009 in the interferon β-1a group (LS mean difference: 0.102 [95% CI 0.031–0.174], nominal $p = 0.0051$). SMDs in LS mean SDMT scores and z-scores between ozanimod and interferon β-1a were all 0.10–0.14 at months 6 and 12 (trivial effect size) (Table 1).

3.3. SDMT response

A greater proportion of participants in the ozanimod 0.92 mg group achieved clinically meaningful improvement (≥4-point increase) in SDMT score relative to interferon β-1a at months 6 and 12 (Fig. 1A). The related rate ratios favored ozanimod over interferon β-1a at both time

Table 2
Shift table: SDMT response at months 12 relative to baseline based on month 6 response categories.

Month 6 Response	Month 12 Response	Interferon β-1a 30 μg n/N (%)	Ozanimod 0.92 mg n/N (%) RR (95% CI),[a] and Cohen's d[b] vs Interferon β-1a
Improved	Improved	52/93 (55.9)	85/128 (66.4) 1.1 (0.95–1.27), 0.21
	Stable	33/93 (35.5)	39/128 (30.5) 0.9 (0.63–1.33), −0.07
	Worsened	8/93 (8.6)	4/128 (3.1) NE, -0.58
Stable	Improved	56/228 (24.6)	55/204 (27.0) 1.1 (0.78–1.47), 0.06
	Stable	123/228 (53.9)	115/204 (56.4) 1.0 (0.88–1.25), 0.06
	Worsened	49/228 (21.5)	34/204 (16.7) 0.8 (0.53–1.15), −0.18
Worsened	Improved	11/105 (10.5)	12/95 (12.6) 1.2 (0.58–2.65), 0.13
	Stable	31/105 (29.5)	27/95 (28.4) 0.9 (0.59–1.43), −0.08
	Worsened	63/105 (60.0)	56/95 (58.9) 1.0 (0.81–1.24), 0.01

NE = not evaluated due to small n; SDMT = Symbol Digit Modalities Test; n/N = number of participants with corresponding response category at months 6 and 12/number of participants in response category at month 6.
SDMT response is defined as follows: Improvement: ≥4-point increase; worsened: ≥4-point decrease; stable: <4-point change in either direction. A 4-point change is considered clinically meaningful.
[a] All nominal $p > 0.05$.
[b] Interpretation: 0.2 = small effect, 0.5 = medium effect, 0.8 = large effect (Faraone, 2008).

points, being nominally significant but of small effect size (Fig. 1B).

3.4. Maintenance of early SDMT response

In the subgroup of participants with clinically meaningful improvement in SDMT at month 6 relative to baseline, 66.4% of those receiving ozanimod 0.92 mg versus 55.9% of those receiving interferon β-1a showed sustained improvement at month 12 (Table 2). Differences between ozanimod 0.92 mg and interferon β-1a did not achieve nominal significance, and the effect size for sustained improvement was small (Cohen's $d = 0.21$).

Among all participants with SDMT assessments at months 6 and 12, the overall rate of sustained ≥4-point improvement at both time points was 19.9% with ozanimod and 12.2% with interferon β-1a. Rate ratios for sustained improvement at months 6 and 12 favored ozanimod over interferon β-1a (1.6 [95% CI 1.18–2.18], nominal $p = 0.0028$, Cohen's $d = 0.31$ [small effect]).

Some participants with stable or worsened SDMT at month 6 showed clinically meaningful improvement relative to baseline at month 12 (Table 2). These shifts did not achieve nominal significance, and effect sizes were trivial.

3.5. Baseline characteristics by SDMT response category at month 12

Most baseline and disease characteristics were not significantly different in those who had clinically meaningful SDMT improvement versus worsening at month 12 with either ozanimod 0.92 mg or interferon β-1a (Table 3). One exception was that in both treatment groups, baseline SDMT scores were nominally significantly lower in those who subsequently showed ≥4-point SDMT improvement than those who had ≥4-point worsening; the SMD (0.53) was medium in both groups. In the interferon β-1a group, a larger percentage of men experienced SDMT improvement (49/82 [59.8%]) versus worsening (33/82 [40.2%]), whereas a larger percentage of women experienced SDMT worsening (87/157 [55.4%]) versus improvement (70/157 [44.5%]) at month 12; the effect of gender was small (SMD 0.29) but nominally significant ($p = 0.0260$) (Table 3). A similar trend was seen in the ozanimod 0.92 mg group for men (61/93 [65.6%] improved, 32/93 [34.4%] worsened), but women were also more likely to be improved (91/153 [59.5%]) than worsened (62/153 [40.5%]); gender differences did not achieve nominal significance and had a trivial effect size (SMD 0.13). To explore this finding further, we analyzed baseline SDMT by gender and found that mean SDMT scores and z-scores were nominally significantly ($p < 0.0005$) lower at baseline in men (score: 45.3 [SD 14.15]; z-score: −0.14 [SD 1.05]) than women (score: 48.1 [SD 13.07]; z-score: 0.07 [SD 0.97]). When baseline SDMT was added to the MMRM model, gender was not significant ($p = 0.66$).

3.6. Change in brain volume based on SDMT response category at month 12

Ozanimod 0.92 mg was associated with a slower rate of whole brain volume loss over 12 months than interferon β-1a among participants who showed clinically meaningful SDMT improvement at month 12 (difference 0.27% [95% CI 0.09–0.44]; nominal $p = 0.0030$; SMD = 0.26 [small effect]) (Fig. 2A). Brain volume differences at month 12 in participants with ≥4-point worsened SDMT were similar between treatment groups ($p = 0.1368$).

Ozanimod was associated with a slower rate of thalamic volume loss than interferon β-1a in those with clinically meaningful SDMT improvement (difference 0.68% [95% CI 0.25–1.10]; nominal $p = 0.0019$; SMD = 0.28 [small effect]) and those with clinically meaningful SDMT worsening (difference 1.02 [95% CI 0.40–1.64]; nominal $p = 0.0013$; SMD = 0.30 [small effect]) (Fig. 2B). Ozanimod also was associated with a slower rate of CGM loss than interferon β-1a in those with SDMT improvement (difference 1.06% [95% CI 0.83–1.30; nominal $p < 0.0001$; SMD = 0.78 [medium effect]) and those with SDMT worsening (difference 0.80% [95% CI 0.51–1.09]; nominal $p < 0.0001$; SMD = 0.50 [medium effect]) at month 12 (Fig. 2C).

Irrespective of treatment assignment, rates of whole brain volume loss (Fig. 2D), thalamic volume loss (Fig. 2E), and CGM loss (Fig. 2F) were similar among those with ≥4-point SDMT improvement versus ≥4-point SDMT worsening.

4. Discussion

The current secondary analyses further support the original SDMT analyses from SUNBEAM, demonstrating that ozanimod 0.92 mg was associated with greater improvements in CPS at months 6 and 12 compared with interferon β-1a. These differences were nominally significant, although effect size was trivial. At month 6 and month 12, a greater proportion of ozanimod 0.92 mg–treated participants exhibited clinically meaningful (≥4-point) improvements on the SDMT compared with those who received interferon β-1a, and the participants treated with ozanimod 0.92 mg more commonly had clinically meaningful improvement at both those time points.

The SDMT was administered as a component of the MSFC, which is reported in the primary publication of SUNBEAM (Comi et al., 2019). In contrast to the SDMT results, mean change from baseline to month 12 in overall composite MSFC score (average of component z-scores) in the ozanimod 0.92 mg group was not significantly different from interferon β-1a (difference: 0.040 [95% CI −0.009–0.090], nominal $p = 0.1091$).

The MSFC, as originally designed, included the Paced Auditory Serial Addition Test (PASAT) as an assessment of CPS (Drake et al., 2010); however, the SDMT is increasingly preferred because it is a more sensitive and more reliable measure of CPS in MS and its administration is easier for examiners and participants (Drake et al., 2010; Strober et al., 2019; Langdon et al., 2012). A recent pooled analysis of 14 clinical trials by the Multiple Sclerosis Outcome Assessments Consortium found that

Table 3
Baseline demographics and disease characteristics in those with clinically meaningful SDMT improvement (≥4-point increase) or worsening (≥4-point decrease) at month 12.

Data are mean (SD) unless otherwise noted	Interferon β-1a 30 μg			Ozanimod 0.92 mg		
	SDMT Improved (n = 119)	SDMT Worsened (n = 120)	SMD[a]	SDMT Improved (n = 152)	SDMT Worsened (n = 94)	SMD[a]
Age, y	35.8 (9.0)	35.7 (9.2)	−0.01	34.2 (8.9)	35.2 (8.5)	0.11
Gender, n (%)			0.29[b,*]			0.13[b]
Female	70 (58.8)	87 (72.5)		91 (59.9)	62 (66.0)	
Male	49 (41.2)	33 (27.5)		61 (40.1)	32 (34.0)	
Time since MS symptom onset, y	6.4 (5.1)	6.9 (6.2)	0.08	6.7 (5.7)	6.7 (6.4)	0.01
Time since MS diagnosis, y	3.1 (3.7)	3.8 (4.9)	0.16	3.5 (3.9)	3.4 (3.9)	−0.03
Type of MS, n (%)			0.06[b]			−0.01[b]
RRMS	116 (97.5)	118 (98.3)		149 (98.0)	92 (97.9)	
PRMS	2 (1.7)	1 (0.8)		3 (2.0)	2 (2.1)	
SPMS	1 (0.8)	1 (0.8)		0	0	
EDSS score	2.5 (1.0)	2.5 (1.2)	0.04	2.5 (1.2)	2.7 (1.2)	0.21
MSFC score	−0.08 (0.58)	0.09 (0.85)	0.23	0.04 (0.62)	0.13 (0.61)	0.13
SDMT score	44.7 (13.6)	52.1 (14.5)	0.53[†]	45.6 (12.0)	52.5 (14.9)	0.53[‡]
SDMT z-score	−0.18 (1.01)	0.37 (1.08)	0.53[†]	−0.12 (0.89)	0.40 (1.10)	0.53[‡]
MSQOL score	70.8 (15.1)[c]	71.4 (16.5)	0.04	70.8 (17.0)	67.2 (17.1)[d]	−0.21
No. of relapses in 12 mo prior to baseline	1.2 (0.52)	1.3 (0.56)	0.07	1.2 (0.50)	1.3 (0.63)	0.17
Prior DMT, n (%)[e]	38 (31.9)	37 (30.8)	−0.02	50 (32.9)	24 (25.5)	−0.16
No. of GdE lesions	1.8 (3.5)	2.0 (4.0)	0.05	1.8 (3.3)	1.6 (2.8)	−0.08
No. of T2 lesions	52.3 (37.1)	59.1 (39.1)	0.18	52.5 (37.0)	58.4 (40.6)	0.15
T2 lesion volume, cm^3	12.3 (13.8)	14.3 (14.7)	0.14	11.2 (12.9)	12.7 (17.5)	0.10
WBV, cm^3	1439.6 (78.3)	1447.4 (79.7)	0.10	1463.3 (73.7)	1451.4 (75.7)	−0.16
CGM volume, cm^3	519.2 (44.9)[f]	519.9 (49.6)	0.01	532.2 (45.1)	521.9 (44.0)	−0.23
TV, cm^3	15.1 (1.8)	15.1 (2.0)	−0.01	15.6 (1.9)	15.3 (2.0)	−0.15

CGM = cortical grey matter; EDSS = Expanded Disability Status Scale; DMT = disease-modifying therapy; GdE = gadolinium enhancing; MS = multiple sclerosis; MSFC = Multiple Sclerosis Functional Composite; MSQOL = Multiple Sclerosis Quality of Life; PRMS = progressive-relapsing multiple sclerosis; RRMS = relapsing-remitting multiple sclerosis; SD = standard deviation; SDMT = Symbol Digit Modalities Test; SMD, standardized mean difference; SPMS = secondary progressive multiple sclerosis; TV = thalamic volume; WBV = whole brain volume.

[*] Nominal $p < 0.05$ for comparison of SDMT improved vs SDMT worsened

[†] Nominal $p < 0.0001$ for comparison of SDMT improved vs SDMT worsened

[‡] Nominal $p < 0.001$ for comparison of SDMT improved vs SDMT worsened.

[a] SMD was calculated by using the adjusted mean difference of worsened minus improved. Interpretation: 0.2 = small effect, 0.5 = medium effect, 0.8 = large effect (Faraone, 2008).

[b] For categorical variables, the SMD and chi-square test nominal p value were based on the proportion of the majority category to a combination of all minority categories

[c] n = 117

[d] n = 93

[e] Prior DMTs used by any SUNBEAM participants included interferon β-1a, pegylated interferon β-1a, interferon β-1b, glatiramer acetate, daclizumab, dimethyl fumarate, teriflunomide, and mitoxantrone

[f] n = 118.

SDMT does not have floor or ceiling effects, and that a 4-point change is clinically meaningful (Goldman et al., 2019). There are no published data on clinically meaningful change on the PASAT.

Participants whose SDMT performance improved during treatment had lower baseline SDMT scores, and therefore may have had a greater opportunity to show a ≥4-point improvement than those with higher baseline SDMT scores. In both treatment groups, men more commonly experienced clinically meaningful SDMT improvement than worsening. Women more commonly had clinically meaningful SDMT improvement versus worsening if treated with ozanimod 0.92 mg whereas they more commonly worsened if treated with interferon β-1a. SDMT scores were lower at baseline among men. Furthermore, normative scores on the oral SDMT in healthy volunteers are significantly ($p < 0.001$) lower for men than women (Strober et al., 2020). The previously published primary analysis of SUNBEAM did not show a significant variation in ozanimod efficacy by gender, based on ARR, new/enlarging T2 lesion count, or GdE lesion count (Comi et al., 2019).

There are no approved treatments available for slowed CPS in PwMS. Current research includes cognitive rehabilitation (DeLuca et al., 2020) and explorations of whether MS DMTs preserve or improve CPS (Weinstock-Guttman et al., 2012; Benedict et al., 2018; Kappos et al., 2016; Penner et al., 2012). To date, the only other DMT with published, peer-reviewed results of cognitive analyses using the SDMT in a phase 3 trial is daclizumab (Benedict et al., 2018), which was withdrawn from the global market in 2018. Some DMTs (fingolimod, natalizumab, interferon β-1b) showed benefit on the PASAT in published, peer-reviewed phase 3 trials (Weinstock-Guttman et al., 2012; Kappos et al., 2016; Penner et al., 2012), although a second phase 3 trial of natalizumab failed to find benefit versus placebo (Weinstock-Guttman et al., 2012). A recent meta-analysis of 41 studies of the effects of DMTs on CPS (SDMT or PASAT) reported a small to moderate benefit overall, with no advantage identified for any DMT over another (Landmeyer et al., 2020). A separate systematic review of 87 studies concluded that good-quality evidence was still lacking and insufficient to recommend use of DMTs or other pharmacologic therapies to improve cognitive function in PwMS (Chen et al., 2020).

Relative to interferon β-1a, ozanimod was associated with reduced loss of thalamic and CGM volume over 12 months in those with either clinically meaningful SDMT improvement or worsening at month 12. Ozanimod was also associated with reduced whole brain volume loss in those with SDMT improvement, but not SDMT worsening. Whole brain, CGM, and thalamic volume loss were similar (nominal $p > 0.05$, trivial effect sizes) for those with SDMT improvement and those with SDMT worsening at month 12 in either treatment group, which contrasts with previous reports that indicated that SDMT scores correlate with neocortical and all deep grey matter volumes, particularly thalamic

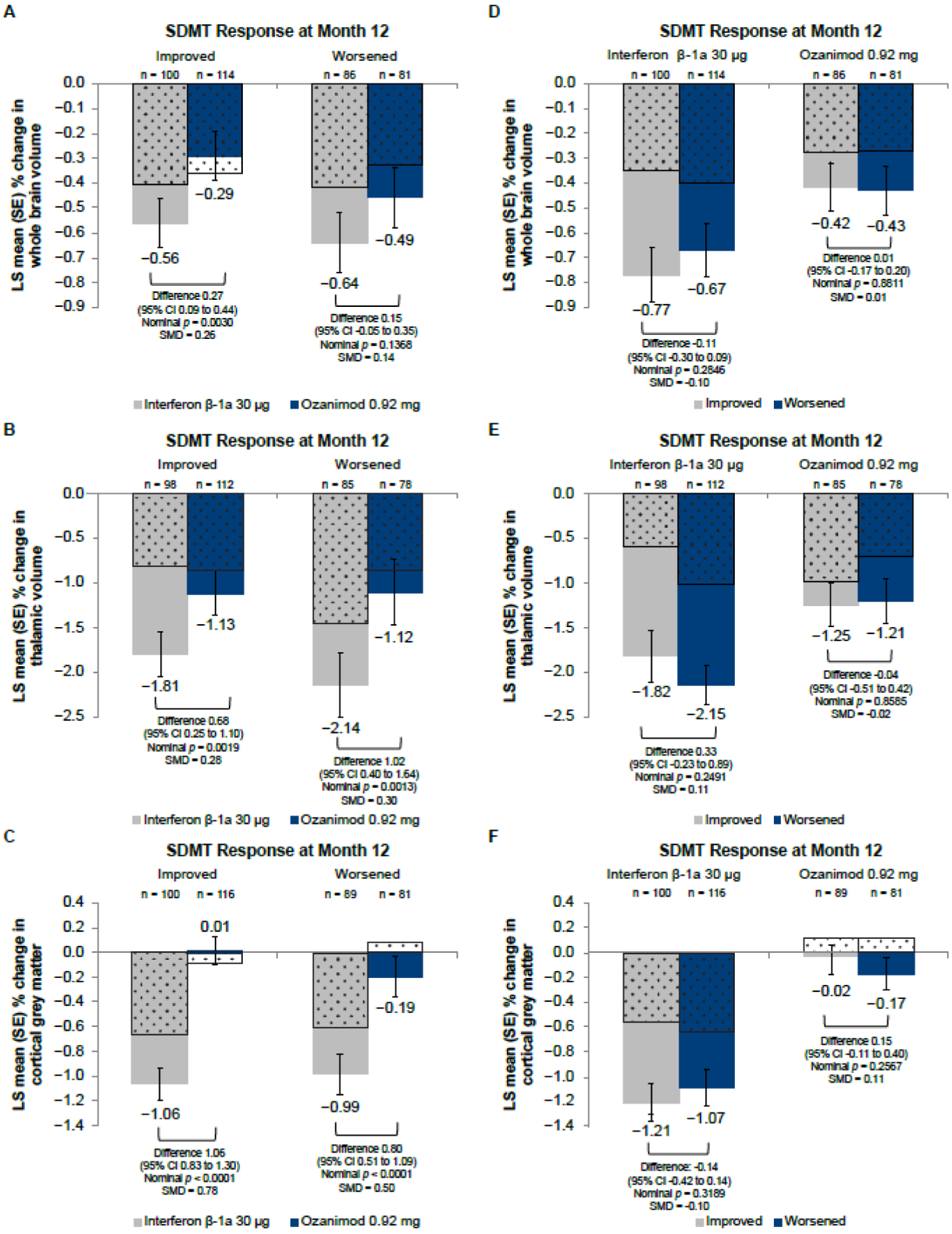


Fig. 2. Change in (A) whole brain volume, (B) thalamic volume, and (C) cortical grey matter volume over 12 months (solid bars) and over 6 months (dotted bars) comparing treatment difference between ozanimod 0.92 mg or interferon β-1a among those with clinically meaningful SDMT improvement and among those with clinically meaningful SDMT worsening at month 12. Change in (D) whole brain volume, (E) thalamic volume, and (F) cortical grey matter volume over 12 months (solid bars) and over 6 months (dotted bars) comparing clinically meaningful SDMT improvement vs SDMT worsening within each treatment group. All comparisons conducted using analysis of covariance model adjusted for region (Eastern Europe vs rest of world), baseline EDSS category (≤3.5 vs >3.5), age at baseline, and baseline brain volume value of interest. CI = confidence interval; EDSS = Expanded Disability Status Scale; LS = least squares; SDMT = Symbol Digit Modalities Test; SE = standard error; SMD = standardized mean difference (Cohen's *d*); interpretation: 0.2 = small effect, 0.5 = medium effect, 0.8 = large effect (Faraone, 2008).

volume (Batista et al., 2012; Bergsland et al., 2016; Bisecco et al., 2018, 2019). It is unclear why results from SUNBEAM, which prospectively evaluated both SDMT and brain volume, failed to corroborate those previous findings. The short (≥12 months) study duration may have hindered the ability to detect an association. Brain atrophy alone might be limited in its capacity to reflect the entire degenerative component of MS. Other factors that may be involved in SDMT change are diffuse white and grey matter damage and dendritic spine loss, which have been described in pathology studies (Kutzelnigg et al., 2005; Bo et al., 2003; Jurgens et al., 2016), but may not be detected by conventional MRI. SDMT results are affected not only by CPS but also visual acuity and ocular motor function, and over repeated assessments patients may learn the symbol-digit associations, facilitating response (Benedict et al., 2017). Finally, negative change or no change in SDMT may reflect limited cognitive reserve/learning capacity in addition to, or even independently from, a poorer performance due to tissue damage. Further studies with CPS as a primary outcome are needed to better understand the relationship between CPS and thalamic volume loss.

Strengths of this analysis include use of a well-established, validated tool (SDMT) for assessment of a clinically relevant cognitive deficit (CPS) in PwMS and use of SDMT and brain volume data derived from a large, well-controlled phase 3 study. It is also notable that ozanimod showed benefit in SDMT results in the prespecified SDMT analysis in SUNBEAM against an active comparator (interferon β-1a) that is known to have some potential benefits with regard to cognition (Mokhber et al., 2014). However, these SDMT exploratory results should be interpreted cautiously given that they are post hoc analyses. The SUNBEAM study sample size determination was based on the primary endpoint (ARR), and the study was not specifically designed to evaluate change in SDMT. Although physical or cognitive disability could potentially interfere with performance on the written SDMT, people with conditions that might hinder implementation of study procedures or interpretation of the study results were excluded, and the mean baseline EDSS indicated limited disability in the study population. It is unknown whether decreases in SDMT or worsening by ≥4 points were related to clinical or cognitive relapse (Giedraitiene et al., 2018; Meli et al., 2020). SDMT data from SUNBEAM were limited to 12 months, as the study ended once the last enrolled participant completed 12 months of treatment, and a limited number of participants had SDMT assessments at subsequent time points. Longer studies are needed to better elucidate the long-term effects of ozanimod on cognition. While the current analyses do not control for type I error, nominally significant differences in least squares mean changes from baseline in SDMT scores and z-scores between ozanimod and interferon β-1a were observed at multiple time points, suggesting that the observations are attributed to a true treatment effect and are not due to chance.

5. Conclusions

These post hoc, exploratory results suggest that ozanimod has modestly beneficial effects on CPS in PwMS. The sustained effect of these encouraging findings needs to be confirmed in prospective, long-term studies focusing on cognitive endpoints. The SDMT is being used as a measure of CPS in both a long-term open-label extension study (study RPC01-3001, DAYBREAK; NCT02576717), as well as in a phase 3b trial (ENLIGHTEN; NCT04140305) where clinically meaningful improvement in CPS is the primary endpoint. The relationship between brain volume loss and changes in SDMT will also be further characterized in these studies.

5.1. Data availability statement

Celgene, a Bristol Myers Squibb company, is committed to responsible and transparent sharing of clinical trial data with patients, healthcare practitioners, and independent researchers for the purpose of improving scientific and medical knowledge as well as fostering innovative treatment approaches. Data requests may be submitted to Celgene, a Bristol Myers Squibb company, at https://vivli.org/ourmember/celgene/ and must include a description of the research proposal.

Declaration of Competing Interest

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