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Ponesimod Compared With Teriflunomide in Patients With Relapsing Multiple Sclerosis in the Active-Comparator Phase 3 OPTIMUM Study
A Randomized Clinical Trial

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IMPORTANCE To our knowledge, the Oral Ponesimod Versus Teriflunomide In Relapsing Multiple Sclerosis (OPTIMUM) trial is the first phase 3 study comparing 2 oral disease-modifying therapies for relapsing multiple sclerosis (RMS).

OBJECTIVE To compare the efficacy of ponesimod, a selective sphingosine-1-phosphate receptor 1 ($S1P_1$) modulator with teriflunomide, a pyrimidine synthesis inhibitor, approved for the treatment of patients with RMS.

DESIGN, SETTING, AND PARTICIPANTS This multicenter, double-blind, active-comparator, superiority randomized clinical trial enrolled patients from April 27, 2015, to May 16, 2019, who were aged 18 to 55 years and had been diagnosed with multiple sclerosis per 2010 McDonald criteria, with a relapsing course from the onset, Expanded Disability Status Scale (EDSS) scores of 0 to 5.5, and recent clinical or magnetic resonance imaging disease activity.

INTERVENTIONS Patients were randomized (1:1) to 20 mg of ponesimod or 14 mg of teriflunomide once daily and the placebo for 108 weeks, with a 14-day gradual up-titration of ponesimod starting at 2 mg to mitigate first-dose cardiac effects of $S1P_1$ modulators and a follow-up period of 30 days.

MAIN OUTCOMES AND MEASURES The primary end point was the annualized relapse rate. The secondary end points were the changes in symptom domain of Fatigue Symptom and Impact Questionnaire–Relapsing Multiple Sclerosis (FSIQ-RMS) at week 108, the number of combined unique active lesions per year on magnetic resonance imaging, and time to 12-week and 24-week confirmed disability accumulation. Safety and tolerability were assessed. Exploratory end points included the percentage change in brain volume and no evidence of disease activity (NEDA-3 and NEDA-4) status.

RESULTS For 1133 patients (567 receiving ponesimod and 566 receiving teriflunomide; median [range], 37.0 [18-55] years; 735 women [64.9%]), the relative rate reduction for ponesimod vs teriflunomide in the annualized relapse rate was 30.5% (0.202 vs 0.290; $P < .001$); the mean difference in FSIQ-RMS, −3.57 (−0.01 vs 3.56; $P < .001$); the relative risk reduction in combined unique active lesions per year, 56% (1.405 vs 3.164; $P < .001$); and the reduction in time to 12-week and 24-week confirmed disability accumulation risk estimates, 17% (10.1% vs 12.4%; $P = .29$) and 16% (8.1% vs 9.9; $P = .37$), respectively. Brain volume loss at week 108 was lower by 0.34% (−0.91% vs −1.25%; $P < .001$); the odds ratio for NEDA-3 achievement was 1.70 (25.0% vs 16.4%; $P < .001$). Incidence of treatment-emergent adverse events (502 of 565 [88.8%] vs 499 of 566 [88.2%]) and serious treatment-emergent adverse events (49 [8.7%] vs 46 [8.1%]) was similar for both groups. Treatment discontinuations because of adverse events was more common in the ponesimod group (49 of 565 [8.7%] vs 34 of 566 [6.0%]).

CONCLUSIONS AND RELEVANCE In this study, ponesimod was superior to teriflunomide on annualized relapse rate reduction, fatigue, magnetic resonance imaging activity, brain volume loss, and no evidence of disease activity status, but not confirmed disability accumulation. The safety profile was in line with the previous safety observations with ponesimod and the known profile of other S1P receptor modulators.

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Supplemental content

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Multiple sclerosis (MS), a chronic autoimmune disease of the central nervous system, is clinically perceived by relapses and progressive loss of neurological function, primarily attributed to inflammatory attacks leading to demyelination, axonal loss, and gliosis culminating in long-term multifocal sclerotic plaques in the brain and spinal cord.[1-3] Oral disease-modifying therapy (DMT) options such as teriflunomide,[4,5] fingolimod,[6] dimethyl fumarate,[7,8] and siponimod[9] have broadened disease management options in MS. Despite significant progress in MS therapy, there is still an unmet need for effective, safe, and convenient treatments that can be used early in the disease course.[10-12] Given the number of alternative options of oral treatments, head-to-head comparative trials to inform choices are still lacking.[13]

Ponesimod is an orally active, highly selective modulator of the sphingosine-1-phosphate receptor 1 ($S1P_1$) with no active metabolites and is thus a limited potential for drug-drug interaction.[14] Ponesimod induces a rapid, dose-dependent, and reversible reduction of peripheral blood lymphocyte counts by blocking the egress of lymphocytes from lymphoid organs.[15,16] Rapid elimination of ponesimod and the reversibility of its effects on lymphocyte levels allows the rapid return of normal immune system function, which may be beneficial in terms of safety for pregnancy planning, serious infections, or vaccinations.[17,18] In a randomized, placebo-controlled, dose-finding phase 2 study[19] in patients with relapsing MS (RMS), among doses tested (10 mg, 20 mg, and 40 mg), the 20-mg dose was found to significantly reduce both the cumulative number of new gadolinium-enhancing (Gd+) T1 lesions and new or enlarging T2 lesions compared with placebo.

We report the findings of the global phase 3 superiority study (the Oral Ponesimod Versus Teriflunomide in Relapsing Multiple Sclerosis [OPTIMUM]). This study was designed to compare the efficacy, safety, and tolerability of ponesimod vs teriflunomide, an approved oral therapy in adult patients with RMS.

Key Points

Question How does the efficacy of ponesimod compare with that of teriflunomide in a phase 3, multicenter, randomized, double-blind, active-comparator superiority study based on relapse rate, fatigue, magnetic resonance imaging–defined disease activity, tissue loss, and disability accumulation in patients with relapsing multiple sclerosis, over 108 weeks?

Findings In this randomized clinical trial, ponesimod was significantly superior to teriflunomide in reducing the annualized relapse rate (−30.5%), Fatigue Symptom and Impact Questionnaire–Relapsing Multiple Sclerosis symptom score (−3.57), and combined unique active lesions on magnetic resonance imaging (−56%).

Meaning In this study, efficacy of ponesimod was superior to teriflunomide, and ponesimod had a safety profile consistent with sphingosine-1-phosphate modulators without any new safety signals.

Methods

Study Design

OPTIMUM (NCT02425644) was a phase 3, multicenter, double-blind, active-comparator, superiority randomized clinical trial designed to compare the efficacy, safety, and tolerability of 20 mg of ponesimod vs 14 mg of teriflunomide in patients with RMS (eFigure 1 in Supplement 1; Trial Protocol in Supplement 2). The study was conducted from April 2015 to May 2019; 162 centers randomized patients across 28 countries in North America, Europe, Mexico, Israel, and Turkey. Randomization was stratified by use of MS DMTs in the last 2 years prior to randomization (presence or absence) and baseline Expanded Disability Status Scale (EDSS) score (≤3.5 or >3.5).

Patient Population

Adult patients aged 18 to 55 years with RMS as defined by the revised (2010) McDonald diagnostic criteria for MS[20] with a relapsing course (ie, RMS or secondary progressive MS with superimposed relapses), an EDSS score between 0 and 5.5, and recent clinical or magnetic resonance imaging (MRI) activity were enrolled. eAppendix 1 in Supplement 1 presents complete inclusion and exclusion criteria.

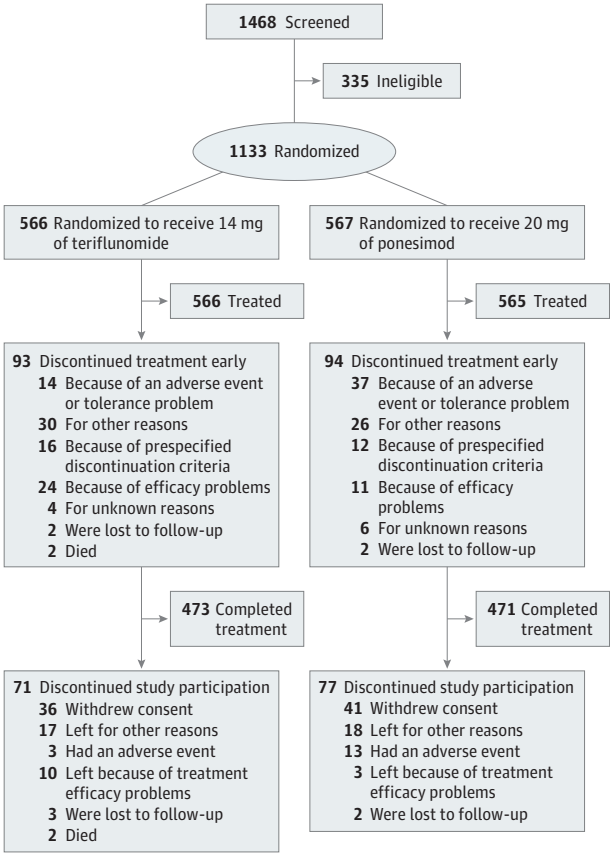
An institutional review board (US) or independent ethics committee (Europe) approved study protocol and amendments at each participating center. The study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice, and applicable regulatory requirements. All participants provided written informed consent.

Study Evaluations

The primary efficacy end point was the annualized relapse rate (ARR) based on the number of confirmed relapses per patient-year from randomization to the end of the study (EOS: end of treatment [EOT] plus follow-up time, as per the intention-to-treat principle). A confirmed relapse was defined as new, worsening, or recurrent neurological symptoms that occurred at least 30 days after the onset of a preceding relapse, lasted at least 24 hours, occurred in the absence of fever or infection, and was accompanied by a documented increase of the EDSS score or its functional system scores from a previous clinical assessment. The EDSS scores were assessed by independent, trained, and certified evaluators using the standardized Neurostatus EDSS examination (https://www.neurostatus.net/).

Secondary efficacy variables were (1) the change from baseline to week 108 in fatigue-associated symptoms, as measured by the symptom domain of the Fatigue Symptom and Impact Questionnaire-Relapsing Multiple Sclerosis (FSIQ-RMS), a validated patient-reported outcome measure[21] (eAppendix 1 in Supplement 1); (2) cumulative number of combined unique active lesions (CUALs) on MRI, defined as new Gd+ T1 lesions or new or enlarging T2 lesions (without double counting of lesions) from baseline to week 108 (assessed in a blinded fashion at a central reading center [Medical Image Analysis Center, Basel, Switzerland]); (3) time to 12-week confirmed disability accumulation (CDA) from baseline to the EOS, defined as an increase in the EDSS score, which was confirmed after 12 weeks (by an increase of at

Figure 1. Patient Disposition



In the ponesimod group, no patient discontinued treatment because of first-dose cardiac effect. Discontinuation in the ponesimod group was attributable to prespecified criteria: macular edema, pregnancy, lymphopenia, or a malignant condition.

least 1.5 with a baseline EDSS score of 0.0, at least 1.0 with baseline EDSS score of 1.0 to 5.0, or at least 0.5 with a baseline EDSS score of 5.5 or more); and (4) time to 24-week confirmed CDA from baseline to the EOS. Predefined exploratory measures included the percentage change in brain volume from baseline to week 108 using the Structural Image Evaluation, using Normalization, of Atrophy (SIENA) methodology.[22,23] Further exploratory end points were no evidence of disease activity (NEDA)-3 status from baseline up to the EOS (a composite of no relapse, no 12-week CDA, no Gd+ T1 or new or enlarging T2 lesions) and NEDA-4 status (a composite of NEDA-3 and no brain volume decrease of ≥0.4% from baseline to EOS).[24,25]

Safety assessments included adverse events recorded verbatim and later coded in accordance with MedDRA version 21 (International Council for Harmonisation) and predefined adverse events of special interest (AESIs) (details on AESIs are in eAppendix 1 in Supplement 1). Clinical laboratory tests (hematology, serum chemistry, virus serology, serum and urine pregnancy tests, and urinalysis), 12-lead electrocardiogram, blood pressure, and pulmonary function tests were also conducted.

Statistical Analysis

The primary statistical analysis was performed on the full analysis set (all participants who were randomized) using a negative binomial regression model for the number of confirmed relapses from baseline to the EOS adjusting for the log time in the study (in years) as an offset. An overall multiple testing strategy was applied to the planned efficacy analyses, which started with testing the primary end point at an overall 2-sided α of .01 for conclusive evidence and .05 for a positive study result, followed hierarchically by a fallback-type procedure for the secondary end points[26] (details are in eFigure 2 in Supplement 1).

Results

Patient Disposition and Baseline Characteristics

Of 1468 patients screened, 1133 were randomized (ponesimod, n = 567; teriflunomide, n = 566) and included in the full analysis set. The study enrolled a representative RMS population (median [range] age, 37.0 [18-55] years; 735 women [64.9%]). Of those randomized, 2 patients in the ponesimod group did not receive study treatment. Of the 1131 patients treated, 471 of 565 (83.1%) receiving ponesimod and 473 of 566 (83.6%) receiving teriflunomide completed the respective treatments (**Figure 1**); there were fewer treatment discontinuations in the ponesimod group for efficacy-associated reasons (ponesimod, 11 [1.9%]; teriflunomide, 24 [4.3%]). However, treatment discontinuations attributable to adverse events or tolerability were more frequent in the ponesimod group (37, vs 14 in the teriflunomide group; Figure 1).

Baseline characteristics were comparable between the 2 treatment groups (**Table 1**), with a small imbalance in the presence of enhancing lesions (ponesimod, 226 of 567 [39.9%] vs teriflunomide, 256 of 566 [45.4%]). Approximately 35% of patients (202 receiving ponesimod [35.6%] and 200 receiving teriflunomide [35.3%]) were considered to have highly active disease, as defined by different combinations of number of relapses, MRI activity at baseline, EDSS score, and previous DMT (Table 1).

Efficacy

Primary End Point: ARR

In total, there were 242 confirmed relapses reported for ponesimod compared with 344 for teriflunomide. Ponesimod reduced ARR by 30.5% compared with teriflunomide (mean ARR, 0.202 vs 0.290; rate ratio, 0.695 [99% confidence limits (CLs), 0.536-0.902]; $P < .001$; **Figure 2**A; **Table 2**). Sensitivity analyses adjusting for presence of enhancing lesions showed consistent results (eAppendix 1 and eTable 4 in Supplement 1).

Secondary End Points

FSIQ-RMS | The change in FSIQ-RMS weekly symptom score from baseline to week 108 was lower (where higher scores indicate more fatigue) for fatigue symptoms in the ponesimod group than the teriflunomide group. The least-square means

were 0.01 vs 3.56 (mean difference, −3.57 [95% CLs, −5.83 to −1.32]; P = .002; Table 2; Figure 2B).

CUALs | Ponesimod reduced the mean number of CUALs per year on annual brain MRIs from baseline to week 108 by 56% compared with teriflunomide (1.405 vs 3.164; rate ratio, 0.444 [95% CLs, 0.364-0.542]; P < .001) (Table 2). Most of CUALs observed were new or enlarging T2 lesions (Table 2; Figure 2C).

CDA | The risk of 12-week CDA was not different in the 2 groups (10.1% vs 12.4%; hazard ratio, 0.83 [95% CLs, 0.58-1.18]; P = .29), and the formal testing procedure stopped, rendering the subsequent analyses exploratory. In this exploratory analysis, risk of 24-week CDA was also not different (hazard ratio, 0.84 [95% CLs, 0.57-1.24]; P = .37; Table 2; Figure 2D; eFigure 3 in Supplement 1).

Exploratory Outcomes

Brain Volume Loss | Brain volume loss from baseline to week 108 was lower in the ponesimod group vs the teriflunomide group. The least-squares mean percentage change was −0.91% vs −1.25% (mean difference, 0.34 [95% CL, 0.17-0.50] percentage points; exploratory P < .001; Table 2; eFigure 4 in Supplement 1).

NEDA-3 and NEDA-4 | In the ponesimod group vs the teriflunomide group, the estimated percentage for NEDA-3 from baseline to week 108 was 25.0% vs 16.4%, respectively; the odds ratio for achieving 2-year NEDA-3 was 1.70 (95% CLs, 1.27-2.28; Table 2). The most frequent reason for not achieving NEDA-3 was the presence of new or enlarging T2 lesions (all randomized patients: ponesimod, 301 [53.4%]; teriflunomide, 364 [65.2%]). The estimated percentage achieving NEDA-4 from baseline to week 108 was 11.4% vs 6.5% in the ponesimod vs teriflunomide groups (odds ratio, 1.85 [95% CLs, 1.24-2.76]; P = .003). A total of 171 patients (32.5%) in the ponesimod and 225 patients (42.3%) in the teriflunomide groups, respectively, had annual brain volume losses of 0.4% or more compared with baseline values.

Table 1. Demographic and Baseline Characteristics in the Full Analysis Set

Characteristic	Patients, No. (%)	
	Ponesimod, 20 mg (n = 567)	Teriflunomide, 14 mg (n = 566)
Female	363 (64.0)	372 (65.7)
Age, mean (SD), y	36.7 (8.74)	36.8 (8.74)
White race	551 (97.2)	553 (97.7)
Baseline Expanded Disability Status Scale >3.5 strata	94 (16.6)	95 (16.8)
Disease-modifying treatment received within 2 y prior to randomization	213 (38)	211 (37)
Baseline Expanded Disability Status Scale score, mean (SD)	2.57 (1.17)	2.56 (1.23)
Time since first symptom at randomization, mean (SD), y	7.63 (6.78)	7.65 (6.78)
Relapses in last year prior to study entry, mean (SD), No.	1.2 (0.61)	1.3 (0.65)
Multiple sclerosis subtype		
Relapsing-remitting	552 (97.4)	552 (97.5)
Secondary progressive	15 (2.6)	14 (2.5)
Fatigue symptom score at baseline, mean (SD)[a]	31.9 (20.4)	32.8 (19.1)
Presence of gadolinium-enhancing T1 lesions at baseline[b]	226 (39.9)	256 (45.4)
Volume of T2-weighted lesions, mean (SD), mm^3	8301.4 (10 346.28)	9489.2 (11 265.42)
Highly active disease[c]	202 (35.6)	200 (35.3)

[a] Based on Fatigue Symptom and Impact Questionnaire–Relapsing Multiple Sclerosis.

[b] From the central reader.

[c] Two or more relapses within the 1 year prior to study entry, a baseline Expanded Disability Status Scale score more than 2, and baseline magnetic resonance imaging or 1 or more gadolinium-enhancing T1 lesion; or any disease-modifying treatment received within 12 months prior to randomization and 1 or both of the following: (1) 1 or more relapse within 1 year prior to study entry and baseline magnetic resonance imaging either with 1 or more gadolinium-enhancing T1 lesion and/or 9 or more T2-weighted lesions or (2) a number of relapses within 1 year prior to study entry equal to or greater than the number of relapses between 2 years and 1 year prior to study entry, for patients with 1 or more relapse within the 2 years prior to study entry.

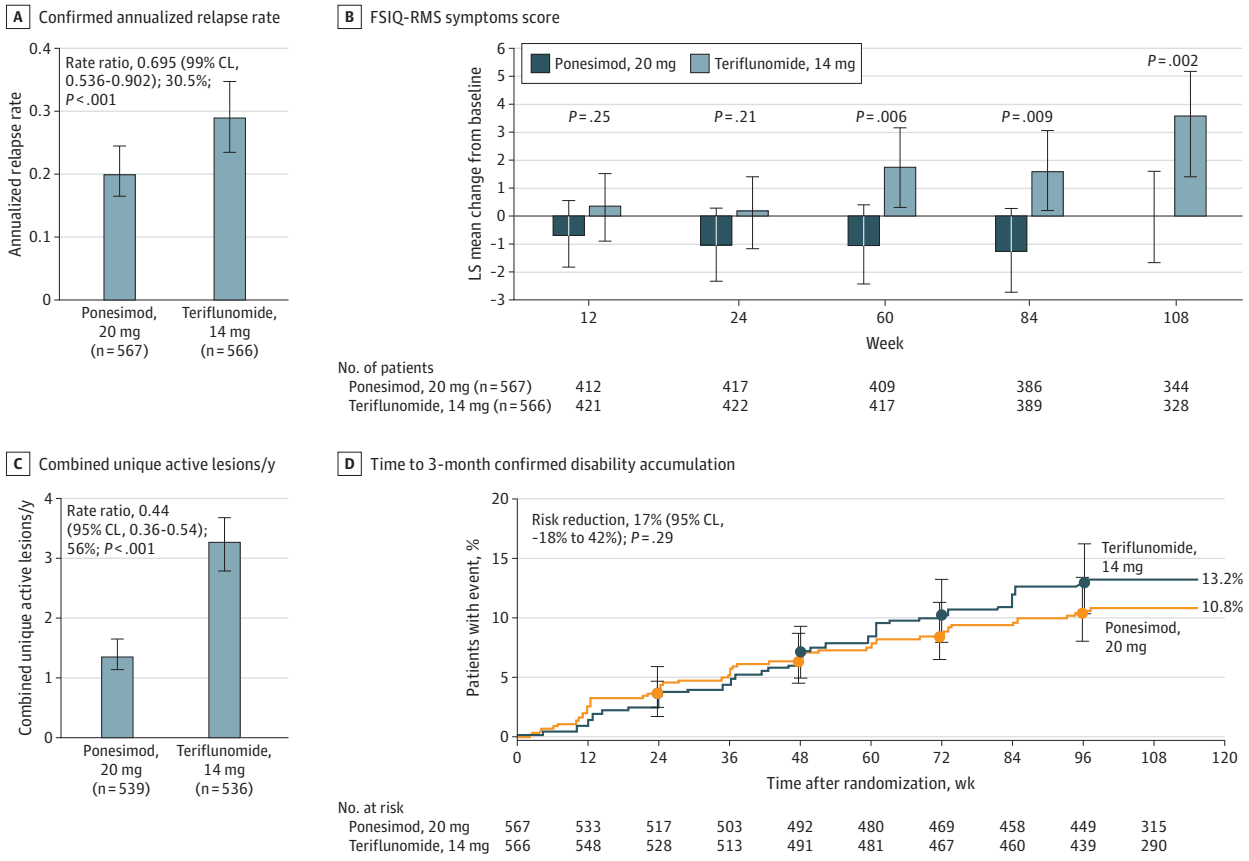
Safety

Overall, the proportion of patients who experienced at least 1 treatment-emergent adverse event (TEAE) was similar between the 2 groups (ponesimod, 502 [88.8%]; teriflunomide, 499 [88.2%]) (**Table 3**). The most common TEAEs (≥10% in either group) were an increased alanine aminotransferase (ALT) level (110 [19.5%] vs 53 [9.4%]), nasopharyngitis (109 [19.3%] vs 95 [16.8%]), headache (65 [11.5%] vs 72 [12.7%]), upper respiratory tract infection (60 [10.6%] vs 59 [10.4%]), and alopecia (18 [3.2%] vs 72 [12.7%]) in the ponesimod vs teriflunomide groups, respectively.

The proportions of patients who experienced at least 1 treatment-emergent serious adverse event were similar in both treatment arms (49 [8.7%] vs 46 [8.1%]). Overall, no pattern or clustering of serious events was observed in either treatment group. Two patients in the teriflunomide group died: 1 of coronary artery insufficiency and 1 of MS (adjudicated as sudden cardiac death). Both deaths were considered by the investigators to be not associated with the study drug. Overall, TEAEs leading to treatment discontinuation were more frequent in the ponesimod group (49 of 565 [8.7%] vs 34 of 566 [6.0%]); dyspnea (6 [1.1%] vs 0), an increased ALT level (5 [0.9%] vs 6 [1.1%]), an increased aspartate aminotransferase level (3 [0.5%] vs 5 [0.9%]), and macular edema (6 [0.9%] vs 0) were the most commonly reported reasons.

The overall incidence of first-dose heart rate and rhythm AESIs on day 1 (at a 2-mg dose) of up-titration (eTable 1 in Supplement 1) or treatment reinitiation was 2.1% in the ponesimod group (n = 12) compared with 0.4% (n = 2) in the teriflunomide group, with none reported as serious or leading to treatment discontinuation (eTable 2 in Supplement 1). No second-degree or higher-degree atrioventricular blocks occurred. The maximum mean (SD) reduction in heart rate from

Figure 2. Primary and Secondary End Points in the Full Analysis Set



A, Confirmed relapses up to end of study, with annualized relapse rate from negative binomial regression for ponesimod (0.202) and teriflunomide (0.290); 30.5% indicates risk reduction. B, Symptoms domain of Fatigue Symptom and Impact Questionnaire–Relapsing Multiple Sclerosis (FSIQ-RMS): change from baseline to week 108. C, Number of combined unique active lesions per year on magnetic resonance scans up to week 108; 56% indicates risk reduction. D, Time to 12-week confirmed disability accumulation. With regardt to nonsignificant results, the formal testing procedure stopped. The stratified log-rank test *P* value and stratified Cox regression risk reduction estimate are displayed. CL indicates confidence limits; LS, least squares.

predose to postdose on day 1 was observed at 2 hours postdose in the ponesimod group (−8.7 [8.68] beats per minute), compared with −1.7 (8.95) beats per minute in the teriflunomide group, with 3 patients having an asymptomatic postdose heart rate of 40 beats per minute or less; all 3 of these patients had a pretreatment heart rate of less than 55 beats per minute.

An overview of treatment-emergent AESIs up to the EOT plus 15 days is shown in Table 3. To address the concern regarding confounding effects of the accelerated elimination procedure for teriflunomide on liver enzymes, an analysis up to the EOT plus 1 day was also performed. Most frequently occurring AESIs (up to the EOT plus 15 days, unless otherwise specified) with ponesimod vs teriflunomide were in the categories of hepatobiliary disorders or liver enzyme abnormalities (up to EOT plus 1 day) (128 [22.7%] vs 69 [12.2%]), hypertension (57 [10.1%] vs 51 [9.0%]), pulmonary events (45 [8.0%] vs 15 [2.7%]), and herpetic infection (each 27 [4.8%]). A total of 6 patients (2 receiving ponesimod and 4 receiving teriflunomide) had a serious hepatobiliary disorder or liver enzyme abnormality AESI (up to EOT plus 1 day).

A similar proportion of patients in the ponesimod group (45 [8.0%]) and teriflunomide group (44 [7.8%]) experienced at least 1 AESI of hypertension. Three patients in the ponesimod group discontinued the study treatment because of hypertension AESIs, and 1 patient in each group had a serious hypertension AESI.

The most frequently reported pulmonary AESI was dyspnea (ponesimod: 30 [5.3%]; teriflunomide: 7 [1.2%]); premature treatment discontinuation due to pulmonary AESI was reported in 7 patients (1.2%) receiving ponesimod (6 with dyspnea). Treatment-emergent AESIs of macular edema were reported in 6 patients receiving ponesimod and none receiving teriflunomide; all cases resolved with treatment discontinuation, including 1 with sequelae.

Four patients with macular edema AESIs had a relevant medical history or concomitant eye disorder, and 1 patient had diabetes. In the ponesimod group, 8 patients (1.4%) experienced seizures, compared with 1 patient (0.2%) receiving teriflunomide. Of the 8 patients in the ponesimod group, 5 patients had concomitant neurologic diseases at baseline (epilepsy: n = 2; partial seizures with secondary generaliza-

Table 2. Summary of Efficacy Results in the Full Analysis Set

End point from baseline to week 108	Ponesimod, 20 mg (n = 567)	Patients included in analysis, No.	Teriflunomide, 14 mg (n = 566)	Patients included in analysis, No.	RR (99% CL) or Difference, RR, or HR (95% CL)	*P* value
Primary end point						
Mean annualized relapse rate/y (95% CL)[a]	0.202 (0.173-0.235)	567	0.290 (0.254-0.331)	566	0.695 (0.536-0.902)[b]	<.001
Secondary end points						
LS mean FSIQ-RMS weekly symptoms score change (95% CL)[c]	−0.01 (−1.60 to 1.58)	449	3.56 (1.96-5.16)	458	−3.57 (−5.83 to −1.32)[d]	.002
Mean cumulative combined unique active lesions/y (95% CL)[e]	1.405 (1.215-1.624)	539	3.164 (2.757-3.631)	536	0.444 (0.36-0.54)[f]	<.001
Patients with first 12-wk confirmed disability accumulation, No. (%)[g]	57 (10.1)	567	70 (12.4)	566	0.83 (0.58-1.18)[h]	.29
Exploratory end points						
Patients with first 24-wk confirmed disability accumulation, No. (%)[g]	46 (8.1)	567	56 (9.9)	566	0.84 (0.57 to 1.24)[h]	.37
Mean cumulative new gadolinium-enhancing T1 lesions/scan (95% CL)	0.18 (0.141-0.224)	540	0.43 (0.351-0.525)	538	0.42 (0.31-0.56)[f]	<.001
LS mean change in brain volume, % (95% CL)[i]	−0.91 (−1.03 to −0.79)	436	−1.25 (−1.36 to −1.13)	434	0.34 (0.17 to 0.50)[d]	<.001
Estimated mean NEDA-3, % (95% CL)[i]	25.0 (21.4-29.0)	564	16.4 (13.5-19.8)	558	1.70 (1.27 to 2.28)[j]	<.001
Estimated mean NEDA-4, % (95% CL)[k]	11.4 (8.7-14.6)	526	6.5 (4.7-9.0)	532	1.85 (1.24-2.76)[j]	.003

Abbreviations: CL, confidence limit; DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; FSIQ-RMS, Fatigue Symptom and Impact Questionnaire–Relapsing Multiple Sclerosis; HR, hazard ratio; LS, least squares; NEDA, no evidence of disease activity; OR, odds ratio; RR, rate ratio.

[a] Confirmed relapses up to the end of the study; a negative binomial model was applied with Wald CLs and *P* value, the offset log time (years) to the end of the study, and covariates of EDSS strata (≤3.5 or >3.5), DMT in the last 2 years prior to randomization strata, and the number of relapses in the year prior study entry (≤1 or ≥2).

[b] RR (99% CL).

[c] Mixed-effects, repeated-measurements model with unstructured covariance, treatment, visit, treatment by visit interaction, baseline by visit interaction as fixed effects, baseline FSIQ-RMS score, EDSS strata (≤3.5 or >3.5), and DMT in the 2 years prior to randomization as covariates. A negative change from baseline indicates an improvement in fatigue symptoms.

[d] Difference (95% CL).

[e] Negative binomial model was applied with Wald 95% CIs, a *P* value, and an offset of log time (years) up to last magnetic resonance imaging scan and covariates of EDSS strata (≤3.5 or >3.5), DMT within the 2 years prior to randomization, and gadolinium-enhancing T1 lesions at baseline.

[f] RR (95% CL).

[g] Change from baseline to end of study; stratified by EDSS category and DMT within 2 years, Cox regression with 95% Wald CLs and a log-rank *P* value.

[h] HR (95% CL).

[i] Mixed model with linear time effect and covariates of EDSS strata (≤3.5 or >3.5), DMT within the 2 years prior to randomization strata, gadolinium-enhancing T1 lesions at baseline, and baseline brain volume.

[j] OR (95% CL).

[k] Logistic regression with treatment as factor, adjusted for covariates EDSS strata (≤3.5 or >3.5), DMT in the 2 years prior to randomization, the number of relapses in the year prior to study entry (≤1 or ≥2), and the presence of gadolinium-enhancing T1 lesions at baseline.

tion: n = 1; hydrocephalus: n = 1; polyneuropathy: n = 1). Three seizure AESIs among patients receiving ponesimod were reported as serious, and 1 event resulted in discontinuation of the study treatment.

The proportion of patients who experienced an ALT level increased 3 or more times greater than the upper limit of normal (ULN) levels (reference range: men, 44 U/L; women, 33 U/L [to convert to microkatals per liter, multiply by 0.0167]; EOT plus 1 day) was higher in the ponesimod group compared with the teriflunomide group (97 [17.3%] vs 47 [8.3%]), while the proportion with an ALT level increased 8 or more times greater than the ULN (the EOT plus 1 day) was higher in the teriflunomide group (4 [0.7%] vs 12 [2.1%]) (eTable 3 in Supplement 1). All ALT level increases of 3 or more times greater than the ULN resolved despite continued ponesimod treatment (n = 86) or after treatment discontinuation (n = 11). Most cases of bilirubin increases of 2 or more times greater than the ULN (5 of 8 patients; reference, 5.1 to 20.5 µmol/L, irrespective of sex; EOT plus 1 day) occurred in patients with a medical history of Gilbert syndrome.

Discussion

OPTIMUM is, to our knowledge, the first phase 3 study comparing efficacy and safety of 2 oral DMTs in RMS. Ponesimod is an orally active, selective $S1P_1$ receptor modulator that causes dose-dependent sequestration of lymphocytes in lymphoid organs. High selectivity for the $S1P_1$ receptor, a low potential for drug-drug interactions, rapid onset, and reversibility of pharmacological effects, along with an up-titration regimen that mitigates cardiac adverse effects, provides added benefits to ponesimod over other $S1P_1$ receptor modulators.[14] Ponesimod was superior to teriflunomide, an oral pyrimidine synthesis inhibitor approved for the treatment of MS,[13] on the primary study outcome, reduction of ARR (by −30.5%). Superiority vs teriflunomide was also shown in the analysis of 2 key secondary outcomes: the reduction of CUAL, an established MRI measure of focal inflammatory disease activity (−56%),[27] and improvement of MS-associated fatigue, as measured with the FSIQ-RMS weekly symptom score (mean dif-

Table 3. Overview of Adverse Events in Safety Analysis Set

Characteristics	Patients, No. (%)	
	Ponesimod, 20 mg (n = 565)	Teriflunomide, 14 mg (n = 566)
TEAEs	502 (88.8)	499 (88.2)
≥1 TEAEs in either group leading to treatment discontinuation, by system organ class terms[a]	49 (8.7)	34 (6.0)
Investigations	12 (2.1)	10 (1.8)
Respiratory, thoracic, and mediastinal disorders	7 (1.2)	NA
Eye disorders	5 (0.9)	NA
Gastrointestinal disorders	4 (0.7)	4 (0.7)
Blood and lymphatic system disorders	3 (0.5)	2 (0.4)
General disorders and administration site conditions	3 (0.5)	2 (0.4)
Hepatobiliary disorders	3 (0.5)	2 (0.4)
Pregnancy, puerperium, and perinatal conditions	3 (0.5)	3 (0.5)
Vascular disorders	3 (0.5)	NA
Nervous system disorders	2 (0.4)	4 (0.7)
Social circumstances	2 (0.4)	1 (0.2)
Cardiac disorders	1 (0.2)	2 (0.4)
Skin and subcutaneous tissue disorders	1 (0.2)	2 (0.4)
Adverse event of special interest[b]		
Hepatobiliary disorders or liver test result abnormality		
End of treatment plus 1 d	128 (22.7)	69 (12.2)
End of treatment plus 15 d	145 (25.7)	82 (14.5)
≥1 Serious adverse event	2 (0.4)	4 (0.7)
Hypertension	57 (10.1)	51 (9.0)
Pulmonary events	45 (8.0)	15 (2.7)
Effect on heart rate and rhythm plus hypotension on day 1	12 (2.1)	2 (0.4)
Herpetic infection	27 (4.8)	27 (4.8)
Infection[c]	9 (1.6)	5 (0.9)
Seizure	8 (1.4)	1 (0.2)
Macular edema	6 (1.1)	1 (0.2)[d]
Skin malignant condition	5 (0.9)[e]	1 (0.2)[f]
Nonskin malignant condition	1 (0.2)	1 (0.2)
Fatal TEAEs	NA	2 (0.4)[g]
Serious adverse events (n ≥1 in either group by system organ class terms	49 (8.7)	46 (8.1)
Nervous system disorders	9 (1.6)	6 (1.1)
Infections and infestations	7 (1.2)	4 (0.7)
Gastrointestinal disorders	6 (1.1)	4 (0.7)
Neoplasms, benign, malignant, and unspecified, including cysts and polyps	6 (1.1)	3 (0.5)
Surgical and medical procedures	5 (0.9)	1 (0.2)
Injury, poisoning, and procedural complications	4 (0.7)	7 (1.2)
Kidney and urinary disorders	4 (0.7)	1 (0.2)
Musculoskeletal and connective tissue disorders	3 (0.5)	4 (0.7)
Reproductive system and breast disorders	3 (0.5)	6 (1.1)
Hepatobiliary disorders	2 (0.4)	7 (1.2)
Investigations	2 (0.4)	3 (0.5)
Respiratory, thoracic, and mediastinal disorders	2 (0.4)	1 (0.2)
Vascular disorders	2 (0.4)	2 (0.4)
Blood and lymphatic system disorders	1 (0.2)	1 (0.2)
Psychiatric disorders	1 (0.2)	2 (0.4)
Cardiac disorders	0	2 (0.4)
Metabolism and nutrition disorders	0	1 (0.2)

Abbreviations: NA, not applicable; TEAE, treatment-emergent adverse events.

[a] Only system organ classes with at least 2 events in at least 1 treatment arm are displayed.

[b] Up to end of treatment plus 15 days, unless otherwise specified.

[c] Infection adverse event of special interests were identified by the adverse events from the infections and infestations system organ class, only if reported as serious or severe.

[d] Adverse event macular hole was not confirmed as macular edema.

[e] Two with basal cell carcinoma, 2 with excision of preexisting benign lesions (nevus), and 1 with malignant melanoma.

[f] One with basal cell carcinoma.

[g] One because of coronary artery insufficiency and 1 because of multiple sclerosis.

ference, −3.57). Despite the well-known negative implications on quality of life and the high socioeconomic burden associated with fatigue,[21,28-30] no previous phase 3 study in MS has addressed fatigue prospectively as a key outcome. This may have been partially because of the poor sensitivity and specificity of the currently available patient-reported outcomes used for the assessment of fatigue. In this study, fatigue was assessed using a validated patient-reported outcome measure specifically developed to assess fatigue in patients with RMS, the FSIQ-RMS scale.[21]

However, no statistically significant difference was seen in the outcome on the predefined key secondary outcome, 12-week CDA. Baseline EDSS scores (mean, 2.6) and the proportion of patients with EDSS scores of 3.5 or less (83.5%) are indicative of a relatively low level of disability, and few 12-week CDA events were observed in both the ponesimod and teriflunomide groups, leading to a limitation in the ability to detect significant differences between treatment groups. This low rate of CDA in both arms and the fact that teriflunomide is the only approved oral DMT for RMS to demonstrate a significant benefit on 12-week confirmed disability progression vs placebo in 2 separate pivotal trials in relapsing-remitting MS[4,5] suggests that OPTIMUM was underpowered to detect a difference within the 2-year treatment period. Interestingly, in the preplanned exploratory analyses of brain volume change after 2 years in the study, patients randomized to receive ponesimod had less brain volume loss than those receiving teriflunomide (a 0.34% difference). A body of evidence supports a correlation at the group level of brain volume loss with medium-term and long-term disability progression, as reflected by the EDSS scores or neuropsychological assessments.[31-33] Together, the effect of

ponesimod on fatigue and the reduction of brain volume loss, shown against a drug with an established effect on brain volume loss,[34] suggests that ponesimod's benefits are not restricted to suppressing relapses and focal lesions reflecting short-term events in the pathogenesis of MS but extend to the prevention of tissue damage accumulation. In accordance with ponesimod's effects on the individual outcome measures, a higher proportion of patients receiving ponesimod remained free of disease activity, both after applying the 3 established criteria for NEDA-3 (no relapse, no confirmed disease worsening, and no new or enlarging MRI lesions) and after adding the criterion of no brain volume change in excess of the upper limit obtained in healthy controls (NEDA-4).[24,25]

Treatment discontinuation rates were similar in the 2 treatment groups. These were at the lower end compared with frequencies reported in other phase 3 studies in relapsing MS.[4,6-8,35-37] More patients in the teriflunomide group discontinued treatment because of reasons of efficacy, consistent with the greater benefit of ponesimod observed across multiple efficacy end points, whereas discontinuations attributable to adverse events or tolerability were more frequent in the ponesimod group. Treatment discontinuations attributed to adverse events in the ponesimod group were mainly by protocol-mandated, study-specific discontinuation criteria associated with anticipated $S1P_1$ modulator class effects on the respiratory system and macular edema and protocol-mandated study specific discontinuation criteria.

In general, the pattern and nature of reported AEs were in line with previous experience with ponesimod[13,19] and other S1P receptor modulators.[21] The 14-day up-titration regimen applied in this trial resulted in an overall low incidence of first-dose heart rate and rhythm AESIs (2.1%). None of these day 1 events was reported as serious or leading to treatment discontinuation. The higher proportion of patients meeting cutoff criteria for liver abnormalities observed in OPTIMUM, compared with the phase 2 ponesimod study, was likely because of the more conservative definition of ULN, along with more frequent testing. A systematic review of the available serious adverse event reports from patients discontinuing the drug during OPTIMUM and the phase 2 study and its extension follow-up phase have not revealed any reports of rebound or severe relapses after ponesimod discontinuation.[38]

Limitations

There were a few limitations associated with this study. First, there was low power to provide a robust evaluation of the effect of ponesimod on disability accumulation vs an active comparator. Second, there were a limited number of patients with secondary progressive MS recruited. Finally, the effect of the accelerated elimination procedure during the safety follow-up period could not be excluded.

Conclusions

In conclusion, OPTIMUM, as the first (to our knowledge) phase 3 study comparing 2 oral DMTs in RMS, showed that ponesimod is superior to teriflunomide, an approved oral DMT, on the primary end point, ARR, and also on 2 of 3 secondary end points: MRI activity and fatigue, a most debilitating MS symptom that until now appears not to have been shown in a prospective phase 3 study to be effectively addressed by other DMTs. Superiority of ponesimod was also shown on the exploratory end points of brain volume loss and NEDA status. Ponesimod was well tolerated, and the safety results were in line with previous observations in its phase 2 dose-finding study[19] and findings on other S1P receptor modulators in controlled studies,[39] including their extensions and postmarketing observations.

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Agli operatori sanitari è richiesto di segnalare qualsiasi reazione avversa sospetta tramite il sistema nazionale di segnalazione all'indirizzo
https://www.aifa.gov.it/content/segnalazioni-reazioni-avverse