Effect of oral ponesimod on clinical disease activity and MRI-based outcomes in patients with relapsing multiple sclerosis: Phase 3 OPTIMUM study

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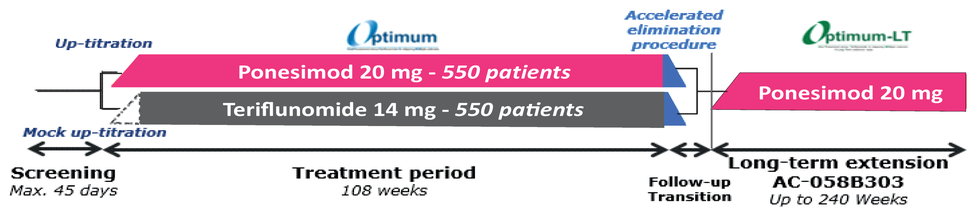
BACKGROUND

- Ponesimod is an orally active, selective $S1P_1$ modulator that causes dose-dependent sequestration of lymphocytes in lymphoid organs thereby reducing the blood lymphocyte count.[1]
- In a double-blind, placebo-controlled phase 2b study (NCT01006265), once daily ponesimod at 10, 20 and 40 mg significantly reduced inflammatory MRI activity and the majority of adverse events were of mild or moderate intensity in patients with relapsing remitting multiple sclerosis (RRMS).[2]
- In the phase 3 OPTIMUM study (NCT02425644), ponesimod 20 mg demonstrated superior efficacy vs teriflunomide 14 mg in reducing annualized relapse rate in patients with relapsing multiple sclerosis (RMS).
- No evidence of disease activity (NEDA) is increasingly used as a meaningful comprehensive outcome of disease-modifying therapies in RMS.[3]
- We report the results for prespecified MRI-based endpoints and NEDA status in patients with RMS from the phase 3 OPTIMUM study.

METHODS

- OPTIMUM was a phase 3, multicenter, randomized, double-blind, active comparator, superiority study designed to compare ponesimod 20 mg versus teriflunomide 14 mg in patients with RMS.



Population	• Patients with RMS aged 18 to 55 years • Active disease with onset within 1 to 24 months prior to baseline screening • Ambulatory patients with an Expanded Disability Status Scale (EDSS) score of 0 to 5.5
Exploratory endpoints*	• **MRI endpoints****: Changes from baseline to week 108 in – Brain volume (using Structural Image Evaluation using Normalization of Atrophy [SIENA]) – Volume of T2-weighted (T2) lesions – Number of new/enlarging T2 lesions and new contrast-enhanced T1-weighted (Gd+T1) lesions – Absence of new/enlarging T2 lesions and new Gd+T1 lesions at week 108 • **NEDA-3 status** from baseline to week 108: absence of confirmed relapse, 12-week confirmed disability accumulation, Gd+T1 and new/enlarging T2 lesions on annual MRIs • **NEDA-4 status** from baseline to week 108: NEDA-3 and no average annual brain volume decrease ≥0.4%

*p-values for these analyses are nominal; **MRI assessments were performed at baseline, week 60 and week 108

RESULTS

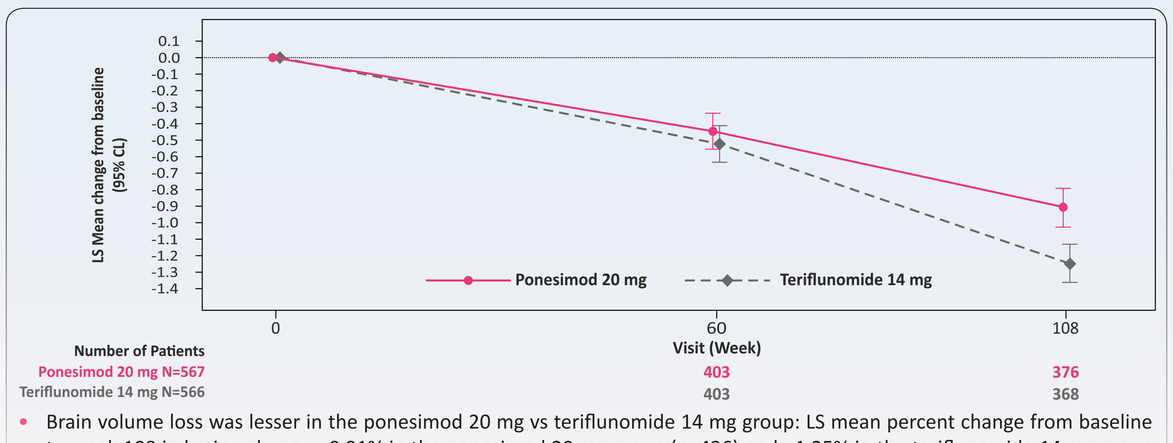
Demographics and baseline disease characteristics

Characteristic	Ponesimod 20 mg (N=567)	Teriflunomide 14 mg (N=566)
Age (years), mean (SD)	36.7 (8.74)	36.8 (8.74)
Female, n (%)	363 (64)	372 (66)
DMT received within 2 years prior to randomization, n (%)		
Yes	213 (38)	211 (37)
Baseline EDSS score, mean (SD)	2.57 (1.17)	2.56 (1.23)
Time since first symptoms at randomization (years), mean (SD)	7.6 (6.78)	7.7 (6.78)
No. of relapses within past year prior to study entry		
	n=567	n=565
Mean (SD)	1.2 (0.61)	1.3 (0.65)
Disease subtype, n (%)		
RRMS	552 (97)	552 (98)
SPMS	15 (3)	14 (3)
Presence of Gd+ T1 lesions at baseline		
	n=567	n=564
n (%)	226 (40)	256 (45)
Volume of T2 lesions		
	n=565	n=563
Mean (mm^3)	8301.4	9489.2

DMT, disease-modifying treatment; EDSS, Expanded Disability Status Score; Gd+T1, T1-weighted gadolinium-enhanced; N, total number of patients; n, number of patients with available data; RRMS, relapsing-remitting multiple sclerosis; SD, standard deviation; SPMS, secondary progressive multiple sclerosis

- Of 1133 patients, 985 (86.9%) completed the study: n=490 (ponesimod 20 mg); n=495 (teriflunomide 14 mg)
- Baseline characteristics were comparable between the two treatment groups.

Percent change in brain volume from baseline to week 108



- Brain volume loss was lesser in the ponesimod 20 mg vs teriflunomide 14 mg group: LS mean percent change from baseline to week 108 in brain volume, −0.91% in the ponesimod 20 mg group (n=436) and −1.25% in the teriflunomide 14 mg group (n=434)*
- The LS mean difference (ponesimod 20 mg − teriflunomide 14 mg) was 0.34% (95% CLs: 0.17, 0.50; p<0.0001) at week 108

*Using mixed model with linear time effect (adjusted for stratification factors, presence/absence of GD+ T1 lesions at baseline, and normalized brain volume at baseline)
LS mean, least square mean; CL, confidence limit; N, total number of patients; n, number of patients with available data

Change in total T2 lesion volume from baseline to week 108, mean numbers of new or enlarging T2 lesions per year and absence of new or enlarging T2 lesions

	Ponesimod 20 mg (N=567)	Teriflunomide 14 mg (N=566)	Ponesimod 20 mg – Teriflunomide 14 mg
Change in total T2 lesion volume (mm^3) at week 108			
	n=518*	n=518*	
LS mean†	−736.3	−337.2	**−399.2**
95% CL (p-value)	−914.5; −558.1	−515.4; −158.9	**−651.5; −146.8 (p=0.002)**
Number of new/enlarging T2 lesions up to week 108			
	n=539**	n=536**	
Cumulative lesions/time (years)	1669/1072	3704/1067	
Mean estimate (lesions per year)‡ (95% CL)	1.40 (1.21; 1.62)	3.16 (2.75; 3.62)	
Treatment effect (rate ratio)	**0.44**		
95% C (p-value)	**0.36; 0.54 (p<0.0001)**		
T2 lesions up to week 108			
	n=523***	n=518***	
Absent, n (%)	222 (42)	154 (30)	**OR (PON vs TER)**
Estimate (mean %)ʕ	39.5	27.7	**1.71**
95% CL (p-value)	35.1; 44.2	23.8; 32.0	**1.30; 2.25 (p=0.0001)**

*Includes patients with available result at week 108; **Patients with baseline and ≥1 post-baseline MRI are included in the analysis; ***From baseline to week 108 for patients with available result at week 108; †Obtained by using a repeated measurements ANOVA model (MMRM; adjusted for stratification factors, presence/absence of Gd+T1 lesions at baseline, as well as T2 lesion volume at baseline; ‡Obtained by fitting a negative binomial regression model (adjusted for stratification factors and presence of Gd+T1 lesions at baseline; ÇObtained by using logistic regression model (adjusted for stratification factors and presence of Gd+T1 lesions at baseline). CL, confidence limit; Gd+T1, T1-weighted gadolinium-enhanced; LS mean, least square mean; N, total number of patients; n, number of patients with available data; OR, odds ratio; PON, ponesimod; TER, teriflunomide

- Total T2 lesion volume showed greater decrease in the ponesimod 20 mg vs teriflunomide 14 mg group.
- The mean number of new/enlarging T2 lesions per year was lower in the ponesimod 20 mg vs teriflunomide 14 mg group.
- A higher percentage of patients in the ponesimod 20 mg vs teriflunomide 14 mg group were new/enlarging T2 lesion-free at week 108.

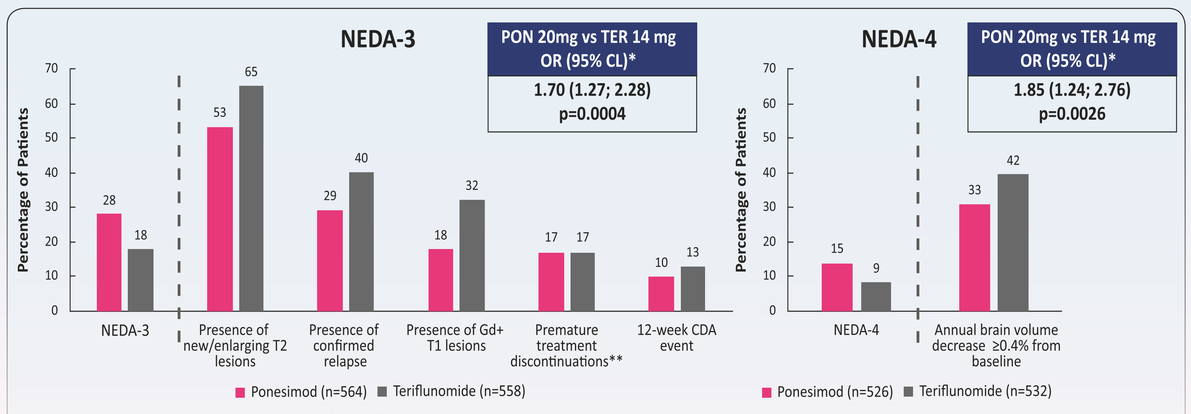
Mean numbers of new Gd+T1 lesions per scan and absence of new Gd+T1 lesions

	Ponesimod 20 mg (N=567)	Teriflunomide 14 mg (N=566)	Ponesimod 20 mg – Teriflunomide 14 mg
Number of new Gd+T1 lesions up to week 108			
	n=540*	n=538*	
Cumulative lesions/scans	240/1054	584/1050	
Mean estimate (lesions per scan)† (95% CL)	0.18 (0.14; 0.22)	0.43 (0.35; 0.52)	
Treatment effect (rate ratio)	**0.42**		
95% CL (p-value)	**0.31; 0.56 (p<0.0001)**		
Gd+T1 lesions at week 108			
	n=508**	n=510**	
Absent, n (%)	406 (80)	332 (65)	**OR (PON vs TER)**
Estimate (mean %)‡	82.4	68.3	**2.18**
95% CL (p-value)	78.7; 85.6	63.8; 72.5	**1.61; 2.95 (p<0.0001)**

*Patients with baseline and at least one post-baseline MRI are included in the analysis; **Only includes patients with available result at week 108; †Obtained by fitting a negative binomial regression model (adjusted for stratification factors and presence of Gd+T1 lesions at baseline); ‡Obtained by using a logistic regression model (adjusted for stratification factors and presence of Gd+ T1 lesions at baseline). CL, confidence limit; Gd+T1, T1-weighted gadolinium-enhanced; LS mean, least square mean; N, total number of patients; n, number of patients with available data; OR, odds ratio; PON, ponesimod; TER, teriflunomide

- The mean number of new Gd+T1 lesions per scan was lower in the ponesimod 20 mg vs teriflunomide 14 mg group.
- A higher percentage of patients in the ponesimod 20 mg vs teriflunomide 14 mg group were new Gd+T1 lesion-free at week 108.

NEDA-3 and NEDA-4 status at week 108



*Obtained using a logistic regression model (adjusted for stratification factors and presence of Gd+ T1 lesions at baseline); **A patient was not considered to have achieved NEDA-3/NEDA-4 if ≥1 criteria was not fulfilled or if the patient prematurely discontinued the study; Patients with missing information were excluded from the analysis. CL, confidence limit; Gd+T1, T1-weighted gadolinium-enhanced ; n, number of patients included in the analysis; NEDA, no evidence of disease activity; OR, odds ratio; PON, ponesimod; TER, teriflunomide

- At week 108, a higher percentage of patients in the ponesimod vs teriflunomide group achieved NEDA-3 and NEDA-4 status
  - NEDA-3: ponesimod-20 mg, 28%; teriflunomide-14 mg, 18%
  - NEDA-4: ponesimod-20 mg, 15%; teriflunomide-14 mg, 9%

CONCLUSIONS

- **Results for focal MRI activity showed superior efficacy for ponesimod 20 mg vs teriflunomide 14 mg in patients with RMS.**
- **Ponesimod 20 mg was superior to teriflunomide 14 mg in preventing brain atrophy.**
- **A higher proportion of patients on ponesimod 20 mg achieved NEDA-3 and NEDA-4 status as compared with patients on teriflunomide 14 mg.**

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1. D'Ambrosio D et al. Ther Adv Chronic Dis. 2016;7(1):18-33; 2. Olsson T et al. J Neurol Neurosurg Psychiatry. 2014;85(11):1198-208; 3. Banwell B et al. Mult Scler Relat Disord. 2013;2(2):65-7

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