Long-term efficacy and safety of ponesimod: Results from randomized phase II core and extension studies in relapsing-remitting multiple sclerosis

Mark S. Freedman[1], Carlo Pozzilli[2], Eva Kubala Havrdova[3], Patricia K. Coyle[4], Alexandre Lemle[5], Michel Burcklen[5], Anna Larbalestier[5], Brian Hennessy[5], Tatiana Scherz[5], Andrea Vaclavkova[5], Tomas Olsson[6]

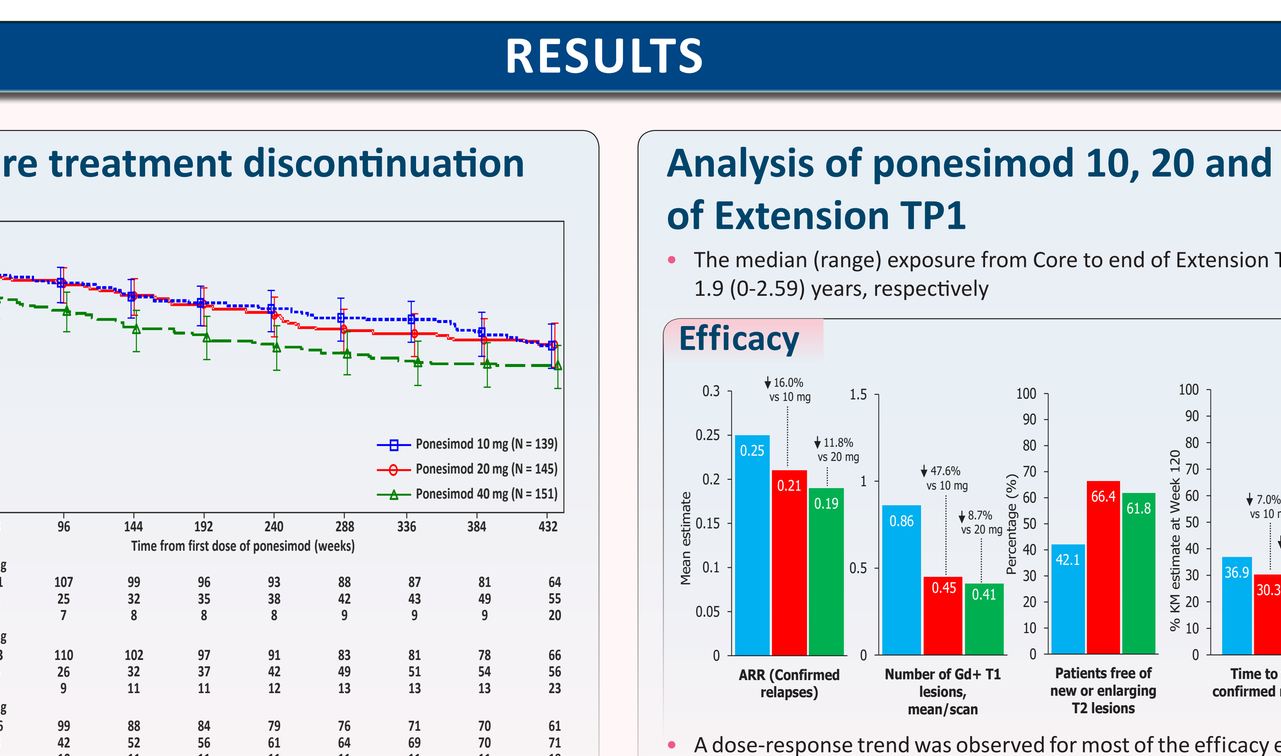
[1]Multiple Sclerosis Research Unit, The University of Ottawa and The Ottawa Hospital Research Institute, Ottawa, Ontario, Canada; [2]Sapienza University of Rome, Rome, Italy; [3]First Medical Faculty, Charles University, Prague, Czech Republic; [4]Stony Brook University Medical Center, Stony Brook, NY, USA; [5]Actelion Pharmaceuticals Ltd, Part of Janssen Pharmaceutical Companies of Johnson & Johnson, Allschwil, Switzerland; [6]Karolinska Institute, Stockholm, Sweden

BACKGROUND

- Ponesimod is an orally active, selective $S1P_1$ modulator that induces rapid, dose-dependent, and reversible reductions in peripheral blood lymphocyte count by preventing the lymphocyte egress from lymphoid organs.[1]
- In a 24-week multicenter, double-blind phase IIb (Core) study (NCT01006265) in patients with relapsing remitting multiple sclerosis (RRMS), once daily ponesimod at 10, 20 and 40 mg significantly and dose-dependently reduced inflammatory MRI activity vs placebo.[2]
- Patients completing the Core study were offered enrollment into the currently ongoing double-blind long-term Extension study (NCT01093326).
- We report the results of the combined data from the Core and Extension studies that led to dose-selection during the course of the study, and long-term (up to approximately 9 years) safety and efficacy results of the continuous ponesimod 20 mg in patients with RRMS.

METHODS

Study design and patient flow



*Patients who discontinued/completed during Core or TP1 had EOT visit and follow-up visits at 8 and 30 days after the last study drug intake; **Patients who discontinued/completed during TP2 or TP3 had EOT visit and follow-up visits at 8, 30 and 90 days after the last study drug intake; Placebo period was excluded from the analysis. Patients were grouped according to their first randomized ponesimod dose (10/20/40 mg). n is the number of patients randomized in each period. EDSS, Expanded Disability Status Scale; EOT, end of treatment; TP, treatment period; RRMS, relapsing remitting multiple sclerosis

Endpoints

Efficacy

- Annualized relapse rate (ARR)
- Time to first confirmed relapse
- Number of total T1 Gd+ lesions and percentage of patients free of new or enlarging T2 lesions
- Time to 6-month confirmed disability accumulation (CDA)

Safety

- Treatment-emergent adverse events, clinical laboratory tests, 12-lead ECGs, systolic and diastolic blood pressure, and pulmonary function tests

Analyses

- The data presented here cover the entire ponesimod treatment period of Core and Extension studies, including a total of 435 patients who received at least one dose of ponesimod at any time during the studies (Ponesimod Analysis Set).
- Placebo period in the Core study was excluded.
- The cutoff date for the combined analysis: 31 March 2019 (up to 9 years of total study treatment).

RESULTS

Patient disposition and premature treatment discontinuation

	Ponesimod 10 mg	Ponesimod 20 mg	Ponesimod 40 mg	Total
Randomized and treated with ponesimod at any time*, n	139	145	151	435
Completed treatment at any time*	9 (6.5)	13 (9.0)	11 (7.3)	33 (7.6)
Treatment ongoing	73 (52.5)	75 (51.7)	66 (43.7)	214 (49.2)
Interrupted treatment for planned pregnancy	-	-	2 (1.3)	2 (0.5)
Prematurely discontinued treatment at any time*	57 (41.0)	57 (39.3)	72 (47.7)	186 (42.8)

Data are presented as n (%) unless otherwise noted

Placebo period was excluded from the analysis. Patients were grouped according to their first randomized ponesimod dose (10/20/40 mg); *At any time during the core or extension studies; TP, treatment period.

- A higher rate of premature treatment discontinuation was observed in the 40 mg group than in the 20 mg and 10 mg groups.
- Treatment was ongoing in 214 (49%) patients as of 31 March 2019.

Analysis of ponesimod 10, 20 and 40 mg: from Core up to end of Extension TP1

- The median (range) exposure from Core to end of Extension TP1 in 10, 20 and 40 mg was 2.0 (0-2.57), 2.1 (0-2.76), and 1.9 (0-2.59) years, respectively

Efficacy

Safety

Parameter, n (%)	Ponesimod 10 mg (N=139)	Ponesimod 20 mg (N=145)	Ponesimod 40 mg (N=151)
Patients with ≥1 TEAE	125 (89.9)	126 (86.9)	140 (92.7)
Patients with ≥1 serious TEAE	14 (10.1)	15 (10.3)	7 (4.6)
Patients with ≥1 TEAE leading to treatment discontinuation	17 (12.2)	12 (8.3)	27 (17.9)
Death	0	0	0

The most frequently reported TEAEs (≥10% of patients in any group): nasopharyngitis, headache, URTI, ALT increased, influenza, dyspnea, cough, and peripheral edema

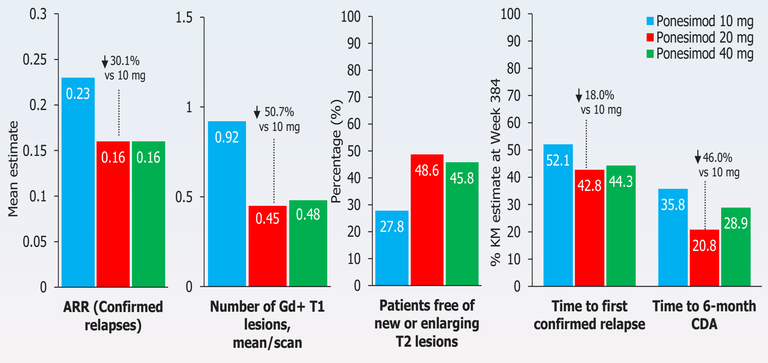
- A dose-response trend was observed for most of the efficacy endpoints, suggesting an increased benefit with the 20 and 40 mg doses vs the 10 mg dose. However, ponesimod 40 mg dose was associated with reduced tolerability compared with the lower doses.
- The overall benefit/risk profile of 20 mg dose was favorable compared to 40 mg, which supported the decision to stop the development of 40 mg dose and re-randomize patients receiving 40 mg dose to 10 mg or 20 mg at the entry of TP2.

ALT, alanine aminotransferase; ARR, annualized response rate; CDA, confirmed disability accumulation; T1 Gd+, T1-weighted gadolinium-enhanced; TEAEs, treatment-emergent adverse events; TP, treatment period; URTI, upper respiratory tract infection; UTI, urinary tract infection. Placebo period was excluded from the analysis. Patients were grouped according to their first randomized ponesimod dose (10/20/40 mg).

Benefit-risk analysis of ponesimod 10 and 20 mg: from Core up to end of Extension TP2

- The median (range) exposure from Core to end of Extension TP2 in 10 and 20 mg was 6.9 (0-8.12) and 6.7 (0-8.07) years, respectively

Efficacy



Safety

Parameter, n (%)	Ponesimod 10 mg (N=139)	Ponesimod 20 mg (N=145)	Ponesimod 40 mg (N=151)
Patients with ≥1 TEAE	132 (95.0)	132 (91.0)	146 (96.7)
Patients with ≥1 serious TEAE	23 (16.5)	23 (15.9)	20 (13.2)
Patients with ≥1 TEAE leading to treatment discontinuation	19 (13.7)	15 (10.3)	34 (22.5)
Death	0	1 (0.7)*	0

The most common TEAEs (≥10% of patients) in the 10 or 20 mg groups: nasopharyngitis, headache, URTI, bronchitis, back pain, UTI, fatigue, ALT increased, influenza, dizziness, and rhinitis.

*A 52-year old male with multiple CV risk factors experienced MACE (sudden cardiac death), approximately 6 years after the first dose of ponesimod.

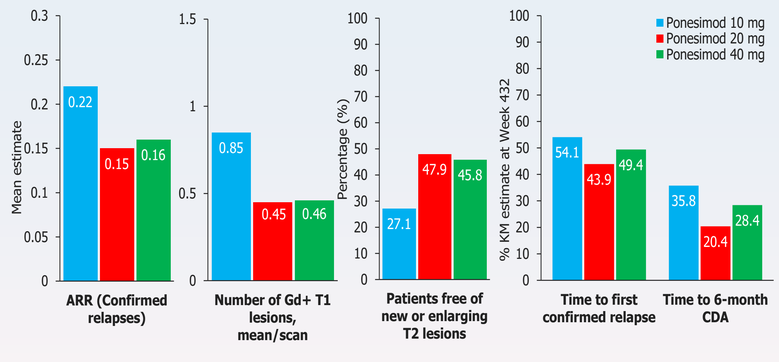
- Ponesimod 20 mg demonstrated improved efficacy compared with 10 mg with a similar safety and tolerability profile.
- These findings supported the decision to discontinue the 10 mg dose and switch these patients to 20 mg at entry in TP3.

ALT, alanine aminotransferase; ARR, annualized response rate; CDA, confirmed disability accumulation; CV, cardiovascular; MACE, major cardiac adverse event; T1 Gd+, T1-weighted gadolinium-enhanced; TEAEs, treatment-emergent adverse events; TP, treatment period; URTI, upper respiratory tract infection; UTI, urinary tract infection. Placebo period was excluded from the analysis. Patients were grouped according to their first randomized ponesimod dose (10/20/40 mg).

Long-term efficacy of ponesimod 20 mg: from Core up to end of Extension TP3

- The cumulative exposure across all doses was 2372.5 patient-years and the median (range) exposure in the 20 mg group was 8.0 (0-9.4) years

Efficacy



Safety

Parameter, n (%)	Ponesimod 10 mg (N=139)	Ponesimod 20 mg (N=145)	Ponesimod 40 mg (N=151)	Total (n=435)
Patients with ≥1 TEAE	132 (95.0)	132 (91.0)	148 (98.0)	412 (94.7)
Patients with ≥1 serious TEAE	27 (19.4)	27 (18.6)	23 (15.2)	77 (17.7)
Patients with ≥1 TEAE leading to treatment discontinuation	20 (14.4)	16 (11.0)	34 (22.5)	70 (16.1)
Death	0	1 (0.7)	0	1 (0.2)

The most common TEAEs (≥10% of patients) in total ponesimod group: nasopharyngitis, headache, URTI, bronchitis, back pain, UTI, ALT increased, fatigue, influenza, cough, dizziness, and dyspnea.

- The effects on MS disease control were maintained with ponesimod 20 mg over the long-term treatment period up to 9 years
- The overall pattern of TEAEs or serious TEAEs with long-term ponesimod treatment was comparable to that reported in the Core study

ALT, alanine aminotransferase; ARR, annualized response rate; CDA, confirmed disability accumulation; T1 Gd+, T1-weighted gadolinium-enhanced; TP, treatment period; URTI, upper respiratory tract infection; UTI, urinary tract infection; Placebo period was excluded from the analysis. Patients were grouped according to their first randomized ponesimod dose (10/20/40 mg).

CONCLUSIONS

- **Results of this study support the choice of ponesimod 20 mg as a treatment in RMS.**
- **The results observed in the clinical and MRI parameters suggest that the effects on MS disease control could be maintained with ponesimod 20 mg for up to 9 years.**
- **No new safety concerns were identified with ponesimod 20 mg treatment during the combined study periods.**
- **With sustained benefits on disease activity for those patients staying on medication, along with a favorable safety profile over a long-term period, ponesimod 20 mg dose was considered for further evaluation in patients with RMS.**

References: 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

Disclosures

Mark S. Freedman: Honoraria or consulting fees: Actelion, Bayer HealthCare, Biogen, Chugai, EMD Canada, Genzyme, Hoffmann-La Roche, Merck Serono, Novartis, Sanofi-Aventis, and Teva Canada Innovation; **Advisory role:** Actelion, Bayer HealthCare, Biogen, Hoffmann-La Roche, Merck Serono, Novartis, Opexa, and Sanofi-Aventis; **Speaker's bureau:** Genzyme
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