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Analysis of post-treatment relapse activity in the phase 3 OPTIMUM study of ponesimod compared with teriflunomide

Ludwig Kappos[1], Robert J. Fox[2], Michel Burcklen[3], Mark S Freedman[4], Brian Hennessy[3], Antoine Stos[3], Philippe Linscheid[3], Andrea Vaclavkova[3], Hilke Kracker[3], Tatiana Sidorenko[3], Carlo Pozzilli[5]

[1]Neurology and Research Center for Clinical Neuroimmunology and Neuroscience Basel, Departments of Clinical Research, Biomedicine and Biomedical Engineering University Hospital and University of Basel, Basel, Switzerland; [2]Cleveland Clinic, Cleveland, OH, USA; [3]Actelion Pharmaceuticals, Part of Janssen Pharmaceutical Companies, Allschwil, Switzerland; [4]University of Ottawa, Department of Medicine and The Ottawa Hospital Research Institute, Ottawa, ON, Canada; [5]S. Andrea MS Centre, Sapienza University of Rome, Rome, Italy

BACKGROUND

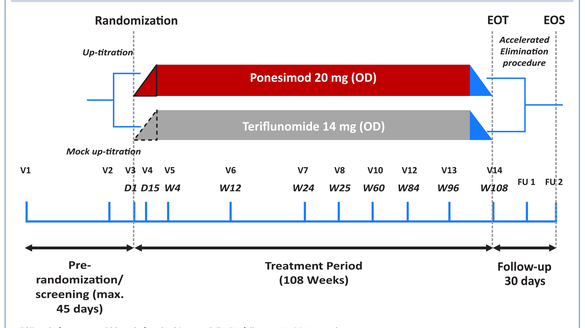
- Ponesimod is an orally active, selective S1P1 modulator that induces rapid, dose-dependent, and reversible reductions in peripheral blood lymphocyte count by preventing lymphocyte egress from lymphoid organs[1]
- In the phase 3 OPTIMUM study (NCT02425644), ponesimod 20 mg demonstrated superior efficacy vs teriflunomide 14 mg in reducing annualized relapse rate in patients with relapsing multiple sclerosis (RMS)[2]
- Cases of exacerbation of MS disease activity have been reported after discontinuation of S1P-receptor modulators[3,4]
- The assessment of the relapse rate of patients post disease modifying therapy discontinuation, will provide insight into the potential implications of treatment interruptions or "wash out" before switching to other treatments, critical to both MS patients and their health care providers

We report on post-treatment relapse activity in the OPTIMUM study of ponesimod in patients with RMS

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
- Patients (18-55 years) were randomized 1:1 to ponesimod (20 mg) or teriflunomide (14 mg) for 108 weeks
- All patients who completed treatment (108 weeks), regardless of treatment group, underwent a treatment interruption of at least 2 weeks and accelerated elimination procedure for teriflunomide
- Patients who stopped treatment prematurely or after completing the treatment period entered safety follow-up (at least 30 days after the last dose) and a post-treatment observation period (from last dose up to 108 weeks after randomization)
- Patients included in the present analysis had an observation period from one day up to 182 days after end of treatment

Figure 1. Study Design



EOT, end of treatment; EOS, end of study; OD, once daily; FU, follow-up; V, visit; W, week

RESULTS

Table 1. Demographics and baseline characteristics

Full Analysis Set	Ponesimod 20 mg N=567	Teriflunomide 14 mg N=566
Females, n (%)	363 (64.0)	372 (65.7)
Age, years, mean (SD)	36.7 (8.74)	36.8 (8.74)
Race – white, n (%)	551 (97.2)	553 (97.7)
Baseline EDSS (strata) >3.5, n (%)	94 (16.6)	95 (16.8)
DMT within 2 years prior to randomization (strata) – Yes, n (%)	224 (39.5)	223 (39.4)
Baseline EDSS score, mean (SD)	2.57 (1.17)	2.56 (1.23)
Time since first symptom at randomization , years, mean (SD)	7.63 (6.78)	7.65 (6.78)
Number of relapses in last year prior study entry, mean (SD)	1.2 (0.61)	1.3 (0.65)
Presence of Gd+ T1 lesions* at baseline, n (%)	226 (39.9)	256 (45.4)

*from the central reader

DMT, MS disease-modifying treatment; EDSS, Expanded Disability Status Scale; Gd+, Gadolinium-enhancing

- A total of 1124 (of the 1133 randomized) patients had post-treatment observation in the OPTIMUM study (ponesimod: 559; teriflunomide: 565)
- Of the 1124 patients, 8 ponesimod and 14 teriflunomide patients experienced 23 post-treatment relapses within 182 days of last dosage of study drug
- Available post-treatment follow-up during this period was similar for both treatment arms

Figure 2. Patient flow

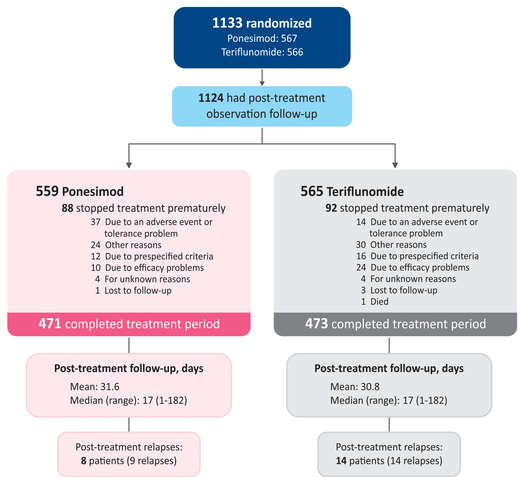
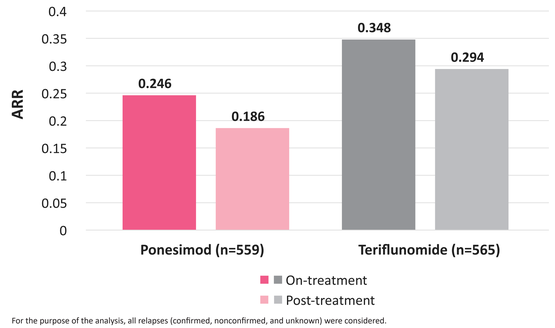


Figure 3. Annualized relapse rate (ARR*) including nonconfirmed relapses

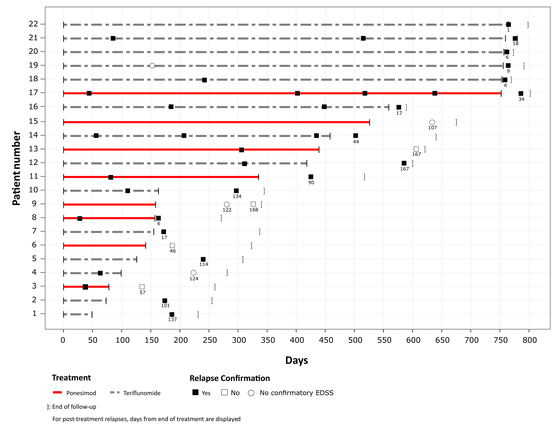


For the purpose of the analysis, all relapses (confirmed, nonconfirmed, and unknown) were considered.

*Annualized Relapse Rate (ARR) is defined as the total number of relapses during the observation period up to 182 days divided by the length of observation expressed in years

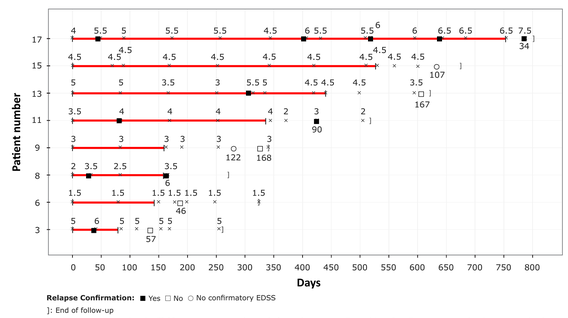
- The post-treatment ARR did not exceed the on-treatment ARR for ponesimod
- These findings are consistent with main study results up to end of study

Figure 4. Post-treatment relapse within 182 days from end of treatment



- On-treatment relapses (8 confirmed) in 5 ponesimod patients
- Post-treatment relapses in 8 ponesimod patients (3 confirmed, 4 nonconfirmed, 2 unknown) occurred between 6 and 168 days without any pattern of latency or severity

Figure 5. EDSS scores over time for ponesimod patients with post-treatment relapses



Relapse Confirmation: ■ Yes □ No ○ No confirmatory EDSS

]: End of follow-up

Numbers are representing the EDSS assessment over the study for each corresponding subject. Baseline assessment has been set to day 0

- Three patients with an EDSS score increase of 1.0 during relapse compared with pre relapse (patient number 8, 11 and 17)
- Four patients with no increase in EDSS score post relapse compared with pre relapse (patient number 3, 6, 9 and 13*)
- One patient with no EDSS score during or post relapse (patient number 15)

*Patient number 13 had an EDSS score of 3.5, which was not included in this analysis (day 231 post end of treatment)

CONCLUSIONS

- **In this post hoc analysis of the OPTIMUM study, the prospectively obtained short-term post-treatment observation data in patients who stopped ponesimod treatment, did not support increased early post-treatment relapse frequency as compared to that on-treatment or to the comparator**
- **There is no data to indicate that post-treatment relapses were unusually severe or leading to persistent disability**
- **There was no clear pattern of disease reactivation beyond return of disease activity in some patients post ponesimod discontinuation**

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