DMT09

Ponesimod demonstrated increased clinical benefit over teriflunomide in early disease subgroup compared with overall population

Allitia DiBernardo[1], Ibrahim Turkoz[2], Michael Kutch[2], Maria Ait-Tihyaty[1]

[1]Global Medical Affairs– Janssen Research & Development, LLC, Titusville, NJ; [2]Clinical Biostatistics – Janssen Research & Development, LLC, Titusville, NJ

BACKGROUND

- OPTIMUM, a phase III, randomized, double-blind study,[1] demonstrated superiority of ponesimod over teriflunomide:
  - Ponesimod reduced annualized relapse rate (ARR) by 30.5% vs. teriflunomide, rate ratio (RR): 0.695 [99% CLs: 0.536, 0.902]
  - Ponesimod reduced the mean number of combined unique active lesions (CUALs) per year on annual brain MRIs from baseline to week 108 by 56% vs. teriflunomide, RR: 0.444 [95% CLs: 0.364, 0.542]
  - The change in Fatigue Symptom and Impact Questionnaire–Relapsing Multiple Sclerosis (FSIQ–RMS) weekly symptom score from baseline to week 108 was significantly lower for fatigue symptoms in the ponesimod group than the teriflunomide group; a decrease from baseline represents improvement in fatigue symptoms, mean difference: -3.57 [95% CLs: -5.83, -1.32]
- It is well established that early treatment in multiple sclerosis (MS) with higher-potency therapies improve long-term outcomes.
- Subgroup analyses of the OPTIMUM study were performed to test whether a patient population with early disease has a differential benefit with ponesimod compared with teriflunomide.

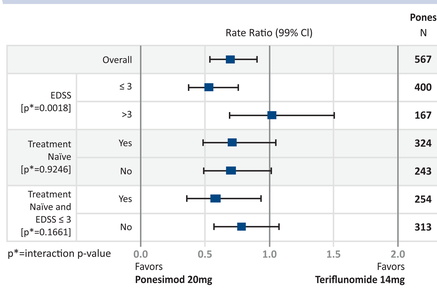
METHODS

- The study design and treatment details of the OPTIMUM study have been published previously.[1]
- In the OPTIMUM study, baseline Expanded Disability Status Scale (EDSS) scores were between 0-5.5
- This subgroup analysis examined patients with EDSS ≤3 (up to moderate disability in one function, or mild disability in three or four functions; no impairment to walking), and/or who were treatment naïve.
- Treatment differences on ARR, CUALs and MS-fatigue in these subgroups were compared with the overall population.
- All statistical analyses were performed on all participants who were randomized.
- ARR differences and mean number of CUALs were examined using a negative binomial regression model with adjusting for the log time in the study (in years) as an offset.
- Changes in FSIQ-RMS scores were examined using mixed effect model repeated measures models with baseline score as a covariate.
- Interaction terms with subgroups were also added to test if the observed treatment differences differed within each subgroup.

RESULTS

- Of 1468 patients screened, 1133 were randomized (ponesimod, n = 567; teriflunomide, n = 566) and were included in the analysis.

Figure 1. Annualized relapse rate (ARR)



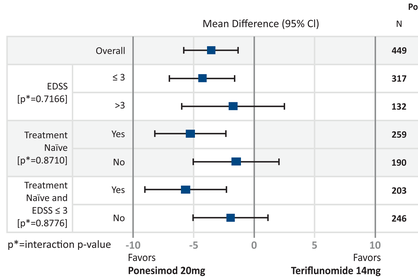
		Ponesimod 20mg N	Ponesimod 20mg Mean Rate	Teriflunomide 14mg N	Teriflunomide 14mg Mean Rate	Rate Ratio (99% CI)	P-value
Overall		567	0.202	566	0.290	**0.695** (0.536, 0.902)	**0.0003**
EDSS [p*=0.0018]	≤ 3	400	0.143	391	0.271	**0.530** (0.372, 0.755)	**<0.0001**
	>3	167	0.404	175	0.396	**1.020** (0.692, 1.505)	**0.8943**
Treatment Naïve [p*=0.9246]	Yes	324	0.189	321	0.265	**0.714** (0.486, 1.049)	**0.0241**
	No	243	0.260	245	0.369	**0.703** (0.488, 1.014)	**0.0133**
Treatment Naïve and EDSS ≤ 3 [p*=0.1661]	Yes	254	0.137	241	0.236	**0.580** (0.361, 0.933)	**0.0032**
	No	313	0.286	325	0.365	**0.785** (0.572, 1.076)	**0.0481**

p*=interaction p-value

Overall model only: Negative binomial model with Wald confidence intervals, offset: log time (years) up to end of study (EOS), covariates: EDSS strata, MS disease modifying therapy (DMT) within last 2 years prior to randomization strata, and number of relapses in year prior to study entry. Subgroup models did not include covariate adjustments.

In the EDSS ≤3 subgroup, ponesimod treatment reduced ARR by 47%, RR= 0.530 [99% CLs: 0.372, 0.755]

Figure 2. Fatigue Symptoms and Impacts Questionnaire – Relapsing Multiple Sclerosis (FSIQ-RMS)



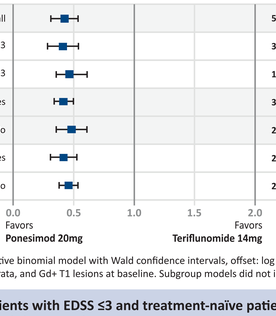
		Ponesimod 20mg N	Ponesimod 20mg LSMean (95% CI)	Teriflunomide 14mg N	Teriflunomide 14mg LSMean (95% CI)	Mean Difference (95% CI)	P-value
Overall		449	**0.0** (-1.60, 1.58)	458	**3.6** (1.96, 5.16)	**-3.57** (-5.83,-1.32)	**0.0019**
EDSS [p*=0.7166]	≤ 3	317	**-0.2** (-2.05, 1.68)	310	**4.1** (2.21, 6.04)	**-4.31** (-6.99,-1.63)	**0.0017**
	>3	132	**0.5** (-2.53, 3.61)	148	**2.3** (-0.62, 5.21)	**-1.75** (-5.98,2.48)	**0.4157**
Treatment Naïve [p*=0.8710]	Yes	259	**-1.1** (-3.23, 0.94)	264	**4.2** (2.08, 6.23)	**-5.30** (-8.25,-2.35)	**0.0004**
	No	190	**1.3** (-1.15, 3.82)	194	**2.9** (0.33, 5.37)	**-1.51** (-5.05,2.02)	**0.4008**
Treatment Naïve and EDSS ≤ 3 [p*=0.8776]	Yes	203	**-0.6** (-2.97, 1.70)	193	**5.0** (2.63, 7.46)	**-5.68** (-9.05,-2.31)	**0.0010**
	No	246	**0.5** (-1.73, 2.67)	265	**2.4** (0.29, 4.59)	**-1.97** (-5.05,1.10)	**0.2082**

p*=interaction p-value

Overall model only: Negative binomial model with Wald confidence intervals, offset: log time (years) up to end of study (EOS), covariates: EDSS strata, MS disease modifying therapy (DMT) within last 2 years prior to randomization strata, and number of relapses in year prior to study entry. Subgroup models did not include covariate adjustments.

- **Change from baseline to week 108 in the MS-fatigue was statistically significantly lower in the ponesimod group compared with the teriflunomide group for the EDSS ≤3 subgroup (mean difference: −4.31 [95% CLs: −6.99, −1.63]; an increase from baseline indicates worsening in fatigue symptoms**
- **Changes in MS-fatigue in treatment-naïve patients were further increased in favor of ponesimod, with mean difference of -5.30 [95% CLs: -8.25, -2.35]**

Figure 3. Combined Unique Active Lesions (CUALs)



		Ponesimod 20mg N	Ponesimod 20mg Mean Rate	Teriflunomide 14mg N	Teriflunomide 14mg Mean Rate	Rate Ratio (95% CI)	P-value
Overall		539	1.405	536	3.164	**0.444** (0.364, 0.542)	**<.0001**
EDSS [p*=0.6206]	≤ 3	384	1.695	374	3.999	**0.424** (0.329, 0.546)	**<.0001**
	>3	155	1.753	162	3.663	**0.478** (0.318, 0.721)	**0.0004**
Treatment Naïve [p*=0.4713]	Yes	315	1.718	306	4.179	**0.411** (0.310, 0.545)	**<.0001**
	No	224	1.705	230	3.532	**0.483** (0.346, 0.673)	**<.0001**
Treatment Naïve and EDSS ≤ 3 [p*=0.6108]	Yes	247	1.815	231	4.402	**0.412** (0.298, 0.570)	**<.0001**
	No	292	1.628	305	3.529	**0.461** (0.346, 0.615)	**<.0001**

p*=interaction p-value

Overall model only: Negative binomial model with Wald confidence intervals, offset: log time (years) up to last MRI scan, covariates: EDSS strata, MS DMT within last 2 years prior to randomization strata, and Gd+ T1 lesions at baseline. Subgroup models did not include covariate adjustments.

As for CUAL, patients with EDSS ≤3 and treatment-naïve patients benefited from ponesimod compared with teriflunomide, and these results were consistent with the overall population.

CONCLUSIONS

- **Ponesimod demonstrated increased clinical benefit as compared with teriflunomide in early disease subgroups and compared with the overall population.**
- **This subgroup analysis confirms the advantage of using ponesimod as an early high efficacy treatment.**

References

1. Kappos L et al. JAMA Neurol. 2021;78(5):558–567.

Disclosure

All authors are employees or contractors of Janssen Research & Development, LLC and may hold stock in Johnson & Johnson, Inc.

Acknowledgements

- The authors would like to thank all investigators, study site staff, patients and their families, caregivers, and supporters, without whom this study would have not been feasible.
- The authors would also like to CROSNT, KVS and Janssen internal medical writing Team for their help with this analysis and presentation.

Funded by Janssen Research & Development, LLC

Poster presented at CMSC Annual Meeting 2022, June 01-04, National Harbor, MD