Comparative Efficacy of Relapsing Multiple Sclerosis Therapies: A Model-Based Meta-Analysis for Annualized Relapse Rate

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BACKGROUND

- Multiple sclerosis (MS), an inflammatory autoimmune disorder, is responsible for progressive neurological disability among young adults. The key objectives in the management of MS are reducing the rate of relapses and preventing, or at least delaying, disease progression.[1]
- Ponesimod, an orally administered highly selective sphingosine-1-phosphate receptor 1 (S1PR1) immunomodulator was investigated for its efficacy and safety in the pivotal Phase 3 study AC-058B301 (OPTIMUM) as compared with teriflunomide 14 mg.
- This model-based meta-analysis (MBMA) was pre-planned to estimate the efficacy of Ponesimod 20 mg for the prevention of annualized relapse rate (ARR) as compared with placebo.
- We aimed to assess the effect of Ponesimod 20 mg vs. placebo on ARR and relative to other disease modifying treatments (DMTs) for treatment of RMS.

METHODS

Multiple Sclerosis Database Development

Certara Inc. developed a database consisting of results from 154 unique clinical trials and 411 treatment arms in MS subjects involving 58 different drugs.

The following criteria were used for the selection of trials from the database:

- Randomized controlled trials (RCTs) with at least 25 subjects per treatment arm
- Trials including patients with relapsing forms of MS.
- Trials including patients receiving monotherapy (add-on studies were excluded)
- Treatment duration was at least 48 weeks for all trials

Annualized Relapse Rate

- Annualized relapse rate (ARR) data were modeled in the log-transformed domain, with the assumption that the rate ratio (RR) for ARR for a specific drug vs. placebo is constant across trials, according to the general model:

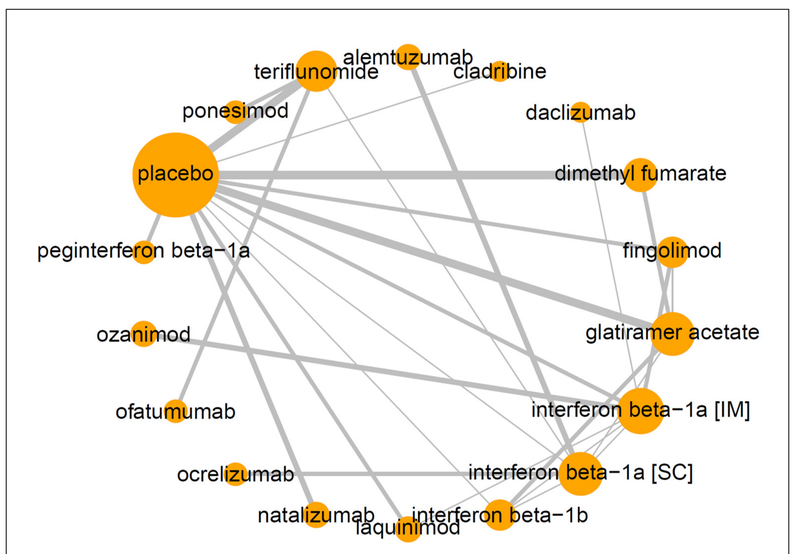
$$ARR_{ij} = log^{-1}\left(pbo.eff_i + drg.eff_d(dose_{ijd}, \theta_{ij})\right) + \widehat{SE}_{ij} \cdot \varepsilon_{ij}$$

for the i^{th} trial, j^{th} arm, and d^{th} drug; θ is a covariate on drg.eff; $\widehat{SE}$ is the derived standard error for ARR; and $\varepsilon \sim N(0,1)$

- Arm-level variables explored as effect modifiers included: proportion of patients with RRMS, patients receiving DMT within past 2 years, trial start year, mean duration of disease, relapses in prior year, mean age, and mean baseline expanded disability status scale (EDSS) score.
- 10,000 sets of drug effect model parameters were randomly sampled with uncertainty to estimate confidence intervals for ARR RR (i.e., exp[drg.eff$_d$]) for each drug, including Ponesimod 20 mg, vs. placebo.

RESULT

Analysis Dataset Summary



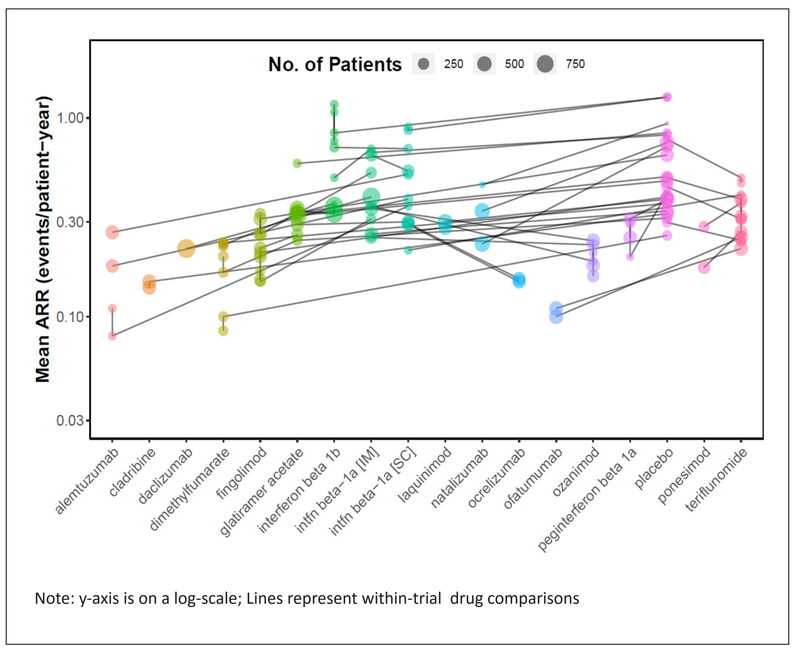
Note: Larger symbols represent more trials assessing that drug, thicker lines represent more trials directly comparing those drugs.

RCT: randomized controlled trials; ARR: annualized relapse rate

- The database used for analysis contained 41 RCTs (106 treatment arms) reporting mean (or median) ARR

No. of Trials	**41**
No. of Arms	106
No. of Datapoints	106
No. of Subjects	33,904

Data summary: Mean ARR by drug used in trial network



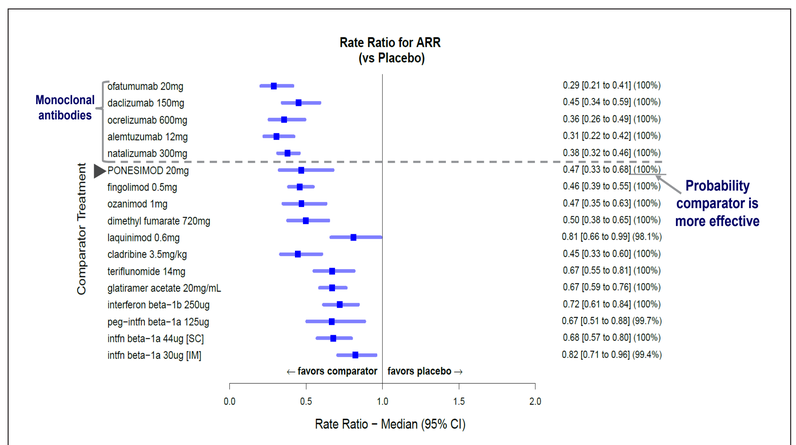
Note: y-axis is on a log-scale; Lines represent within-trial drug comparisons

Included covariates and dose-response estimates

Covariate Parameter	Estimate	95% CI
% patients with prior DMT [% change in log(RR) per unit ↑ in % with prior DMT]	0.21%*	[-0.03%, 0.45%]
Linear Dose-Response on log(RR) [additive change in log(RR) for 2x dose]		
Interferon β-1a [SC]	-0.083	[-0.49, 0.33]
Peginterferon β-1a	-0.24	[-0.89, 0.41]
Interferon β-1b	-0.19	[-0.36, -0.031]
Teriflunomide	-0.26	[-0.67, 0.14]
Dimethyl fumarate	-0.052	[-0.97, 0.87]
Ozanimod	-0.50	[-1.06, 0.062]
Fingolimod	-0.033	[-0.17, 0.10]
Alemtuzumab	-0.55	[-1.28, 0.18]

* Translates to ~15% ↓ in RR vs. placebo for DMT naïve vs. experienced population (e.g., 44% vs. 52% RR for ponesimod 20 mg)

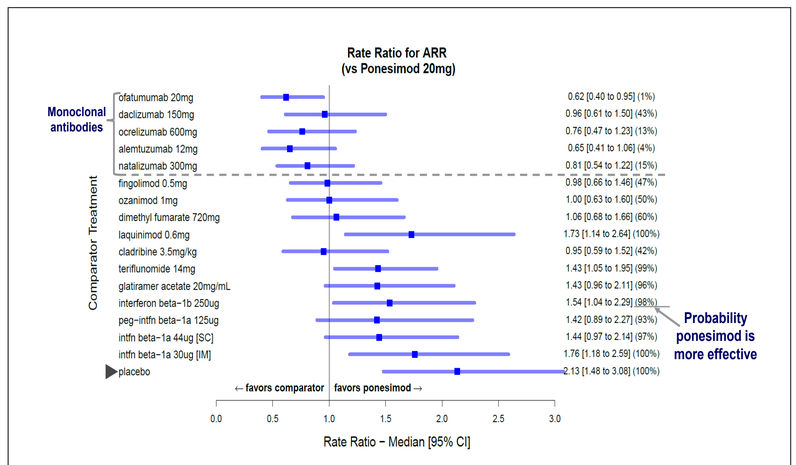
Efficacy of 17 different DMTs in RMS as assessed by ARR rate ratio versus placebo*



ARR: annualized relapse rate; DMT: disease modifying therapy; RMS: relapsed multiple sclerosis; CI: confidence interval; RR: rate ratio; * Results are specific to population where 37% patients had a prior DMT

- All drugs demonstrated reduced relapses as compared with placebo (upper bound of RR 95% CI was above one in all cases). Ponesimod reduced the ARR by 53%.

Efficacy of 17 different DMTs in RMS as assessed by ARR rate ratio versus PONESIMOD 20 mg*



DMTs: disease modifying treatments; RMS: relapsed multiple sclerosis; ARR: annualized relapse rate; * Results are specific to population where 37% patients had a prior DMT

- Ponesimod significantly reduced the ARR in patients with RMS as compared to placebo, teriflunomide 14 mg, interferon-β-1a (intramuscular), laquinimod, and interferon β-1b.

CONCLUSIONS

- **A model-based meta-analysis was successfully developed to quantify the relative effects (RR) on ARR for 17 unique treatments using published data from 41 clinical trials treating patients with RMS.**
- **Relative drug effects were influenced by percentage of patients with prior DMT, as well as dose.**
- **Ponesimod significantly reduced the ARR in RMS patients as compared with placebo, teriflunomide 14 mg, interferon β-1a (intramuscular), laquinimod, and interferon β-1b.**

References:
1. Smith AL. Neurotherapeutics. 2017 Oct; 14(4): 952–960.

Disclosures:
MZ, AK are employees and shareholders of Janssen Research & Development. HK, TS, and BH are employees and shareholders of Acetelion Pharmaceuticals Ltd.

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