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ARTICLE

# An exposure-response analysis of ponesimod clinical efficacy in a randomized phase III study in patients with relapsing multiple sclerosis

**Belén Valenzuela**[1] | **Per Olsson Gisleskog**[2] | **Italo Poggesi**[3] | **Tatiana Sidorenko**[4] | **Michel Burcklen**[4] | **Hilke Kracker**[4] | **Juan Jose Pérez-Ruixo**[1]

[1]Janssen-Cilag Spain, Part of Janssen Pharmaceutical Companies, Madrid, Spain

[2]POG Pharmacometrics, London, UK

[3]Janssen-Cilag Italy, Part of Janssen Pharmaceutical Companies, Cologno Monzese, Italy

[4]Actelion Pharmaceuticals Ltd, Part of Janssen Pharmaceutical Companies, Allschwil, Switzerland

**Correspondence**
Belén Valenzuela, Paseo de las Doce Estrellas 5, 28042 Madrid, Spain.
Email: BValenz2@ITS.JNJ.com

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**Abstract**

The efficacy of ponesimod and teriflunomide for the treatment of relapsing multiple sclerosis (MS) was compared in a randomized phase III trial. This study explores the exposure-response (E-R) relationships of efficacy end points (annualized relapse rate [ARR] and combined unique active lesions [CUALs]) of ponesimod observed in this trial. The E-R relationships were described using nonlinear mixed effects models for count data. The effect of baseline covariates (demography and prognostic factors) was also explored. Ponesimod 20 mg reduced ARR (primary end point) by 30.5% (95% confidence interval [CI]: 9.8% to 46.4%) and the number of CUALs by 56% (95% CI: 46% to 64%) between baseline and week 108 compared to teriflunomide 14 mg. The E-R analyses indicated a significant relationship between ARR and CUAL. In turn, CUAL was significantly related to ponesimod systemic exposure. Based on these relationships, the predicted reduction of ARR was relatively flat in the range of ponesimod systemic exposure achieved with the 20 mg clinical dose: the expected ARR decrease ranged from 28% (95% CI: 11% to 42%) at the 5th percentile of ponesimod exposure to 34% (95% CI: 19% to 47%) at the 95th percentile. No significant baseline covariates affected the ponesimod effects and, consequently, dosage adjustments are not warranted by these analyses. Although significant relationships were found between ARR and CUAL and between ponesimod exposure and CUAL, these analyses were supportive of the use of a flat 20 mg maintenance dose for ponesimod in adult patients with MS.

Italo Poggesi is now an employee of Certara Solbiate Arno, Italy.

**Trial registration number and date of registration:** ClinicalTrials.gov NCT02425644; April 21, 2015.

**Study Highlights**

**WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?**

The phase III Oral Ponesimod Versus Teriflunomide In Relapsing Multiple Sclerosis (OPTIMUM) trial in patients with relapsing multiple sclerosis (MS) showed that ponesimod was superior to teriflunomide on annualized relapse rate (ARR) reduction, fatigue, magnetic resonance imaging activity, and brain volume loss. This follow-up analysis explored exposure-response (E-R) relationships from this trial.

**WHAT QUESTION DID THIS STUDY ADDRESS?**

The current analysis characterized the E-R relationship between the ponesimod area under the curve at steady state and the clinical efficacy end points ARR and cumulative number of combined unique active lesions (CUALs) by magnetic resonance imaging (MRI).

**WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?**

The results of this study showed a statistically significant effect of ponesimod on CUALs, a reliable outcome measure of inflammatory MS disease activity, compared to teriflunomide.

**HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?**

Ponesimod approval based on the OPTIMUM results represent a new treatment option for patients with MS.

## INTRODUCTION

Multiple sclerosis (MS) is a chronic autoimmune disease of the central nervous system that is primarily attributed to inflammatory attacks leading to demyelination, axonal loss, and gliosis culminating in chronic multifocal sclerotic plaques in the brain and spinal cord.[1–3] As of 2020, the number of people suffering from MS was estimated at more than 2.8 million people worldwide and accounted for more than 18,000 deaths.[4,5] Although there is no cure for MS, immunomodulatory and anti-inflammatory therapies prove to be effective in modifying the course of the disease.

Ponesimod (JNJ-67896153/ACT-128800), an iminothiazolidinone derivative, is an orally active sphingosine-1-phosphate (S1P) receptor modulator.[6,7] Unlike other approved S1P modulators, ponesimod is selective for $S1P_1$, which is widely expressed in tissues. $S1P_1$ expression on lymphocytes controls lymphocyte egress from lymphoid organs.[8,9] Through modulation of $S1P_1$, ponesimod causes a rapid, dose-dependent, reversible reduction in peripheral blood lymphocyte counts (LCs) and prevents lymphocyte recruitment to sites of inflammation.[10,11]

A phase II study showed that ponesimod is effective in reducing inflammatory disease activity on magnetic resonance imaging (MRI).[12] A ponesimod dose of 20 mg q.d. was selected as a maintenance dose in the Oral Ponesimod Versus Teriflunomide In Relapsing Multiple Sclerosis (OPTIMUM) study (NCT02425644) based on the data from the phase IIb clinical study (AC-058B201).[12,13] In the AC-058B201 study, ponesimod was administered q.d. at doses of 10-, 20-, and 40-mg for 24 weeks. The exposure-response (E-R) analysis showed that ponesimod area under the curve at steady state ($AUC_{ss}$) was indirectly associated with annualized relapse rate (ARR) through the cumulative number of new gadolinium (Gd)+ T1 (primary end point).[12] A 30% and 38% decrease of ARR was expected at ponesimod $AUC_{ss}$ achieved with 20- and 40-mg daily dose. Therefore, increasing the ponesimod daily dose from 20- to 40-mg provided limited additional reduction of ARR, which may not justify the risk-benefit of the higher dose, and supported the selection of 20 mg q.d. as maintenance dose. In addition, whereas 20 mg was a well-tolerated dose, 40 mg dose was associated with an increased incidence of adverse events, such as dyspnea, peripheral edema, and cough. To minimize the transient negative chronotropic effect during treatment initiation,[14] ponesimod was given to patients in phase III trials using a 2-week gradual uptitration (2, 2, 3, 3, 4, 4, 5, 6, 7, 8, 9, 10, 10, and 10 mg) before starting the proposed daily maintenance dose of 20 mg given once daily.[15] The OPTIMUM study compared the efficacy and safety of ponesimod and teriflunomide in patients with relapsing MS and showed that ponesimod 20 mg/day significantly reduces ARR, the study's primary end point, by 30.5% compared to teriflunomide 14 mg/day (95% CI: 15% to 43%, $p = 0.0003$).[16–19]

The current analysis characterized the E-R relationship between the clinical efficacy end points ARR and cumulative number of CUALs observed from baseline to week 108.

# METHODS

## Study design and patient eligibility criteria

This prospective, multicenter, randomized, double-blind, parallel-group, active-controlled, phase III, superiority study compared the efficacy, safety, and tolerability of ponesimod and teriflunomide in patients with relapsing MS (NCT02425644). For full study details, refer to Kappos et at., 2021.[18] All procedures were performed in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. In this two-arm study, patients were randomized (1:1) to 20 mg ponesimod or 14 mg teriflunomide. The primary efficacy end point was ARR defined as the number of confirmed relapses per patient-year; CUAL was one of the secondary efficacy end points. Additional details of the clinical study can be found elsewhere.[16,17]

The study population included patients aged 18–55 years presenting with a diagnosis of MS as defined by the 2010 revision of McDonald Diagnostic Criteria,[20] with relapsing course from onset (i.e., relapsing-remitting MS or secondary progressive MS with superimposed relapses). Patients included in the study had active disease evidenced by greater than or equal to one MS relapse(s) with onset within 12 months prior to baseline Expanded Disability Status Scale (EDSS) assessment, or by greater than or equal to two MS relapses with onset within 24 months prior to baseline EDSS assessment, or with greater than or equal to one Gd-enhancing (Gd+) lesion(s) of the brain on a MRI performed within 6 months prior to baseline EDSS assessment. Enrolled patients were to be ambulatory with an EDSS score of up to 5.5 inclusive.

Patients with significant medical conditions (i.e., cardiovascular, pulmonary, immunological, hepatic, ophthalmological, and ocular), contraindications to MRI, clinically relevant medical or surgical conditions that would put the patient at risk, and pregnant or lactating women were not eligible for this study.

## Study treatment and clinical data

Study treatment duration was 108 weeks. A gradual up-titration of ponesimod from a 2 mg/day starting dose to a 10 mg/day dose over a period of 14 days (2, 2, 3, 3, 4, 4, 5, 6, 7, 8, 9, 10, 10, and 10 mg) was administered before starting the maintenance daily dose of 20 mg, and this has been shown to successfully mitigate the transient heart rate reduction upon treatment initiation.[14] Heart rate reduction was shown to disappear following repeated dosing.[15] Teriflunomide was not uptitrated; therefore, 14 mg doses were administered orally once daily from day 1 up to week 108.

The primary efficacy end point of this study was ARR over the study period (e.g., over 108 weeks). A relapse was defined as new, worsening, or recurrent neurological symptom that occurred at least 30 days after the onset of a preceding relapse, and that lasted at least 24 h, in the absence of fever or infection.

Secondary efficacy end points included cumulative number of CUALs (defined as new T1 Gd+ at baseline [T1B] MRI lesions plus new or enlarging T2 lesions [without double-counting of lesions]) from baseline to week 108. T1-weighted imaging was performed before and after intravenous administration of 0.1 mmol/kg body weight (= 0.2 ml/kg) of Gd.

MRI scans were performed at baseline, week 60, and week 108, and following premature treatment discontinuation.

Pharmacokinetic (PK) samples were collected for all patients to provide information about systemic exposure to study drug in the target population. Blood samples were collected predose at weeks 12, 60, and 108. Additionally, at day 1 and week 12, PK samples were drawn 3 h (+/− 15 min) postdose. The concentration of ponesimod in plasma was determined by a validated liquid chromatography-tandem mass spectrometry assay. The lower limit of quantification was 1 ng/ml. The ponesimod PK exposure metrics evaluated for E-R was represented by the $AUC_{ss}$. A maximum a posteriori (MAP) estimation assessment was used to estimate the individual clearance for each patient included in the B301 study using the previously developed population PK models prior information and, in turn, obtain $AUC_{ss}$ as dose/clearance.[21] The pharmacodynamic (PD) marker was total LC by visit up to week 108, which was measured as part of the hematology tests. Post-treatment lymphocyte recovery was measured at 15 days and 30 days after study drug discontinuation. The absolute LC at steady state ($LC_{ss}$) and relative change from baseline in total LC at steady state ($\Delta LC_{ss}$) were calculated for each patient using the empirical Bayesian estimates of the PK-LC model parameters.[22]

## Exposure response models

The purpose of the exposure-efficacy analysis was to assess the relationship between ponesimod exposure and the end

points of clinical and MRI efficacy: ARR and CUAL. The ponesimod exposure metrics evaluated included $AUC_{ss}$, $LC_{ss}$, and $\Delta LC_{ss}$. For the teriflunomide arm, $AUC_{ss}$ was coded as missing value, therefore, ponesimod drug effect only applied for the ponesimod arm.

For the exploratory analysis, ponesimod exposure metrics were classified into quintiles of exposure and ARR and CUAL were plotted by quartile of PK exposure metrics to establish if meaningful trends were present. Similarly, plots stratified by prognostic covariates at baseline (age, sex, weight, race, T1 Gd+ lesions [T1B], EDSS at baseline [EDSSB], and former use of disease modifying therapies [DMTs]) were also prepared.

As both cumulative numbers of CUAL and relapses are discrete events, they were evaluated using count models. Poisson, zero-inflated Poisson, and negative binomial and zero-inflated negative binomial count models were tested for describing the cumulative number of CUALs and cumulative number of relapses adjusted for the respective follow-up time. To identify the best structural and statistical models, a series of models were evaluated, which were perceived to potentially describe the observed data. Drug effects were incorporated into the model using linear, log-linear, power, or maximal effect ($E_{max}$) functions. Models that converged successfully, had low standard errors, and produced reasonable parameter estimates were preferred over others. In addition, for each model, the improvement in the fit was assessed by the change in the minimum value of the objective function (MVOF) and by visual predictive checks (VPCs).

To adjust for differences in follow-up time between patients, the mean number of relapses are calculated as number of relapses up to end of study (EOS) = $\lambda_{ARR}$ * time in study (years), where $\lambda_{ARR}$ is the mean ARR.

Similarly, for CUALs to adjust for differences in MRI follow-up time, the mean number of lesions are modeled as the number of lesions up to the last MRI = $\lambda_{CUAL}$ * time to last MRI (years), where $\lambda_{CUAL}$ is the mean rate of lesions per year.

The effect of prognostic covariates was explored using forward inclusion and backward deletion process. The inclusion or exclusion of a covariate in the E-R models was considered significant if it resulted in a decrease in the MVOF of greater than 3.84 ($\chi^2$ test, df = 1, $p < 0.05$). Covariates were evaluated sequentially, one at a time (univariate analysis).

VPCs for count data were used for diagnostic purposes, comparing the observed counts with the mean and the 95% prediction interval of the model-simulated counts, running 1000 simulations without considering parameter's uncertainty. For CUALs, VPCs were carried out by comparing the distribution of the observed number of lesions, stratified by treatment and $AUC_{ss}$ category, with the 95% prediction interval for the distribution, simulated from the final model. For ARRs, VPCs were carried out by comparing the mean observed ARR, stratified by treatment, $AUC_{ss}$, and CUALs with the simulated distribution of ARRs, based on the final model. VPCs were performed using the nonlinear mixed effects model (NONMEM).

## Computer software

The analysis was performed in accordance with appropriate guidelines by the US Food and Drug Administration and the European Medicines Agency (FDA Guidance 2003; EMEA/CHMP/EWP 2007; FDA Guidance 1999). Data analysis was performed using NONMEM version 7.3.0 (ICON plc). The Fortran compiler was Intel Fortran 64 Compiler Professional, version 11.1. The NONMEM analyses were performed in a validated environment, High Performance Pharmacometrics Platform (HP3) System (Rudraya Sonic Version 4 or higher), based on Good Automated Manufacturing Practice and in accordance with 21 Code of Federal Regulations (CFR) Part 11 and Good Clinical Practice regulations. Small modifications to the analysis dataset, exploratory analysis, diagnostic graphics, and post-processing of NONMEM analysis results and simulations were carried out using R version 3.4.1 or higher (Comprehensive R Network, http://cran.r-project.org) in a validated HP3 environment.

# RESULTS

The results in the following section will be reported for ARR first, which was the primary end point of clinical efficacy, followed by CUAL (secondary end point). Concerning the metrics of systemic exposure used in the E-R assessment, the MAP estimation indicated that ponesimod at the 20 mg dose level provided a mean $AUC_{ss}$ of 3749 ng·h/ml, with a relatively modest percent of coefficient of variation (CV%) of 22.9%. The analogous assessment for LC indicated that the mean $LC_{ss}$ (CV%) was estimated to be 0.75 (57.3%) $10^9$/L and the mean estimated $LC_{ss}$ decrease (CV%) was 63.5% (15.2%).

## Patients

In this study, 1133 patients were randomized 1:1 between ponesimod and teriflunomide; of these patients, 1131 patients were treated: 565 patients received 20 mg/

**TABLE 1** Baseline patient characteristics

| | Treatment | | |
|---|---|---|---|
| | **Ponesimod 20 mg** | **Teriflunomide 14 mg** | **Total** |
| *N* (%) | 565 (50.0%) | 566 (50.0%) | 1,131 (100.0%) |
| Age, years | | | |
| Mean, CV% | 36.63 (23.8%) | 36.79 (23.8%) | 36.71 (23.8%) |
| Median (range) | 36.00 (18.00–55.00) | 37.00 (18.00–55.00) | 37.00 (18.00–55.00) |
| Weight, kg | | | |
| Mean, CV% | 71.62 (22.6%) | 70.91 (22.6%) | 71.27 (22.6%) |
| Median (range) | 70.00 (42.50–146.00) | 68.85 (38.40–132.00) | 69.00 (38.40–146.00) |
| Sex | | | |
| Male | 202 (35.8%) | 194 (34.3%) | 396 (35.0%) |
| Female | 363 (64.2%) | 372 (65.7%) | 735 (65.0%) |
| Race | | | |
| White, not Hispanic or Latino | 519 (91.9%) | 526 (92.9%) | 1,045 (92.4%) |
| Black | 3 (0.5%) | 2 (0.4%) | 5 (0.4%) |
| White, Hispanic or Latino | 24 (4.2%) | 20 (3.5%) | 44 (3.9%) |
| Other | 19 (3.4%) | 17 (3.0%) | 36 (3.2%) |
| *Missing* | 0 (0.0%) | 1 (0.2%) | 1 (0.1%) |
| T1B | | | |
| Mean, CV% | 1.87 (301.2%) | 2.07 (238.3%) | 1.97 (268.6%) |
| Median (range) | 0.00 (0.00–69.00) | 0.00 (0.00–52.00) | 0.00 (0.00–69.00) |
| *Missing* | 0 (0%) | 2 (0.4%) | 2 (0.2%) |
| EDSSB | | | |
| Mean (CV%) | 2.56 (45.8%) | 2.56 (48.1%) | 2.56 (46.9%) |
| Median (range) | 2.50 (0.00–5.50) | 2.50 (0.00–5.50) | 2.50 (0.00–5.50) |
| DMT | | | |
| No | 324 (57.3%) | 321 (56.7%) | 645 (57.0%) |
| Yes | 241 (42.7%) | 245 (43.3%) | 486 (43.0%) |

*Note*: All continuous values are reported with mean (CV%) and median (range), while categories are reported in absolute numbers and percentages.

Abbreviations: CV, percent coefficient of variation; T1B, T1 gadolinium-enhancing (Gd+) lesions; EDSSB, Expanded Disability Status Scale at baseline; DMT, former use of disease modifying therapies.

day of ponesimod, and 566 patients received 14 mg/day of teriflunomide. Of the participants, 471 (83.1%) patients completed ponesimod treatment and 473 (83.6%) completed teriflunomide treatment. Detailed demographics and patient baseline characteristics are shown in Table 1.

## Annualized relapse rate

ARR data were available for all 1131 patients who received treatment (565 in the ponesimod arm and 566 in the teriflunomide arm). The average observed ARR was 0.24 and 0.35 relapses/year in the ponesimod and teriflunomide arms, respectively (Figure 1). This indicated an average of 30.5% (95% CI: 9.8–46.4%) reduction in ARR with ponesimod compared to teriflunomide. However, there was no clear relationship between ARR and ponesimod exposure in this study (Figure 1) with only one dose level administered. Hence, it is concluded that relatively small variability in the observed ponesimod exposure at steady-state for the 20 mg dose is not expected to result in major differences in the expected ARR.

The data were best described by a negative binomial model which resulted in a drop in the NONMEM MVOF of 91.101 points (df = 1, $p < 0.001$) compared to a Poisson model. The inclusion of the treatment arm as a categorical variable improved the model fit ($\Delta$MVOF = 11.3, df = 1, $p < 0.001$) and indicated a significant difference between ponesimod and teriflunomide treatments. Although there was no significant association between ponesimod systemic exposure ($AUC_{ss}$) or PD end points ($LC_{ss}$ or $\Delta LC_{ss}$)

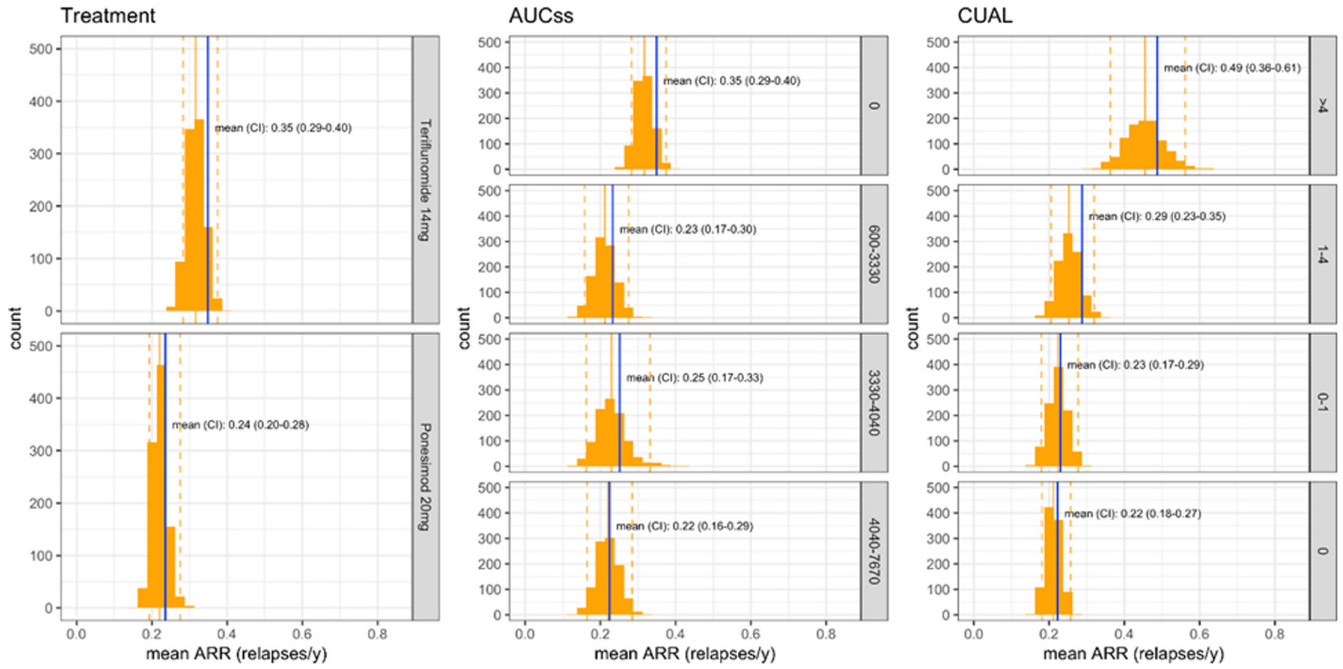


**FIGURE 1** ARR distribution by treatment, $AUC_{ss}$ category, and CUAL category. Observed means are shown as solid blue lines with mean and 95% CI in the legend. Orange histograms show predicted ARR means from the final ARR model. Solid orange lines represent the predicted overall mean and dashed lines represent the 95% prediction interval for the mean. ARR, annualized relapse rate; $AUC_{ss}$, area under the curve at steady-state; CI, confidence interval; CUAL, cumulative number of combined unique lesions from baseline to week 108; mg, milligram; y, years

and ARRs, there was a highly significant association between CUALs and ARRs, resulting in a MVOF decrease of 34.838 points (df = 1, $p < 0.001$). The CUAL effect on ARR was included in the model as follows:

$$\text{ARR} = \text{mean} \cdot (1 + (\text{CUAL} - 0.86) \cdot \text{slope})$$

where 0.86 is the median CUAL across both treatment arms. After including this effect, the treatment arm effect was still significant, but the difference in mean ARR between the treatments was smaller, as expected after adjusting for difference in CUAL between treatment arms. This model was used for the covariate assessment, as further attempts to estimate a different CUAL effect by treatment arm did not improve the MVOF ($\Delta$MVOF = −0.894, df = 1, $p > 0.05$).

Based on the graphical covariate exploration, sex, age, weight, T1B lesions, race, EDSSB, and previous DMTs were tested. Covariate model development resulted in a model with separate EDSSB effects on the ponesimod and teriflunomide mean ARRs, an effect of previous DMTs on the overall mean ARR, and an effect of weight on the teriflunomide mean ARR. The inclusion of these effects dropped the MVOF by 63.922 points with respect to the reference model (df = 4; $p < 0.001$).

After these adjustments, the effect of T1B lesions on the teriflunomide mean was not found to be significant and was removed from the model. This model converged successfully, and was considered the final model, and the parameters estimates are presented in Table 2. All parameters could be estimated with adequate to moderate precision with relative standard error (RSE) from 8.9% to 37.5%. The relationship between CUAL and ARR is shown in Figure 2a.

**TABLE 2** Model parameter estimates for the final exposure – ARR model

| Parameter | Estimate | RSE (%) |
|---|---|---|
| Mean ($\lambda_{ARR}$) ponesimod ARR, relapses/year | 0.174 | 9.5 |
| Mean ($\lambda_{ARR}$) teriflunomide ARR, relapses/year | 0.226 | 8.9 |
| Overdispersion | 0.639 | 20.8 |
| CUAL slope, relapses/year/lesion | 0.0801 | 22.3 |
| EDSSB on ponesimod mean, %/point | 31.1 | 11.0 |
| EDSSB on teriflunomide mean, %/point | 14.7 | 31.8 |
| Previous DMT on treatment means, % | 36.0 | 37.5 |
| Weight on teriflunomide mean, %/kg | −0.895 | 36.2 |

*Note*: Ponesimod relapses were expressed as mean (1+ [CUAL – 0.86 slope). The estimates of mean ($\lambda$) ARR refers to a patient with a CUAL of 0.86/year, an EDSSB of 2.5, a weight of 69 kg, and who did not receive previous DMT.

Abbreviations: ARR, annualized relapse rate; CUAL, cumulative number of combined unique lesions from baseline to week 108; DMT, disease modified treatment; EDSSB, Expanded Disability Status Scale at baseline; RSE, relative standard error.

The VPC of the final model is shown in Figure 1 stratified by study arm, $AUC_{ss}$, and CUAL. Results of the VPC show that the final model is well-suited to describe the distribution of the relapse events in both treatment arms (teriflunomide and ponesimod).

## Combined unique active lesion

For the CUAL analysis, the analysis included 1075 patients (539 and 536 in the ponesimod and teriflunomide groups, respectively, with baseline and at least one post-baseline MRI). In total, 5385 lesions were recorded in these patients, 1671 in the ponesimod arm and 3714 in the teriflunomide arm and were included in the E-R analysis. The average number of observed annualized CUALs was 55% lower in patients given ponesimod treatment compared to teriflunomide (Figure 3). Ponesimod showed a decrease of 56% (95% CI: 46–64%) of observed CUAL compared to teriflunomide.

A negative binomial model fitted the data better than a Poisson model with a MVOF 9376.347 points lower ($df = 1$; $p < 0.001$). The inclusion of the treatment arm as a categorical variable significantly improved the model fit ($\Delta MVOF = -55.113$; $df = 1$; $p < 0.001$), indicating highly

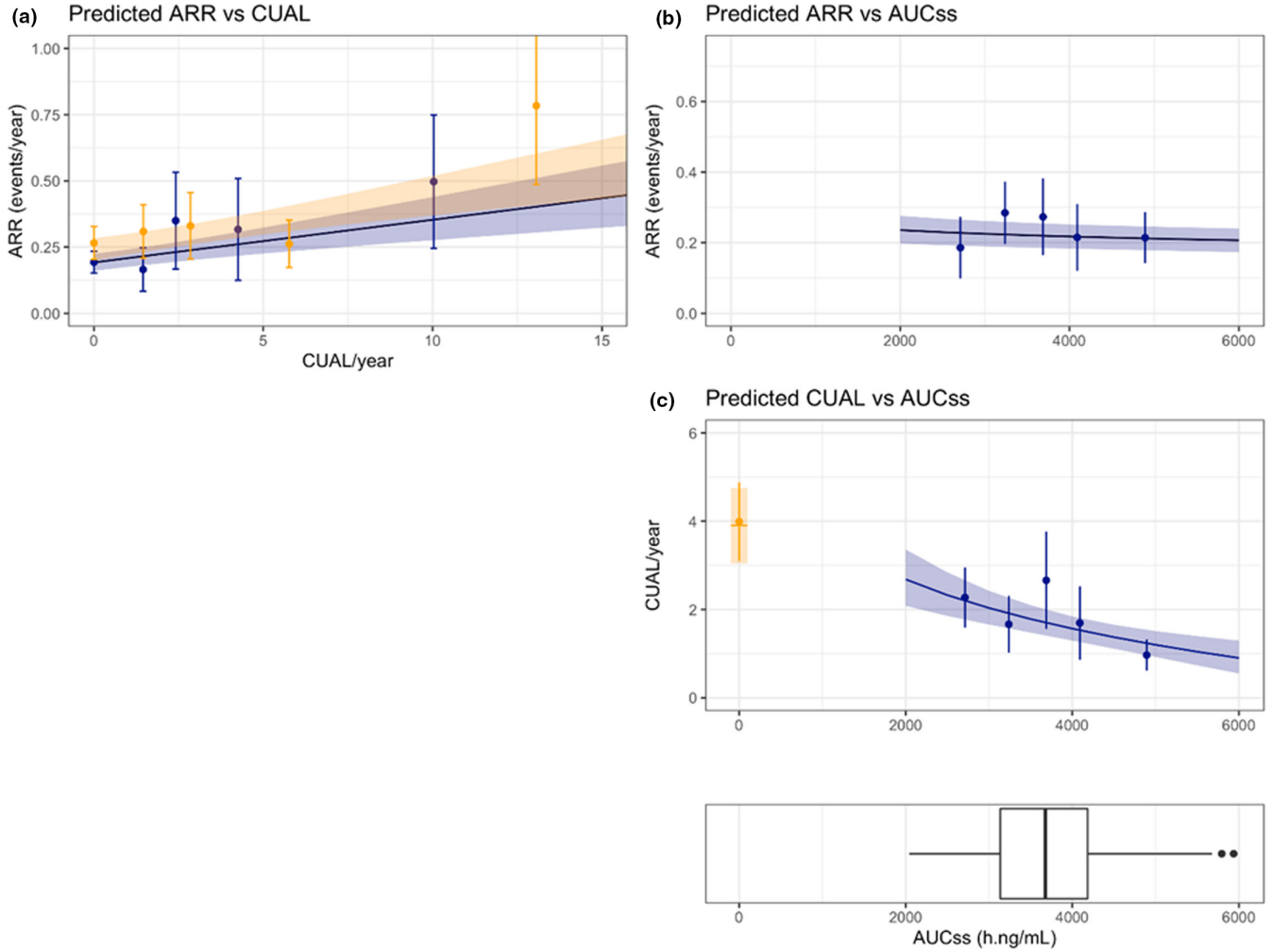


**FIGURE 2** Graphical representation of the models linking ARR to CUAL and CUAL to ponesimod systemic exposure. (a) Observed and model-predicted ARR versus CUAL, final model; points show observed mean ARR (±95% CI) categorized by CUAL quintiles, solid lines and shaded areas indicate typical behavior and 95% CI based on model uncertainty; teriflunomide arm is represented in orange while ponesimod is represented in blue. (b) Indirect relationship between ponesimod systemic exposure and ARR, based on the $AUC_{ss}$-CUAL and CUAL-ARR models, points show observed mean ARR (±95% CI) categorized by $AUC_{ss}$ quintiles, solid lines and shaded areas indicate typical behavior and 95% CI based on model uncertainty. (c) Observed and predicted annualized CUAL by ponesimod $AUC_{ss}$; at the bottom, box plot of ponesimod $AUC_{ss}$. Points show observed mean (±95% CI) CUAL categorized by $AUC_{ss}$ quintiles, solid lines and shaded areas indicate typical behavior and 95% CI based on model uncertainty. Teriflunomide arm is represented in orange (no teriflunomide exposure data were considered in this analysis; observed teriflunomide data are referred to $AUC_{ss} = 0$), whereas ponesimod is represented in blue. ARR, annualized relapse rate; $AUC_{ss}$, area under the curve at steady-state; CI, confidence interval; CUAL, cumulative number of combined unique lesions from baseline to week 108

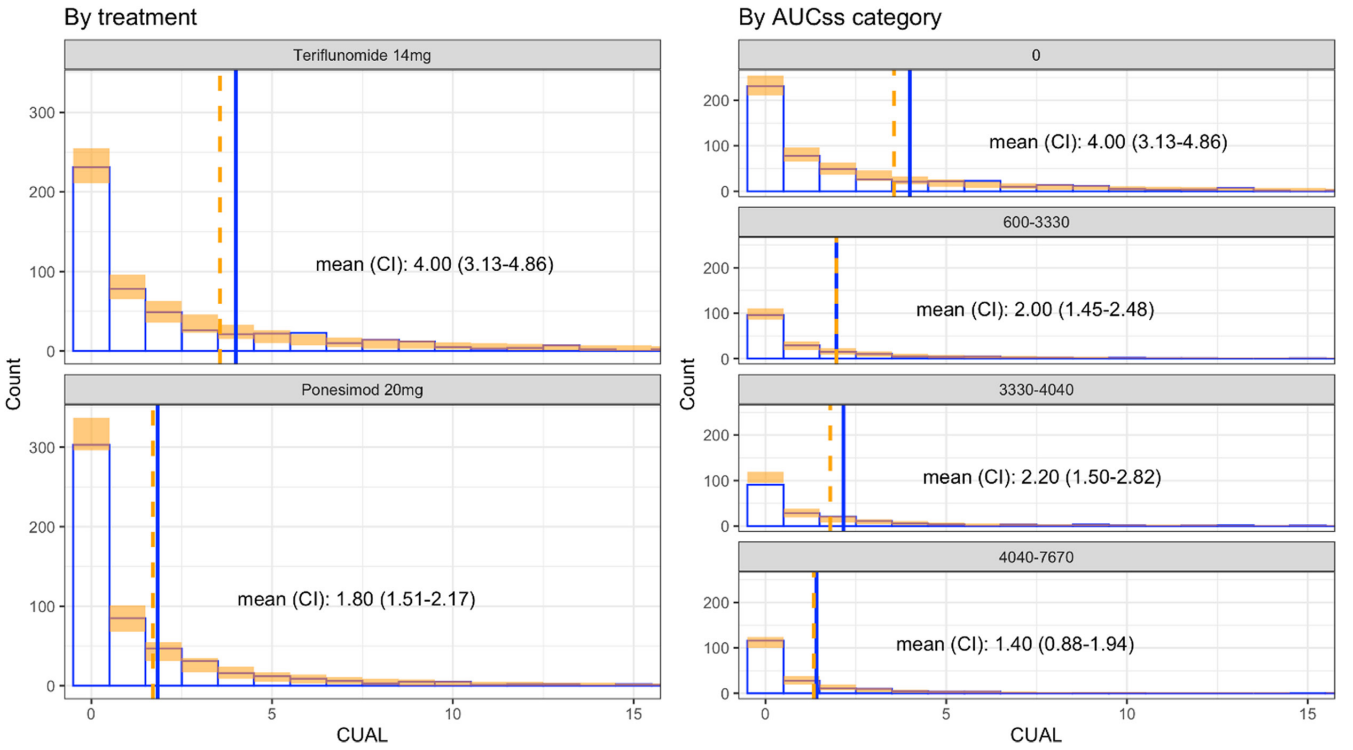


**FIGURE 3** CUAL, stratified by treatment (left) and exposure ($AUC_{ss}$) (right). Observed distributions and means (solid line) in blue. Observed means and 95% CI in legend. Orange dashed lines show the predicted means and orange areas show the 95% prediction intervals of different counts based on the final model. $AUC_{ss}$, area under the curve at steady-state; CI, confidence interval; CUAL, cumulative number of combined unique lesions from baseline to week 108

significant differences between treatments. The inclusion of ponesimod effect as a function of the ponesimod exposure, including linear, log-linear, power, or $E_{max}$ functions driven by $AUC_{ss}$, significantly improved the model fit. The inclusion of ponesimod exposure in the model with a log-linear relationship gave the largest decrease in the MVOF ($\Delta MVOF = -10.032$; $df = 1$; $p < 0.001$) and was selected for the next steps in the model development process. The $AUC_{ss}$ effect over CUALs in patients receiving ponesimod was included in the model as follows:

$$CUAL = \text{Ponesimod Mean CUAL} \cdot [1 + \text{slope} \cdot \log(AUC_{ss}/3687)]$$

where 3687 is the median ponesimod $AUC_{ss}$.

The mean CUAL values (lesions/year) (RSE, %) were estimated to be 1.70 (8.8%) for ponesimod and 3.89 (11.2%) for teriflunomide. The dispersion parameter for (RSE, %), which represents the negative binomial regression increased variability compared to what is expected from a Poisson model (RSE, %), was estimated at 2.78 (6.0%), and the ponesimod exposure effect (RSE, %) expressed as log $AUC_{ss}$ ratio slope was −0.958 (22.0%). This corresponds to a CUAL decrease from 2.69 to 2.03 when increasing $AUC_{ss}$ from 2000 to 3000 ng·h/ml.

Furthermore, the relationship between CUAL with the absolute $LC_{ss}$ or $\Delta LC_{ss}$ was also explored, but none of the attempts to include LC effects on CUAL significantly improved the model fit. No further improvements in the model were obtained and, therefore, this model was considered the reference model to further explore covariate effects.

After covariate model development, effects of age and T1B on the mean CUAL of both arms, and of sex on the

**TABLE 3** Model parameter estimates for the final exposure – CUAL model

| Parameter | Estimate | RSE (%) |
|---|---|---|
| Mean ($\lambda_{CUAL}$) ponesimod CUAL, lesions/year | 0.874 | 9.40 |
| Mean ($\lambda_{CUAL}$) teriflunomide CUAL, lesions/year | 1.56 | 12.4 |
| Overdispersion | 1.98 | 5.91 |
| Log $AUC_{SS}$ slope | −0.700 | 38.6 |
| Age effect on mean, %/year | −4.22 | 10.1 |
| T1B effect on mean, %/lesion | 55.2 | 20.3 |
| Sex effect on mean, teriflunomide arm only | 0.612 | 44.8 |

*Note*: Ponesimod count was expressed as ponesimod mean (1 + slope log [$AUC_{ss}$/3687]).

$AUC_{SS}$, area under the curve at steady-state; CUAL, cumulative number of combined unique lesions from baseline to week 108; RSE, relative standard error; T1B, baseline T1 lesion.

mean of the teriflunomide arm, were included, which led to a decrease of the MVOF of 284.774 (df = 3; $p < 0.001$). The largest mean CUAL was observed in men in the teriflunomide arm. This model converged with a good fit and reasonable parameter standard errors, and was selected as the final model. The parameters of this model are presented in Table 3. The relationship between $AUC_{ss}$ and CUAL is shown in Figure 2d, together with a box plot of the ponesimod $AUC_{ss}$.

The VPC of the final model quantifying the effect of $AUC_{ss}$ over CUAL is displayed in Figure 3 stratified by treatment group (left panel) and by $AUC_{ss}$ (right panel). Both VPCs show that the final model is suitable to describe the distbution of CUAL and the general E-R relationship of the CUAL across treatments and ponesimod exposure levels.

## DISCUSSION

The pivotal OPTIMUM study in relapsing MS met its primary objective and demonstrated a clinically meaningful, statistically significant, and robust effect of ponesimod 20 mg, which was superior to teriflunomide 14 mg in reducing ARRs. The results of this study also showed a statistically significant effect of ponesimod on CUALs, a reliable outcome measure of inflammatory MS disease activity, compared to teriflunomide. In this paper, we report the first E-R analyses based on the phase III results for an S1P modulator. The E-R relationship between $AUC_{ss}$ and the secondary clinical efficacy end point CUAL was assessed using a negative binomial model. This distribution has been previously found to consistently provide one of the better fits to MRI data from patients with MS.[13,14] The effect of ponesimod exposure on CUALs was best described by a log-linear relationship with ponesimod $AUC_{ss}$ within the exposure range observed following the administration of ponesimod at the maintenance dose of 20 mg. The predicted reduction of CUALs (relative to teriflunomide) ranged from 40% (95% CI: 19–56%) to 71.0% (95% CI: 59–80%) at the 5th and 95th percentile of the ponesimod $AUC_{ss}$, respectively (Figure 2d). No significant relationship between either $LC_{ss}$ or $\Delta LC_{ss}$ and CUAL was observed. Significant effects of age and T1B lesions were found on overall CUALs (independently of the treatment arms), indicating a higher MRI disease activity for patients with younger age and larger number of T1 Gd+ lesions at baseline. It is reasonable to assume that patients with a high number of lesions at baseline are in a more active state of the disease, and thus will have higher CUALs. The strongest relationship was found between T1B lesions and the mean annualized CUALs, which increases by 55.2% for each additional T1B lesion. The mean CUALs described by $\lambda$ decreases by 4.22% for a year increase in age. This agrees with studies by Tortorella and co-workers, that Gd+ lesions are more common in younger patients.[23] Weight, race, EDSS, and previous DMTs did not show any significant relationship with CUALs. The effect of ponesimod $AUC_{ss}$ was not found to be related to any of the covariates, and thus there was no indication for a dose adjustment on the basis of these patient's covariates.

A negative binomial regression model was used to describe the ARR data of the B301 study. Neither ponesimod $AUC_{ss}$ nor $LC_{ss}$ following ponesimod treatment were significantly associated with ARRs; however, modeling evidenced a significant relationship between CUAL and ARR (Figure 2a). Thus, by combining the models for exposure-CUAL and CUAL-ARR, an indirect relationship between AUC and ARR can be obtained (Figure 2b). Using this model, ARR is predicted to decrease from 0.32 (95% CI: 0.28 to 0.36) events/year in teriflunomide arm to 0.22 (95% CI: 0.18 to 0.25) events/year in the ponesimod arm, a 31% decrease (95% CI: 15% to 46%) at an $AUC_{ss}$ value of 3687 ng·h/ml (equivalent to the median $AUC_{ss}$ for 20 mg q.d.). At the 5th and 95th percentile of ponesimod $AUC_{ss}$ following the 20 mg daily dosing, the predicted reduction in ARRs relative to teriflunomide is 28% (95% CI: 11% to 42%) and 34% (95% CI: 19–47%), respectively, indicating a relatively flat exposure response in this range of exposure. After including CUAL in the ARR model, a significant difference in the treatment effects of ponesimod and teriflunomide remained, indicating that ponesimod may also act in other ways on reducing relapses than what can be observed through the lowering in CUALs. The covariate analysis indicated that the past use of DMT and increasing EDSSB values increase the mean ARRs. No significant effects of age, sex, T1B lesions, or race could be found, although age and T1B lesions affect ARRs indirectly through changes in CUALs, as outlined above. Mean ARRs increased with EDSSB by 31% in ponesimod arm for each point increase in EDSSB, indicating that ARRs and a higher degree of disability are related. The corresponding effect of EDSSB on ARRs in the teriflunomide arm was lower (14.7%; see Table 2). Mean ARR was 35% higher in patients previously treated with DMT, indicating that these patients may be more severely ill.

In summary, in this phase III study, ponesimod treatment at the clinical dose of 20 mg once daily caused a significant decrease in ARRs relative to teriflunomide, which was significantly associated with decreasing CUALs. The reduction in ARRs relative to teriflunomide did not markedly change with ponesimod $AUC_{ss}$, within the range of ponesimod exposures observed at the 20 mg daily dosing. Ponesimod also demonstrated a decrease of CUAL counts compared to teriflunomide. This decrease was significantly associated with increasing ponesimod

$AUC_{ss}$. None of the covariates evaluated (age, sex, weight, race, Gd+ T1B, EDSSB, and DMT) influences the magnitude of the CUAL effect on ARRs, and so they do not warrant adjustments of the dosing. Taken together, the results of these E-R analyses indicated that a flat 20 mg dose is appropriate in all adult patients with MS.

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## CONFLICT OF INTEREST

B.V. and J.P.-R. are employees and Janssen-Cilag Spain, part of Janssen Pharmaceutical company of Johnson & Johnson and hold stock in Johnson & Johnson. I.P. was an employee of Janssen-Cilag Italy, part of Janssen Pharmaceutical company of Johnson & Johnson and holds stock in Johnson & Johnson. P.O.G. is an employee and stockholder of POG Pharmacometrics, which was paid by Johnson & Johnson for work associated with this study. T.S., H.K., and M.B. are employees of Actelion Pharmaceuticals Ltd., part of Janssen Pharmaceutical Companies and hold stock in Johnson & Johnson.

## AUTHOR CONTRIBUTIONS

All authors wrote the manuscript, designed and performed the research, and analyzed the data.

## ETHICAL APPROVAL

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Protocols were reviewed and approved by an institutional review board.

## CONSENT TO PARTICIPATE

Freely given, informed consent to participate was obtained for all human participants in this study.

## DATA AVAILABILITY STATEMENT

The data sharing policy of Janssen Pharmaceutical Companies of Johnson & Johnson is available at https://www.janssen.com/clinical–trials/transparency. As noted on this site, requests for access to the study data can be submitted through the Yale Open Data Access (YODA) Project site at http://yoda.yale.edu.

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## SUPPORTING INFORMATION

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