Onset of Action of Ozanimod for MRI Outcomes in Patients With RMS

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Introduction

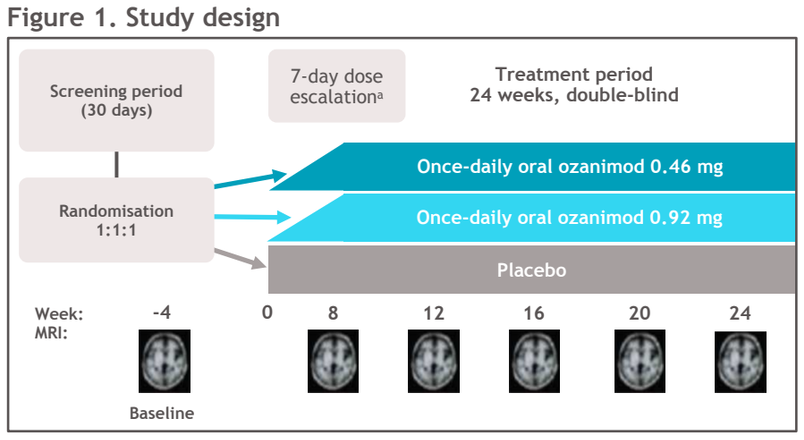
- Ozanimod is a sphingosine 1-phosphate (S1P) receptor 1 and 5 modulator that blocks the capacity of lymphocytes to egress from lymphoid tissue, reducing the number of lymphocytes in peripheral blood[1]
- The safety and efficacy of ozanimod have been demonstrated in the RADIANCE phase 2 study and its dose-blinded extension[2,3] and in the SUNBEAM and RADIANCE phase 3 trials[4,5]
- Ozanimod is approved in multiple countries for the treatment of adults with relapsing forms of multiple sclerosis (RMS) and is approved for the treatment of moderately to severely active ulcerative colitis in the United States[6-8]
- Knowledge of the onset of action for disease-modifying therapies (DMTs) in RMS is important for treatment monitoring
- **Objective:** To estimate the onset of action of ozanimod by analysing monthly MRI scans in this post hoc analysis of the RADIANCE phase 2 trial (NCT01628393),[2] which had earlier and more frequent MRI scans than the phase 3 trials[4,5]

Methods

Study design and procedures

- The RADIANCE phase 2 trial was a randomised, double-blind, placebo-controlled, 24-week study assessing the safety and efficacy of once-daily oral ozanimod 0.46 and 0.92 mg (equivalent to ozanimod hydrochloride 0.5 and 1 mg, respectively) in participants with RMS (**Figure 1**)[2]
  - MRI scans were acquired at baseline (screening visit [week -4]) and weeks 8, 12, 16, 20, and 24
  - A central imaging core laboratory (NeuroRx, Montreal, QC, Canada), with no knowledge of treatment assignment or outcomes, assessed and quantified the MRI scans
  - In this post hoc analysis, we estimated the onset of action for reduction in the number of gadolinium-enhancing (GdE) lesions, the primary study outcome, and reduction in the number of new/enlarging T2 lesions, the number of new unenhancing T1 lesions (black holes), T2 lesion volume, and whole brain volume (WBV), which were all secondary outcomes
  - Onset of action was defined as the earliest MRI time point at which a nominally significant difference ($P<0.05$) in the rate ratio of the least squares (LS) means and 95% CIs between ozanimod 0.92 mg and placebo occurred and was sustained

Figure 1. Study design



[a]Participants randomised to ozanimod received ozanimod 0.23 mg (equivalent to ozanimod HCl 0.25 mg) on days 1-4, 0.46 mg (equivalent to ozanimod HCl 0.5 mg) on days 5-7, and their assigned dose of ozanimod 0.46 or 0.92 mg (equivalent to ozanimod HCl 1 mg) starting on day 8. HCl, hydrochloride.

Statistical analysis

- The numbers of GdE lesions, new/enlarging T2 lesions, and new black holes were compared between participants assigned to ozanimod 0.92 mg and those allocated to placebo at all follow-up time points using a negative binomial regression model with repeated measures adjusted by region and the number of GdE lesions at baseline
- For T2 lesion volume, LS means were estimated using a mixed model for repeated measures, which included T2 lesion volume as the dependent variable, and stratification factors included region and the interaction between treatment and time point as fixed effects, baseline T2 lesion volume as a continuous covariate, and subject as a random effect; an unstructured covariance was used to model within subject errors
- Normalized WBV was quantified using SienaX at baseline and calculated subsequently from the percentage of brain volume changes quantified using paired Jacobian integration[9] at follow-up time points
  - LS means were estimated using a mixed model for repeated measures, which included WBV as the dependent variable, and stratification factors included region and the interaction between treatment and time point as fixed effects, baseline WBV as a continuous covariate, and subject as a random effect; an unstructured covariance was used to model within subject errors
- *P* values presented herein are nominal, as treatment comparisons in this post hoc analysis were not subject to multiplicity adjustment
- MRI outcomes were assessed in the intent-to-treat population (all participants with at least one follow-up MRI scan)

Participant selection

- Relevant key inclusion criteria included the following[2]:
  - Aged 18 to 55 years
  - History of brain MRI lesions
  - Expanded Disability Status Scale score of 0 to 5.0
  - RMS with either 1 or more relapses in the previous 12 months, or 1 or more relapses in the past 24 months with 1 or more GdE lesions on MRI in the 12 months before screening[2]
- Relevant key exclusion criteria included the following[2]:
  - Clinically significant findings on brain MRI scan consistent with conditions other than MS
  - Contraindications to MRI or gadolinium contrast, such as known allergy to gadolinium contrast dyes, renal insufficiency, claustrophobia, a body size incompatible with the scanner, pacemaker, cochlear implants, or intracranial vascular clips
  - More than 20 GdE lesions on the baseline brain MRI scan

Results

Participants

- Baseline demographics and clinical characteristics were generally similar between treatment groups, aside from a longer disease duration and larger proportion of participants with prior DMT use in the placebo group than the ozanimod 0.92 mg group (**Table 1**)[2]
  - Baseline MRI characteristics were generally similar between treatment groups, aside from the number and volume of T2 lesions and the number of black holes being higher in the ozanimod 0.92 mg group than the placebo group
- The mean (standard deviation) exposure to ozanimod 0.92 mg and placebo was 173.5 (8.94) and 171.3 (18.92) days, respectively

Onset of action of ozanimod

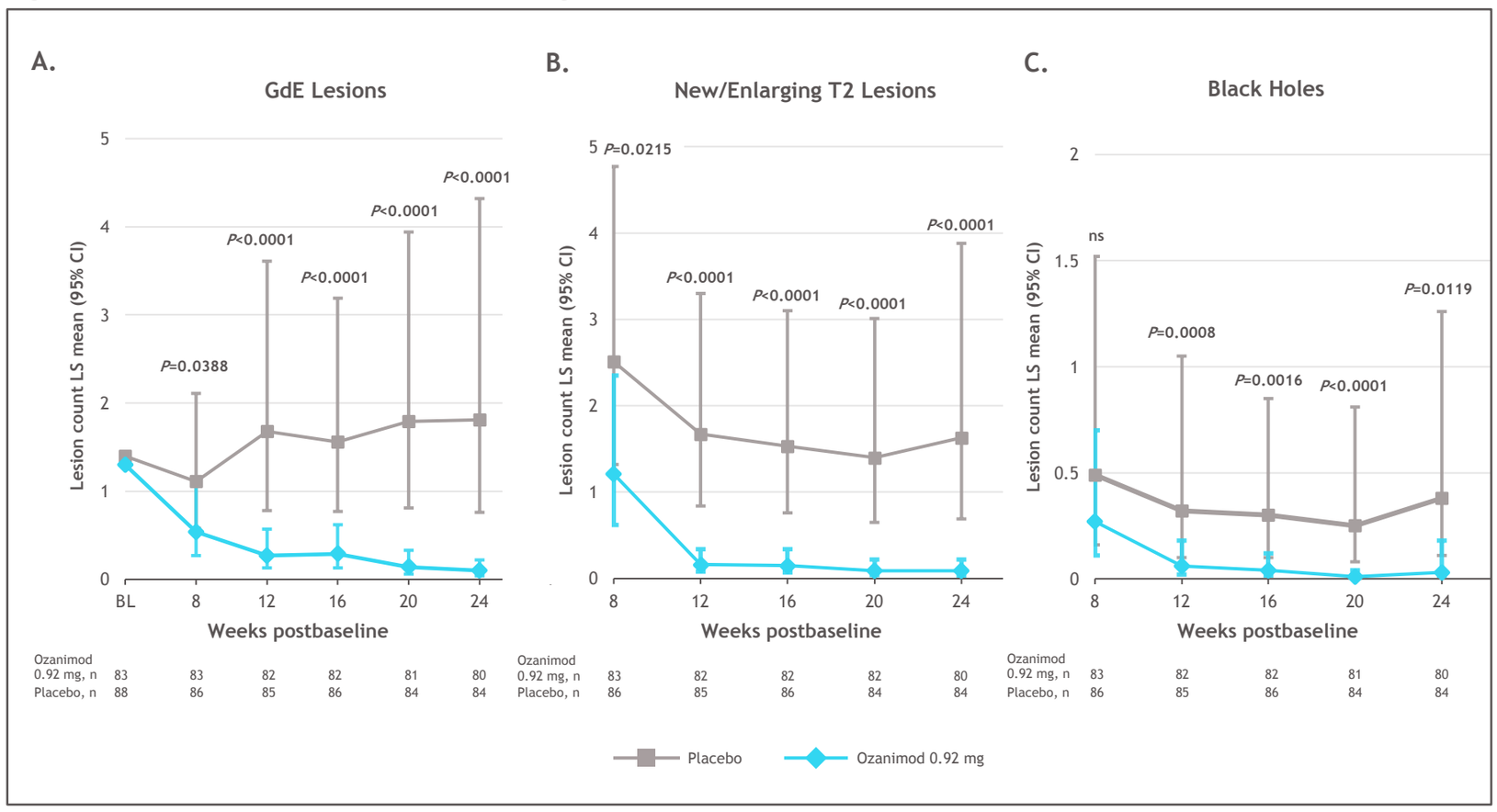
- Reductions in the number of GdE lesions were observed by week 8 for ozanimod 0.92 mg vs placebo, and CIs for the LS means did not overlap from week 12 onward (**Figure 2A**)
- Reductions in the number of new/enlarging T2 lesions were observed by week 8 for ozanimod 0.92 mg vs placebo, and CIs for the LS means did not overlap from week 12 onward (**Figure 2B**)
- Reductions in the number of new black holes were observed at week 12 for ozanimod 0.92 mg vs placebo; however, CIs for the LS means, which were wide in the placebo group, overlapped at all time points except at week 20 (**Figure 2C**)
- No obvious differences were observed for T2 lesion volume or WBV over 24 weeks (data not shown)

Table 1. Baseline demographics and clinical characteristics[2]

	Ozanimod 0.92 mg (n = 83)	Placebo (n = 88)
Age, years	38.4 (9.8)	39.0 (8.7)
Sex, n (%)		
Female	59 (71)	62 (70)
Male	24 (29)	26 (30)
Race, n (%)		
White	83 (100)	87 (99)
Black	0	1 (1)
Ethnicity, n (%)		
Hispanic or Latino	2 (2.4)	0
Not Hispanic or Latino	81 (97.6)	88 (100)
Region, n (%)		
Eastern Europe	76 (91.6)	78 (88.6)
Western Europe	3 (3.6)	6 (6.8)
North America	4 (4.8)	4 (4.5)
BMI, kg/m^2	24.1 (4.9)	24.2 (4.2)
Time since MS symptom onset, years	6.2 (5.8)	8.1 (7.0)
Time since MS diagnosis, years	3.6 (4.4)	4.6 (5.1)
Prior exposure to any MS DMT, n (%)	19 (22.9)	32 (36.4)
Number of GdE lesions	1.3 (2.8)	1.4 (3.4)
Number of T2 lesions	58.2 (44.0)	53.0 (40.4)
Number of black holes	42.3 (38.6)	36.4 (36.7)
Volume of T2 lesions, cm^3	13.4 (13.2)	11.1 (11.5)
Whole brain volume, cm^3	1493.1 (86.1)	1478.3 (85.0)

BMI, body mass index; DMT, disease-modifying therapy; GdE, gadolinium-enhancing; MRI, magnetic resonance imaging; MS, multiple sclerosis; SD, standard deviation. Intent-to-treat population. Data are presented as the mean (SD), unless otherwise indicated.

Figure 2. Onset of action of ozanimod in reducing brain MRI lesion counts



BL, baseline; GdE, gadolinium-enhancing; LS, least-squares; ns, not significant. Intent-to-treat population. The GdE baseline value is presented as the mean; on-treatment values are presented as LS means. *P* values are nominal, as this was a post hoc analysis, and were compared between ozanimod 0.92 mg and placebo using a negative binomial regression model with repeated measures adjusted by region and the number of GdE lesions at baseline.

Conclusions

- Ozanimod 0.92 mg reduced the number of GdE and new/ enlarging T2 lesions vs placebo at week 8, which was the earliest available MRI time point in this phase 2 study, with complete separation of the ozanimod 0.92 mg and placebo groups evident as early as week 12
- Differences between ozanimod 0.92 mg and placebo were also apparent beginning at week 12 for new black holes

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