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Effect of Ozanimod on Circulating Leukocyte Subtypes in Patients With Relapsing Multiple Sclerosis and Comparison With Healthy Volunteers

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Introduction

- Ozanimod is a sphingosine 1-phosphate receptor 1 and 5 modulator 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[1,2]
- Ozanimod blocks the capacity of lymphocytes to egress from lymphoid tissue, reducing the number of lymphocytes in peripheral blood[1]
  - The mechanism by which ozanimod exerts therapeutic effects in MS is unknown but may involve the reduction of lymphocyte migration into the central nervous system[1]
- Ozanimod has differential effects on the reduction of leukocyte populations, with main decreases noted in T and B cell populations[3]
- **Objective:** Post hoc epigenetic analyses were conducted to add to the current understanding of the mechanism of action of ozanimod and determine whether circulating leukocytes remaining during treatment shift towards an immunosuppressive or proinflammatory state

Methods

- A 12-week, phase 1, randomised, open-label, pharmacokinetic/pharmacodynamic study of oral ozanimod 0.46 or 0.92 mg/d (equivalent to ozanimod HCl 0.5 and 1 mg/d, respectively) was conducted in patients with RMS (NCT02797015)
  - The 12-week treatment duration included an initial 7-day dose escalation consisting of ozanimod 0.23 mg (equivalent to ozanimod HCl 0.25 mg) on days 1–4, then 0.46 mg/d on days 5–7
- The study enrolled adults aged 18–55 years with active, clinically stable RMS and an Expanded Disability Status Scale score of 0 to 6 who were otherwise generally healthy
- Key exclusion criteria included active infection or history of chronic infections or immunodeficiency, recent live vaccination, previous lymphocyte-depleting or immunosuppressant therapy, and ALC <1.0 × 10^9/L or white blood cell count <3.5 × 10^9/L
- An additional cohort of healthy volunteers with a comparable age range was assessed for this analysis
- Leukocyte subset counts (day 85) and mean ratios (days 56, 85, and 90) were compared with baseline data and/or with a pool of healthy volunteers using descriptive statistics
- Immunophenotyping was performed with the epigenetic cell counting technology (Epiontis ID) developed by Precision for Medicine, as previously described[4]

Results

Study population

- Twenty-four patients with RMS were randomised to ozanimod 0.46 mg/d (n = 13) or 0.92 mg/d (n = 11)
- A total of 113 healthy volunteers were included for comparison
- Patient demographics and baseline characteristics are presented in **Table 1**

Table 1. Patient demographics and baseline characteristics

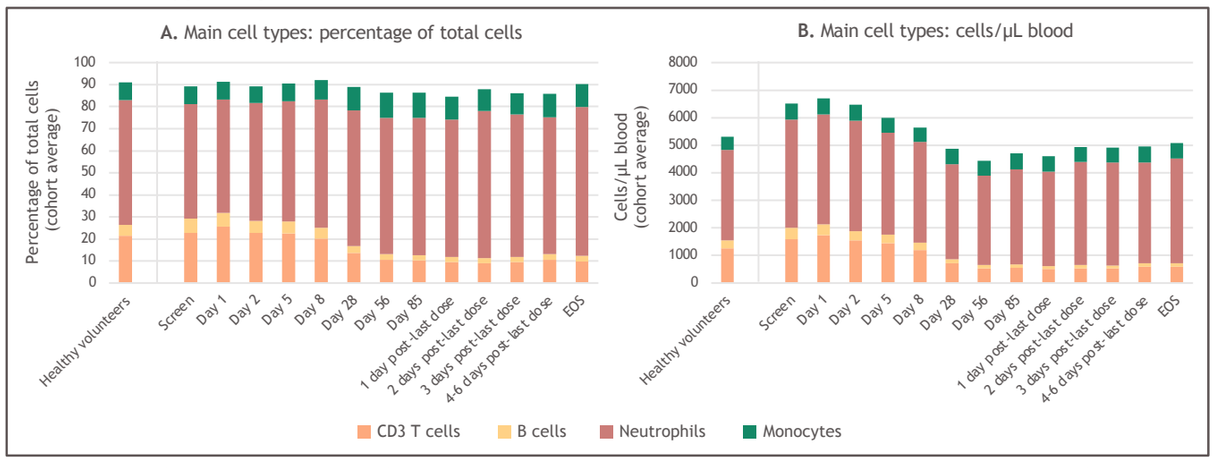
Parameter	Ozanimod 0.46 mg/d (n = 13)	Ozanimod 0.92 mg/d (n = 11)	Healthy Volunteers (n = 113)
Age, mean (SD), years	37 (8.6)	41 (7.9)	42 (13)
Sex			
Male	3 (23.1)	4 (36.4)	54 (47.8)
Female	10 (76.9)	7 (63.6)	59 (52.2)
Ethnicity			
Hispanic or Latinx	1 (7.7)	0	N/A
Not Hispanic or Latinx	12 (92.3)	11 (100)	N/A
Race			
Asian	1 (7.7)	0	N/A
Black or African American	2 (15.4)	3 (27.3)	N/A
White	10 (76.9)	8 (72.7)	N/A
BMI, mean (SD), kg/m²	30 (8.3)	30.5 (7.8)	N/A

BMI, body mass index; N/A, not available; SD, standard deviation. Data are presented as n (%) unless otherwise indicated.

Comparison of cell types in patients with RMS treated with ozanimod vs healthy volunteers

- Patients with RMS had a similar percentage of main cell types as healthy volunteers at baseline, with the percentage of CD3 T cells and B cells decreasing over time and monocytes remaining relatively stable during ozanimod treatment (**Figure 1**)
- When observing percentage cell changes relative to one another, the levels of neutrophils increased over time with ozanimod treatment in patients with RMS (**Figure 1A**); however, absolute neutrophil levels remained relatively similar over time (**Figure 1B**)

Figure 1. Cell types in patients with RMS treated with ozanimod vs healthy volunteers

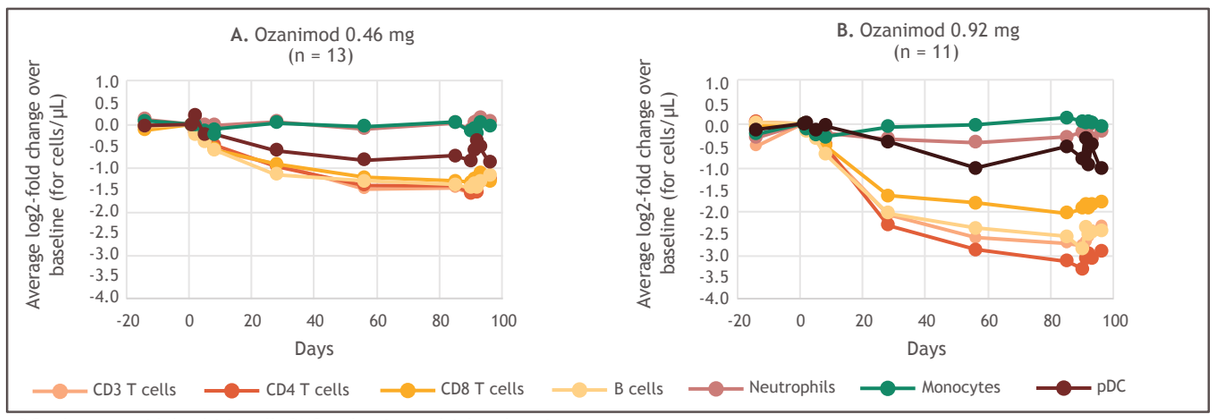


(A) The percentage of total cells shows how the cells remaining in circulation shift relative to one another as opposed to the absolute cell numbers presented in (B). Values were derived from samples from approximately 113 healthy volunteers or ≤24 patients with RMS before, during, and after ozanimod treatment. EOS, end of study; RMS, relapsing multiple sclerosis.

Change over time in lymphocyte subsets in patients with RMS treated with ozanimod

- Dose-dependent effects were observed for T and B cells, where treatment with ozanimod 0.92 mg resulted in greater absolute reductions in T and B cells than ozanimod 0.46 mg (**Figure 2**)

Figure 2. Change from baseline in peripheral lymphocyte subsets in patients with RMS treated with ozanimod

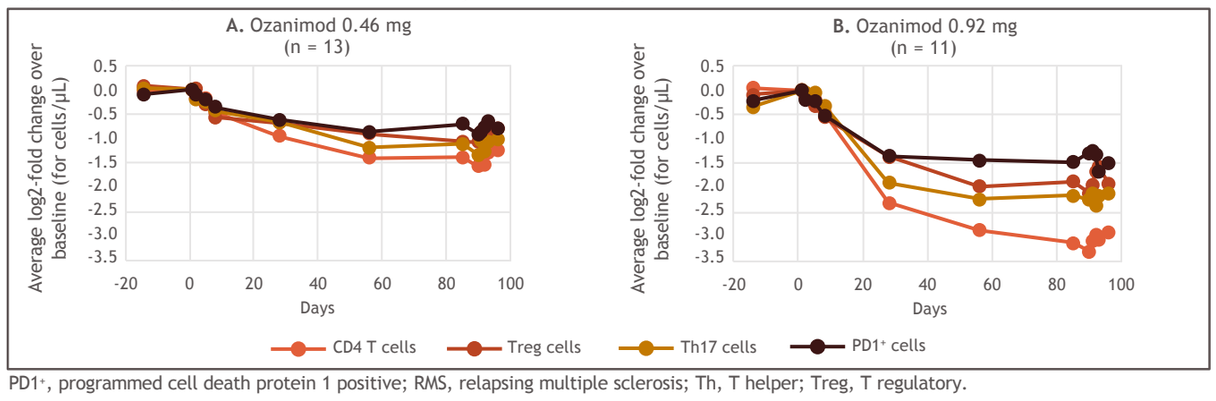


pDC, plasmacytoid dendritic cell; RMS, relapsing multiple sclerosis.

Change over time in leukocyte subsets in patients with RMS treated with ozanimod

- At day 85, treatment with ozanimod reduced the levels of CD4 T, T regulatory (Treg), T helper (Th) 17, and programmed cell death protein 1 positive (PD1⁺) cells from baseline in a dose-dependent manner (**Figure 3**)

Figure 3. Change from baseline in leukocyte subsets in patients with RMS treated with ozanimod

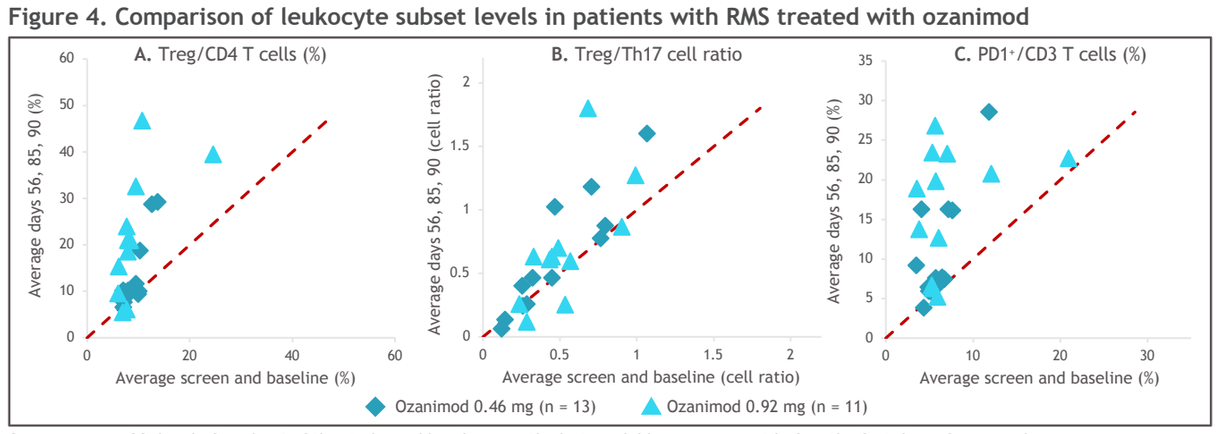


PD1⁺, programmed cell death protein 1 positive; RMS, relapsing multiple sclerosis; Th, T helper; Treg, T regulatory.

Leukocyte subset comparisons in patients with RMS treated with ozanimod

- Treg cells remaining in circulation during treatment with ozanimod were increased within the CD4 T cell population, and there was a relative increase of Treg cells to Th17 cells, suggesting a shift towards an anti-inflammatory state (**Figure 4**)
- Relative to overall CD3 T cells, the number of PD1⁺ cells increased during treatment with ozanimod, suggesting a potential for T cell suppression via the PD1/programmed cell death 1 ligand 1 axis (**Figure 4**)

Figure 4. Comparison of leukocyte subset levels in patients with RMS treated with ozanimod

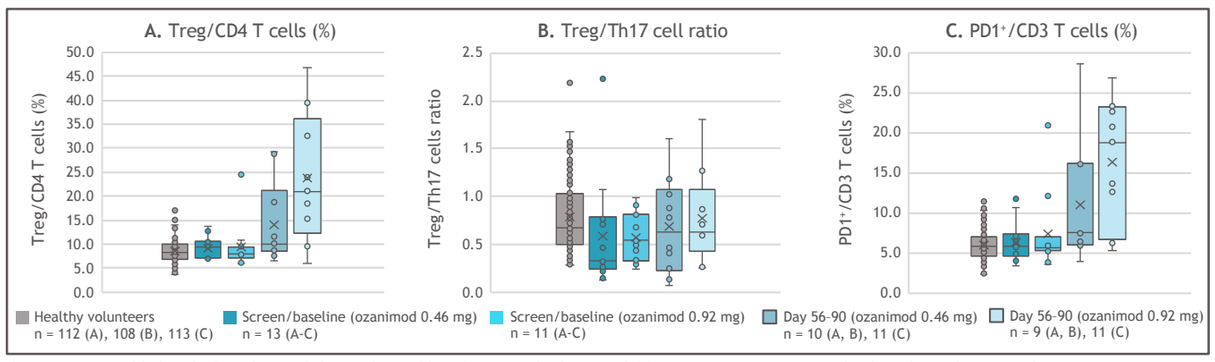


Screening was <28 days before day 1 of the study, and baseline was the last available measurement before the first dose of ozanimod.
PD1⁺, programmed cell death protein 1 positive; RMS, relapsing multiple sclerosis; Th, T helper; Treg, T regulatory.

Leukocyte subset comparisons in patients with RMS treated with ozanimod vs healthy volunteers

- Compared with healthy volunteers, patients with RMS had similar Treg/CD4 T cell and PD1⁺/CD3 T cell levels at screening/baseline, but increased levels while receiving either dose of ozanimod (**Figures 5A and 5C**)
- At baseline, healthy volunteers had a higher Treg/Th17 cell ratio than patients with RMS; however, the Treg/Th17 cell ratio increased toward the healthy volunteer level in patients with RMS during treatment with ozanimod (**Figure 5B**)

Figure 5. Comparison of leukocyte subset levels in patients with RMS treated with ozanimod vs healthy volunteers



Screening was <28 days before day 1 of the study, and baseline was the last available measurement prior to the first dose of ozanimod.
PD1⁺, programmed cell death protein 1 positive; RMS, relapsing multiple sclerosis; Th, T helper; Treg, T regulatory.

Conclusions

- There is a trend toward relatively more anti-inflammatory lymphocytes remaining in circulation during ozanimod treatment than inflammatory lymphocytes
- These results further characterise the mechanism of action of ozanimod in RMS and reinforce the differential effects of ozanimod on leukocyte subsets

References

1. ZEPOSIA® (ozanimod) [package insert]. Princeton, NJ: Bristol Myers Squibb; May 2021.
2. ZEPOSIA® (ozanimod) [summary of product characteristics]. Utrecht, Netherlands, Celgene Distribution BV; May 2020.
3. Harris S, et al. *Neurol Neuroimmunol Neuroinflamm*. 2020;7:e839.
4. Baron U, et al. *Sci Transl Med*. 2018;10:eaan3508. doi:10.1126/scitranslmed.aan3508

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Disclosures

- **SH:** employee and shareholder of Bristol Myers Squibb
- **RM:** employee of Bristol Myers Squibb
- **UH:** employee and shareholder of Precision for Medicine
- **ER:** employee of Precision for Medicine

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