Ozanimod vs Interferon β-1a: Clinical and MRI Results of RADIANCE Part B – A 2-Year Phase 3 Trial in Relapsing Multiple Sclerosis

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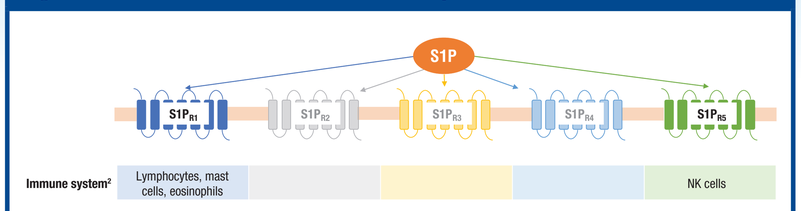
INTRODUCTION

- Extracellular sphingosine 1-phosphate (S1P) interacts with a family of 5 high-affinity G protein–coupled receptors: S1P receptor 1 ($S1P_{R1}$) through $S1P_{R5}$ (Figure 1)[1]
- Ozanimod is selective for $S1P_{R1}$ and $S1P_{R5}$ with high receptor affinity
- Ozanimod prevents the exit of $CCR7^+$ lymphocytes from lymph node reducing numbers in peripheral blood
- $CCR7^-$ lymphocytes, important for viral and tumor surveillance, continue to circulate

Figure 1. Cellular Distribution of S1P Receptors[2]

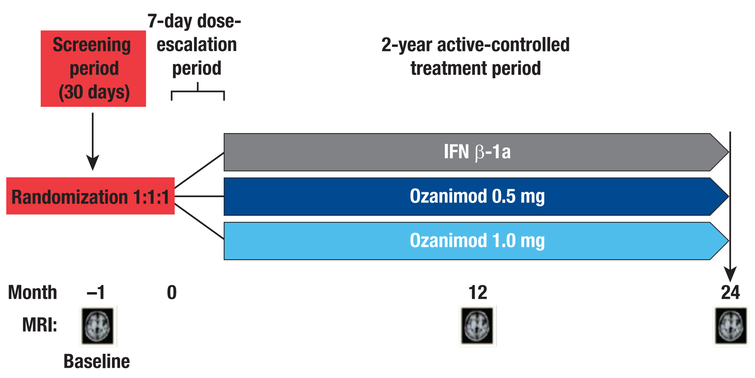


NK, natural killer; S1P, sphingosine 1-phosphate; S1PR, sphingosine 1-phosphate receptor.

METHODS

- RADIANCE Part B was a multicenter, randomized, double-blind, double-dummy, parallel-group, active treatment-controlled phase 3 study of once-daily oral ozanimod HCl 1 mg or 0.5 mg vs weekly interferon β-1a (IFN β-1a) 30 µg intramuscular injection in patients with relapsing multiple sclerosis (RMS) (Figure 2)
- Primary endpoint:
  - Annualized relapse rate (ARR) for each ozanimod dose versus IFN β-1a over 2 years
- Secondary endpoints:
  - New or enlarging T2 brain lesions from baseline over 2 years
  - Gadolinium-enhancing (GdE) brain lesions at 2 years
  - Three-month confirmed disability progression pre-specified as a pooled analysis of two phase 3 studies, RADIANCE Part B and SUNBEAM
  - Whole brain volume loss at 2 years
- The intent-to-treat population was used for all efficacy analyses
- The safety population was used for all safety analyses

Figure 2. Study Design



EDSS: every 3 months and at time of relapse
All MRI analyses performed by a blinded central imaging facility

EDSS, Expanded Disability Status Scale; IFN β-1a, interferon β-1a; MRI, magnetic resonance imaging.

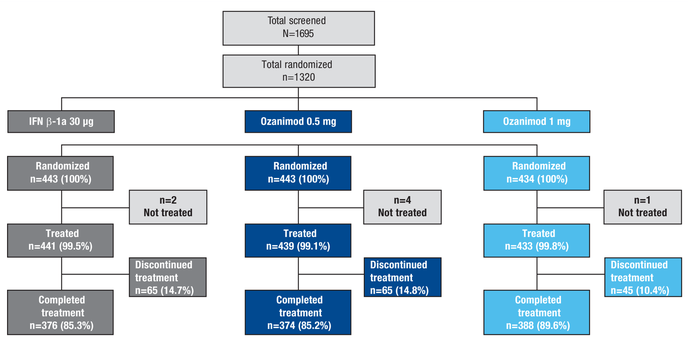
- Key inclusion criteria:
  - Age 18 to 55 years
  - MS diagnosis by 2010 McDonald criteria
  - ≥1 documented relapse in the prior year, ***or*** ≥ 1 documented relapse in prior 2 years and ≥ 1 GdE lesion in the prior year
  - Expanded Disability Status Scale score between 0.0 and 5.0
  - Clinically stable, with no relapse or corticosteroid treatment 1 month prior to screening
- Key exclusion criteria:
  - Specific cardiac conditions including recent myocardial infarction or stroke, prolonged Fridericia-corrected QT interval
  - Resting heart rate <55 beats per minute (bpm) at screening
  - Diabetes mellitus type 1, or uncontrolled diabetes mellitus type 2 with hemoglobin A1c >7%, or diabetic patients with significant co-morbidities
  - (Patients with controlled diabetes mellitus type 2 or macular edema were **not** excluded)

RESULTS

Baseline Demographics and Patient Disposition

- RMS patients were enrolled in 21 countries with similar baseline characteristics across treatment groups (Table 1)
- A total of 90% of ozanimod 1 mg and 85% of 0.5 mg patients vs 85% of IFN patients completed study treatment (Figure 3)

Figure 3. Patient Disposition



IFN β-1a, interferon β-1a.

DISCUSSION

- Both ozanimod doses demonstrated superiority to IFN β-1a on ARR and magnetic resonance imaging endpoints
  - A dose response was consistently demonstrated across these efficacy endpoints
- Whole brain volume loss, cortical gray matter volume loss, and thalamic volume loss were slowed compared with IFN β-1a
- Pooled analysis of 3-month confirmed disability progression had a very low event rate observed and did not reach statistical significance
- Overall, ozanimod was generally safe and well tolerated
  - No subjects had a second degree or higher AV block
  - Infection risk with ozanimod was comparable to treatment with IFN β-1a
  - AEs of ALT increase were transient and generally resolved without study drug discontinuation
- These efficacy and safety results demonstrate a favorable benefit:risk profile for ozanimod in RMS

RESULTS

Table 1. Demographics and Baseline Characteristics

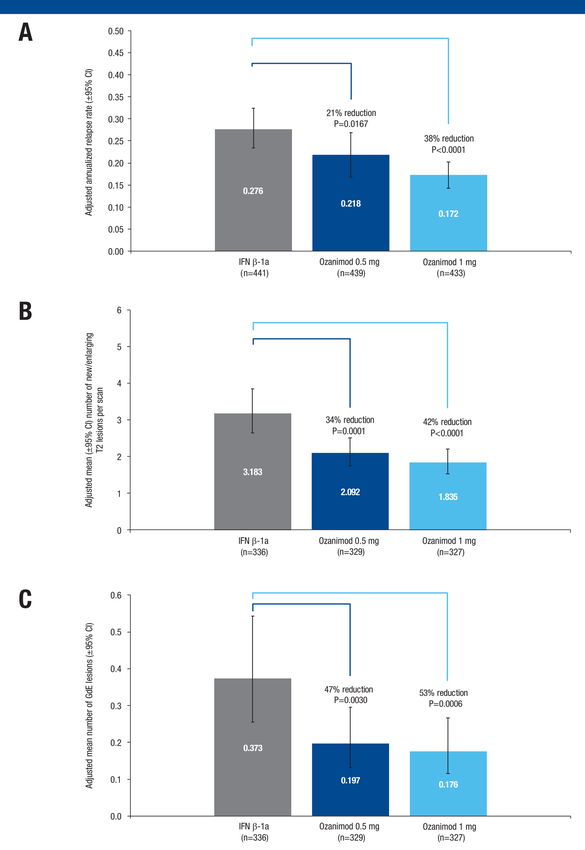
	IFN β-1a (n=441)	Ozanimod 0.5 mg (n=439)	Ozanimod 1 mg (n=433)
Age, mean years (SD)	35.1 (9.07)	35.4 (8.82)	36.0 (8.89)
Female, n (%)	304 (68.9)	287 (65.4)	291 (67.2)
Time since diagnosis, mean years (SD)	3.6 (4.61)	3.5 (4.21)	4.0 (5.17)
EDSS, mean (SD)	2.5 (1.16)	2.5 (1.17)	2.6 (1.15)
Number of relapses in prior year, mean (SD)	1.3 (0.58)	1.4 (0.64)	1.3 (0.56)
Patients previously treated with a DMT, n (%)	126 (28.6)	131 (29.8)	123 (28.4)
Patients with GdE lesions, n (%)	196 (44.4)	190 (43.3)	178 (41.1)
Normalized whole brain volume, median cm^3	1455.66	1452.88	1445.98

DMT, disease-modifying treatment; EDSS, Expanded Disability Status Scale; GdE, gadolinium-enhancing; INF β-1a, interferon β-1a; SD, standard deviation.

Efficacy

- Ozanimod 1 and 0.5 mg reduced ARR by 38% (0.172, P<0.0001) and 21% (0.218, P=0.0167) vs IFN β-1a (0.276), respectively (Figure 4A)
- Adjusted mean number of new/enlarging T2 lesions over 24 months was reduced 42% for ozanimod 1 mg (1.835, P<0.0001) and 34% for 0.5 mg (2.092, P=0.0001) vs IFN β-1a (3.183) (Figure 4B)
- Adjusted mean number of GdE lesions at 24 months was reduced 53% for ozanimod 1 mg (0.176; P=0.0006) and 47% for 0.5 mg (0.197; P=0.0030) vs IFN β-1a (0.373) (Figure 4C)
- In the pre-specified pooled analysis of both phase 3 studies, the rate of 3-month confirmed disability progression was low across all treatment groups (estimated probabilities at month 24: ozanimod 1 mg, 0.102; ozanimod 0.5 mg, 0.080; IFN β-1a, 0.099), with the ozanimod 1 and 0.5 mg groups showing 5.0% and 17.8% risk reduction, respectively, vs IFN β-1a (Figure 5)
- Ozanimod 1 mg and 0.5 mg slowed whole brain volume loss (27% and 25% reductions in median percent change from baseline, respectively; both P<0.0001) at 24 months compared with IFN β-1a (Figure 6); even more robust effects of ozanimod were seen on slowing of cortical gray matter volume loss (58% and 57%, respectively; both P<0.0001) and thalamic volume loss (32% [P<0.0001] and 30% [P=0.0012], respectively)

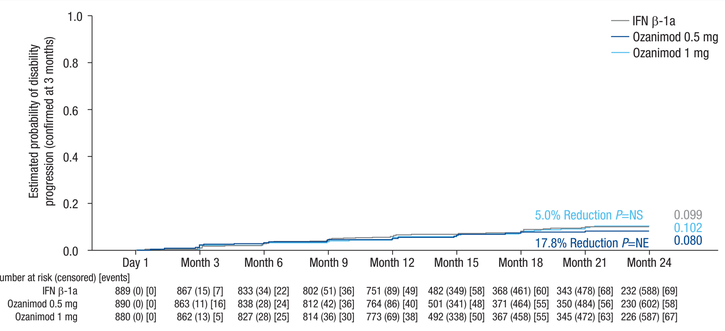
Figure 4. (A) Primary Endpoint: ARR Over 2 Years (B) Secondary Endpoint: Number of New/Enlarging T2 Lesions Over 2 Years (C) Secondary Endpoint: Number of GdE Lesions at 2 Years



Annualized relapse rate (ARR) was analyzed using a Poisson regression model adjusted for region (Eastern Europe vs Rest of World), baseline age, and baseline number of GdE lesions, with natural log transformation of time on study as an offset term. Analysis of T2 and GdE lesions based on a negative binominal regression model using observed data adjusted for region (Eastern Europe vs Rest of World), baseline age, and baseline number of gadolinium-enhancing lesions, with natural log transformation of number of available scans over 24 months as an offset term.

CI, confidence interval; GdE, gadolinium-enhancing; IFN β-1a, interferon β-1a.

Figure 5. Pooled Phase 3 Studies (RADIANCE and SUNBEAM): Time to 3-Month Confirmed Disability Progression



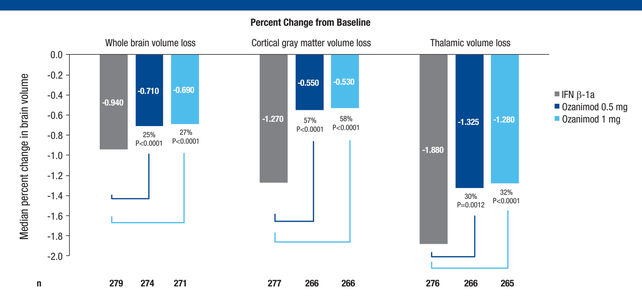
Number at risk (censored) [events]

IFN β-1a	889 (0) [0]	867 (15) [7]	833 (34) [22]	802 (51) [36]	751 (89) [49]	482 (349) [58]	368 (461) [60]	343 (478) [68]	232 (588) [69]
Ozanimod 0.5 mg	890 (0) [0]	863 (11) [16]	838 (28) [24]	812 (42) [36]	764 (86) [40]	501 (341) [48]	371 (464) [55]	350 (484) [56]	230 (602) [58]
Ozanimod 1 mg	880 (0) [0]	862 (13) [5]	827 (28) [25]	814 (36) [30]	773 (69) [38]	492 (338) [50]	367 (458) [55]	345 (472) [63]	226 (587) [67]

Time to onset of confirmed disability progression analyzed using a Cox proportional hazards model adjusted for region (Eastern Europe vs Rest of World), baseline age, baseline Expanded Disability Status Scale, and study. Estimated proportion based on Kaplan–Meier estimates.

IFN β-1a, interferon β-1a; NS, not significant; NE, not evaluated due to the hierarchical statistical testing procedure.

Figure 6. Brain Volume Loss Over 2 Years



P-value for comparison between the ozanimod and interferon β-1a (IFN β-1a) treatment groups are nominal and are based on rank analysis of covariance model, adjusted for region (Eastern Europe vs Rest of the World), and Expanded Disability Status Scale category per Interactive Voice Response System, with the residual of the rank at baseline as the dependent variable regressed on rank of percent change from baseline.

IFN β-1a, interferon β-1a.

Safety

- Incidence of adverse events (AEs), serious AEs, and AEs leading to discontinuation was balanced across treatment groups (Table 2)
  - AEs that differed in incidence between ozanimod- and IFN β-1a–treated patients are shown in Table 3
- Cardiac safety:
  - The largest mean supine heart rate reduction on day 1, hours 1–6, was 0.6 bpm at hour 5. Minimum supine heart rates are shown in Table 4
  - No atrioventricular (AV) block of second degree or higher were reported during the study
  - Serious cardiac AEs were infrequent and balanced across treatment groups (IFN β-1a: 2 [0.5%]; ozanimod 0.5 mg: 3 [0.7%]; 1 mg: 0 [0%])
- AEs of alanine aminotransferase (ALT) increased were transient and generally resolved without study drug discontinuation
- Infections AEs and serious AEs were infrequent and balanced across treatment groups (Table 5)
- No serious opportunistic infections were reported

Table 2. Summary of AEs

	IFN β-1a (n=440)	Ozanimod 0.5 mg (n=439)	Ozanimod 1 mg (n=434)
Any AE, n (%)	365 (83.0)	326 (74.3)	324 (74.7)
At least one moderate or severe AE[a], n (%)	235 (53.4)	169 (38.5)	170 (39.2)
At least one severe AE[a], n (%)	19 (4.3)	19 (4.3)	15 (3.5)
Serious AE, n (%)	28 (6.4)	31 (7.1)	28 (6.5)
AE leading to study drug discontinuation, n (%)	18 (4.1)	14 (3.2)	13 (3.0)
Death[b], n (%)	0	1 (0.2)	0

[a]As reported by the investigator; [b]One death was reported during the study as death by drowning on study day 637 considered unrelated to study drug in a subject in the ozanimod 0.5 mg group.
AE, adverse event; IFN β-1a, interferon β-1a.

Table 3. Adverse Events in ≥5% of Patients in an Ozanimod Treatment Group With at Least 1% Difference From IFN β-1a

	IFN β-1a (n=440)	Ozanimod 0.5 mg (n=439)	Ozanimod 1 mg (n=434)
Nasopharyngitis, n (%)	48 (10.9)	59 (13.4)	68 (15.7)
Headache, n (%)	53 (12.0)	55 (12.5)	44 (10.1)
Alanine aminotransferase increased, n (%)	20 (4.5)	29 (6.6)	26 (6.0)
Influenza-like illness, n (%)	215 (48.9)	26 (5.9)	27 (6.2)
Hypertension, n (%)	14 (3.2)	20 (4.6)	24 (5.5)
Gamma-glutamyltransferase increased, n (%)	9 (2.0)	16 (3.6)	25 (5.8)
Pharyngitis, n (%)	15 (3.4)	24 (5.5)	17 (3.9)
Urinary tract infection, n (%)	17 (3.9)	22 (5.0)	19 (4.4)

Adverse events (AEs) where the incidence in either ozanimod group was higher than in the interferon β-1a (IFN β-1a) group or where the incidence in the IFN β-1a group is higher than in either ozanimod group are shown. Highest incidences are highlighted by red boxes. AEs are sorted by decreasing incidence in all ozanimod-treated patients (not shown).

Table 4. Minimum Supine Heart Rate

Minimum supine heart rate (day 1, hours 1–6), bpm, n (%)	IFN β-1a (n=438)	Ozanimod 0.5 mg[a] (n=438)	Ozanimod 1 mg[a] (n=434)
≥65	274 (62.6)	189 (43.2)	187 (43.1)
55–64	147 (33.6)	209 (47.7)	200 (46.1)
45–54	17 (3.9)	39 (8.9)	44 (10.1)
40–44[b]	0	1 (0.2)	3 (0.7)
<40	0	0	0

[a]On Day 1, all patients in the ozanimod treatment groups received a dose of ozanimod 0.25 mg; [b]Patients with heart rate 40–44 were asymptomatic and resolved by hour 7 or 8.
bpm, beats per minute; IFN β-1a, interferon β-1a.

Table 5. Infections

At any time during the study	IFN β-1a (n=440)	Ozanimod 0.5 mg[a] (n=439)	Ozanimod 1 mg[a] (n=434)
Infections: AEs, n (%)	186 (42.3)	171 (39.0)	182 (41.9)
Infections: SAEs, n (%)	4 (0.9)	4 (0.9)	4 (0.9)
AEs: herpetic infections[a], n (%)	11 (2.5)	10 (2.3)	9 (2.1)

[a]Preferred terms include: oral herpes, herpes zoster, herpes simplex, herpes virus infection, herpes dermatitis, and varicella zoster virus infection.
AE, adverse event; IFN β-1a, interferon β-1a; SAE, serious adverse event.

DISCLOSURES

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LITERATURE

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