Ozanimod Demonstrates Efficacy and Safety in a Phase 3 Trial of Relapsing Multiple Sclerosis (SUNBEAM)

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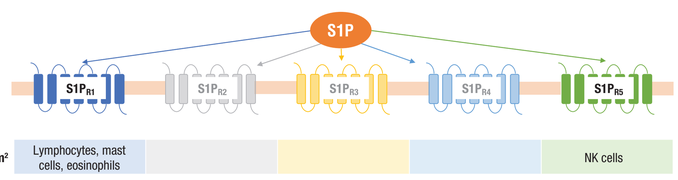
INTRODUCTION

- Sphingosine 1-phosphate (S1P), a lysophospholipid secreted by platelets and leukocytes, interacts with a family of 5 high-affinity G protein–coupled receptors: S1P receptor 1 ($S1P_{R1}$) through S1P receptor 5 ($S1P_{R5}$) (Figure 1)[1]
- Ozanimod is an oral, once-daily immunomodulator that selectively targets $S1P_{R1}$ and $S1P_{R5}$, resulting in the retention of autoreactive, $CCR7^+$ T cells and B cells in lymphoid tissues
- $CCR7^-$ lymphocytes continue to circulate, maintaining viral and tumor surveillance

Figure 1. Cellular Distribution of S1P Receptors[2]

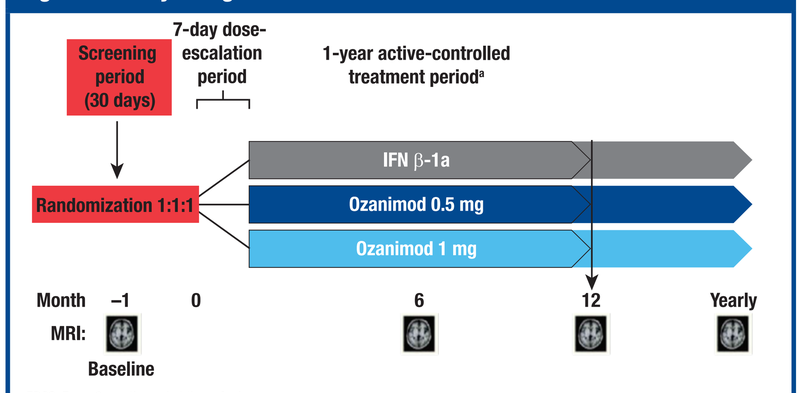


NK, natural killer; S1P, sphingosine 1-phosphate; S1PR, sphingosine 1-phosphate receptor.

METHODS

- SUNBEAM was a multicenter, randomized, double-blind, double-dummy, parallel-group, active treatment–controlled study of once-daily oral ozanimod HCl 1 or 0.5 mg versus 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 during the treatment period
- Secondary endpoints:
  - New or enlarging T2 lesions from baseline over 1 year
  - Gadolinium-enhancing (GdE) lesions at 1 year
  - 3-month confirmed disability progression prespecified as a pooled analysis of the SUNBEAM and RADIANCE Part B phase 3 studies
  - Whole brain volume loss at 1 year
- The intent-to-treat (ITT) 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

[a]All patients continued on treatment until the last patient completed 1 year.
EDSS, Expanded Disability Status Scale; IFN β-1a, interferon β-1a; MRI, magnetic resonance imaging.

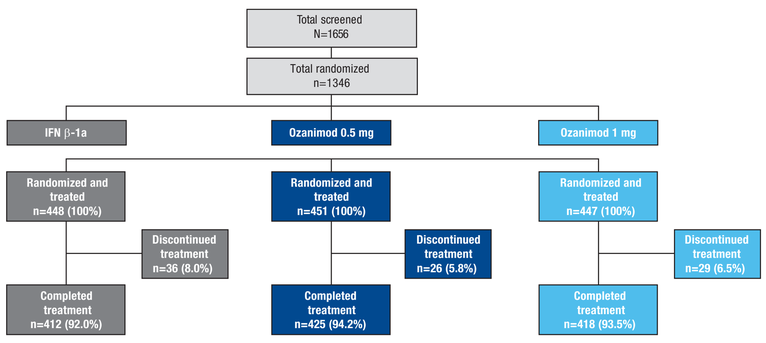
- Key inclusion criteria:
  - Age 18 to 55 years
  - Multiple sclerosis diagnosis by 2010 McDonald criteria
  - ≥1 documented relapse in prior year, ***or*** ≥1 documented relapse in prior 2 years and ≥1 GdE lesion in prior year
  - Expanded Disability Status Scale score between 0.0 and 5.0
  - Clinically stable, with no relapse or corticosteroid treatment 1 month prior to screening
- Key exclusion criteria:
  - Specific cardiac conditions, including recent myocardial infarction, stroke, or prolonged Fridericia-corrected QT interval
  - Resting heart rate <55 beats per minute (bpm) at screening
  - Diabetes mellitus type 1, uncontrolled diabetes mellitus type 2 with hemoglobin A1c >9%, or diabetic patients with significant comorbidities
  - (Patients with controlled diabetes mellitus type 2 or macular edema were not excluded)

RESULTS

Baseline Demographics and Patient Disposition

- 1346 RMS patients were enrolled in 20 countries, with similar baseline characteristics across treatment groups (Figure 3, Table 1)
- Mean treatment duration was 13.6 months

Figure 3. Patient Disposition



DISCUSSION

- Both ozanimod doses demonstrated superiority to IFN β-1a on ARR and MRI 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
- A 31% risk reduction for ozanimod 1 mg and a 11% risk reduction for ozanimod 0.5 mg versus IFN β-1a in 3-month confirmed disability progression was observed in SUNBEAM
- 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

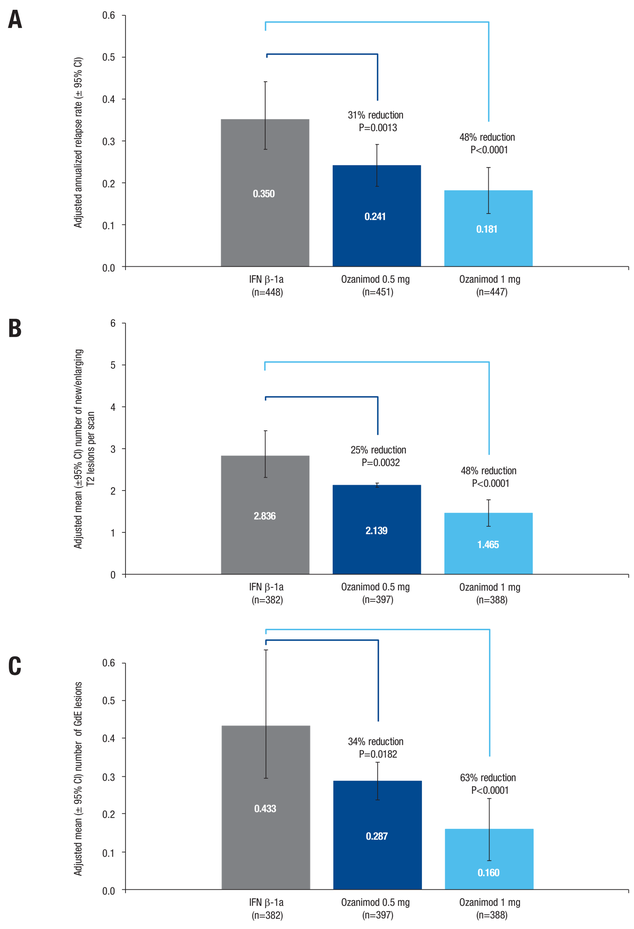
	IFN β-1a (n=448)	Ozanimod 0.5 mg (n=451)	Ozanimod 1 mg (n=447)
Age, mean years (SD)	35.9 (9.11)	36.0 (9.43)	34.8 (9.24)
Female, n (%)	300 (67.0)	311 (69.0)	283 (63.3)
Time since diagnosis, mean years (SD)	3.7 (4.36)	3.7 (4.52)	3.6 (4.19)
EDSS, mean (SD)	2.6 (1.14)	2.7 (1.14)	2.6 (1.16)
Number of relapses in prior year, mean (SD)	1.3 (0.55)	1.3 (0.57)	1.3 (0.57)
Patients previously treated with a DMT, n (%)	151 (33.7)	132 (29.3)	128 (28.6)
Patients with GdE lesions, n (%)	216 (48.2)	202 (44.8)	214 (47.9)
Normalized whole brain volume, median cm^3	1445.53	1453.03	1458.30

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

Efficacy

- Ozanimod 1 and 0.5 mg reduced ARR by 48% (0.181, P<0.0001) and 31% (0.241, P=0.0013), respectively vs IFN β-1a (0.350) (Figure 4A)
- Adjusted mean number of new/enlarging T2 lesions per scan over 12 months was reduced 48% for ozanimod 1 mg (1.465; P<0.0001) and 25% for ozanimod 0.5 mg (2.139; P=0.0032) vs IFN β-1a (2.836) (Figure 4B)
- Adjusted mean number of GdE lesions at 12 months was reduced 63% for ozanimod 1 mg (0.160; P<0.0001) and 34% for ozanimod 0.5 mg (0.287; P=0.0182) vs IFN β-1a (0.433) (Figure 4C)
- The rate of 3-month confirmed disability progression was low across all treatment groups (estimated probabilities at month 15: ozanimod 1 mg, 0.030; ozanimod 0.5 mg, 0.039; IFN β-1a, 0.045), with the ozanimod 1 mg and 0.5 mg groups showing 31% and 11% reduction, respectively, vs IFN β-1a (Figure 5)
- Ozanimod 1 mg and 0.5 mg slowed whole brain volume loss (33% [P<0.0001] and 12% [P=0.0615] reductions in median percent change from baseline, respectively) at 12 months compared with IFN β-1a. Even greater effects of ozanimod were observed for cortical gray matter volume loss (84% and 61%, both P<0.0001) and thalamic volume loss (39% and 34%, both P<0.0001) (Figure 6)

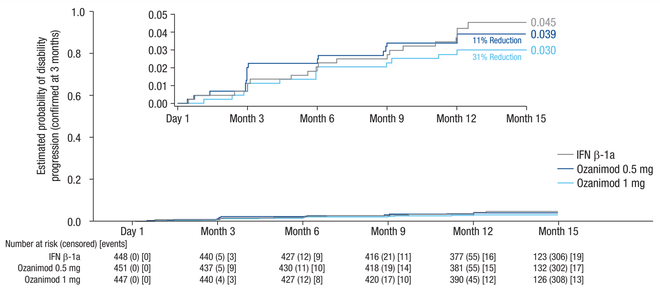
Figure 4. (A) Primary Endpoint: Annualized Relapse Rate During Treatment Period (B) Secondary Endpoint: Number of New/Enlarging T2 Lesions Over 1 Year (C) Secondary Endpoint: Number of GdE Lesions at 1 Year



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. Analyses of T2 and GdE lesions were based on negative binominal regression models using observed data adjusted for region (Eastern Europe vs Rest of World), baseline age, and baseline number of GdE lesions, with natural log transformation of number of available scans over 12 months as an offset term.

ARR, annualized relapse rate; CI, confidence interval; GdE, gadolinium-enhancing; IFN β-1a, interferon β-1a.

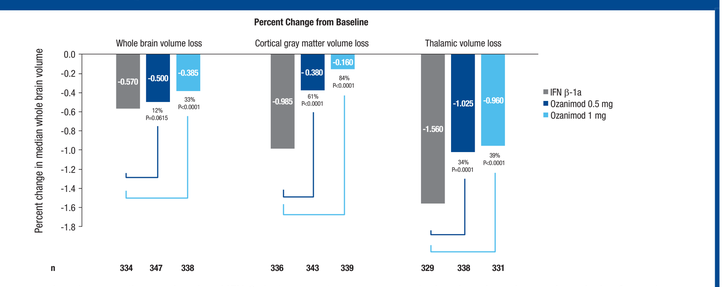
Figure 5. Time to Onset of 3-Month Confirmed Disability in SUNBEAM



Time to onset of 3-month confirmed disability progression analyzed using a Cox proportional hazards model adjusted for region (Eastern Europe vs Rest of World), baseline age, and baseline EDSS. Estimated proportions based on Kaplan-Meier estimates. Results for SUNBEAM are shown above. Formal statistical testing of this endpoint was prospectively planned as a pooled analysis using data from both Phase 3 studies (SUNBEAM and RADIANCE Part B).

EDSS, Expanded Disability Status Scale; IFN β-1a, interferon β-1a.

Figure 6. Secondary Endpoint: Whole Brain Volume Loss over 1 Year



P-value for comparison between the ozanimod and 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

- Treatment-emergent adverse events (AEs), serious AEs, and AEs leading to discontinuation were similar across treatment groups (Table 2)
  - Most treatment-emergent AEs were mild
  - Incidence of serious AEs was low, with no distinct pattern reported
  - AEs that differed in incidence between ozanimod– and IFN β-1a–treated patients are shown in Table 3
- AEs of alanine aminotransferase (ALT) increased were transient and generally resolved without study drug discontinuation
- Cardiac safety:
  - The largest mean supine heart rate reduction on day 1, hours 1–6, was -1.8 bpm at hour 5. Minimum supine heart rates are shown in Table 4
  - No atrioventricular (AV) block of second degree or higher was reported during the study
  - Serious cardiac AEs were infrequent and balanced across treatment groups
- Infections:
  - Serious infection AEs were infrequent and balanced across treatment groups (Table 5)
  - No serious opportunistic infections were reported in ozanimod-treated patients

Table 2. Summary of Adverse Events

	IFN β-1a (n=445)	Ozanimod 0.5 mg (n=453)	Ozanimod 1 mg (n=448)
Any AE, n (%)	336 (75.5)	259 (57.2)	268 (59.8)
At least one moderate or severe AE[a], n (%)	182 (40.9)	113 (24.9)	138 (30.8)
At least one severe AE[a], n (%)	10 (2.2)	10 (2.2)	7 (1.6)
Serious AE, n (%)	11 (2.5)	16 (3.5)	13 (2.9)
AE leading to study drug discontinuation, n (%)	16 (3.6)	7 (1.5)	13 (2.9)
Death, n (%)	0	0	0

[a]As reported by the investigator.
AE, adverse event; IFN β-1a, interferon β-1a.

Table 3. Adverse Events in ≥2% of Patients in an Ozanimod Treatment Group with at Least 1% Difference from IFN β-1a

	IFN β-1a (n=445)	Ozanimod 0.5 mg (n=453)	Ozanimod 1 mg (n=448)
Nasopharyngitis, n (%)	36 (8.1)	44 (9.7)	30 (6.7)
Headache, n (%)	25 (5.6)	27 (6.0)	34 (7.6)
Upper respiratory tract infection, n (%)	24 (5.4)	31 (6.8)	18 (4.0)
Influenza-like illness, n (%)	227 (51.0)	18 (4.0)	17 (3.8)
ALT increased, n (%)	8 (1.8)	12 (2.6)	21 (4.7)
Back pain, n (%)	9 (2.0)	10 (2.2)	17 (3.8)
Gamma-glutamyltransferase increased, n (%)	2 (0.4)	10 (2.2)	15 (3.3)
Respiratory tract infection, viral, n (%)	3 (0.7)	10 (2.2)	15 (3.3)
Urinary tract infection, n (%)	10 (2.2)	8 (1.8)	17 (3.8)

Highest incidences are highlighted as denoted by red boxes. AEs are sorted by decreasing incidence in all ozanimod-treated patients (not shown).
ALT, alanine aminotransferase; IFN β-1a, interferon β-1a.

Table 4. Minimum Supine Heart Rate

Minimum supine heart rate (day 1, hours 1–6), bpm	IFN β-1a (n=445)	Ozanimod 0.5 mg[a] (n=452)	Ozanimod 1 mg[a] (n=448)
≥65, n (%)	256 (57.5)	167 (36.9)	151 (33.7)
55–64, n (%)	167 (37.5)	242 (53.5)	246 (54.9)
45–54, n (%)	22 (4.9)	43 (9.5)	51 (11.4)
<45, n (%)	0	0	0

[a]On day 1, all patients in the ozanimod treatment groups received a dose of ozanimod 0.25 mg
bpm, beats per minute; IFN β-1a, interferon β-1a.

Table 5. Infections

At any time during the study	IFN β-1a (n=445)	Ozanimod 0.5 mg (n=453)	Ozanimod 1 mg (n=448)
Infections: AEs, n (%)	119 (26.7)	131 (28.9)	128 (28.6)
Infections: serious AEs, n (%)	3 (0.7)	1 (0.2)	5 (1.1)
AEs: herpetic infections[a], n (%)	5 (1.1)	3 (0.7)	4 (0.9)

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

DISCLOSURES

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LITERATURE

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