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

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BACKGROUND

- Ozanimod is an oral, once-daily immunomodulator that selectively targets sphingosine 1-phosphate receptor 1 ($S1P_{R1}$) and $S1P_{R5}$
- The S1P receptor specificity and pharmaceutical properties (eg, low maximum plasma concentration) of ozanimod, combined with use of an initial dose-escalation regimen, are anticipated to result in a favorable benefit-risk profile

OBJECTIVES

- Report results from SUNBEAM (NCT02294058), one of two phase 3 studies comparing once-daily ozanimod with interferon (IFN) β-1a in patients with relapsing multiple sclerosis (RMS)

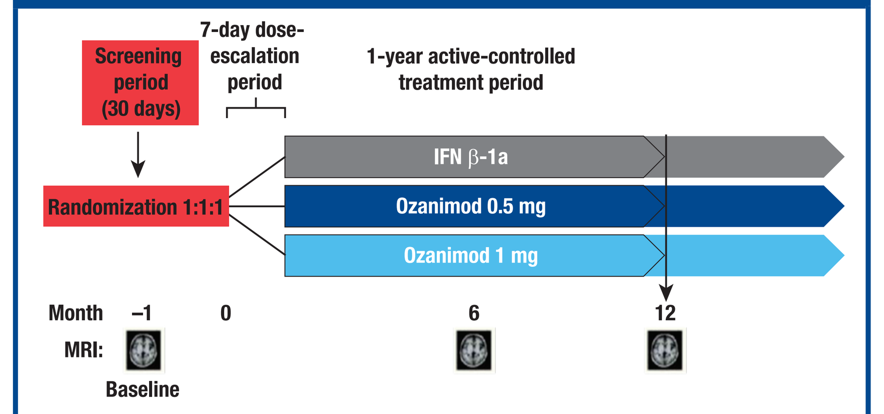
METHODS

- SUNBEAM was a multicenter, randomized, double-blind, double-dummy, parallel-group, active-controlled study (Figure 1)
- Key inclusion criteria:
  - Age 18–55 years
  - Multiple sclerosis diagnosis by 2010 McDonald criteria
  - ≥1 documented relapse in prior year or ≥1 documented relapse in prior 2 years plus ≥1 gadolinium-enhancing (GdE) lesion in prior year
  - Expanded Disability Status Scale score between 0–5.0
  - 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 QTcF interval
  - Resting heart rate <55 bpm at screening
  - Diabetes mellitus type 1, uncontrolled diabetes mellitus type 2 with hemoglobin A1c >9%, or diabetes patients with significant comorbidities
    - Patients with controlled diabetes mellitus type 2 or macular edema were eligible
- Patients were randomized (1:1:1) to once-daily oral ozanimod HCl 1 mg or 0.5 mg or once-weekly intramuscular IFN β-1a 30 μg for ≥1 year
- An initial 7-day dose-escalation regimen was employed for all participants. Participants randomized to ozanimod received 0.25 mg on days 1–4, 0.5 mg on days 5–7, and their assigned ozanimod dose starting on day 8

METHODS

- Patients received randomized, blinded treatment until the last active patient was treated for ≥12 months
- 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
  - GdE lesions at 1 year
  - Time to 3-month confirmed disability progression was evaluated in each phase 3 study (see Results section for SUNBEAM results) and was prespecified as a pooled analysis of SUNBEAM and RADIANCE Part B
  - Whole brain volume loss at 1 year
- Exploratory endpoints:
  - Cortical gray matter volume and thalamic volume loss at 1 year
- The intent-to-treat population, defined as all patients who were randomized and received ≥1 dose of study drug, was used for all efficacy analyses
- The safety population, defined as all patients who received ≥1 dose of study drug, was used for all safety analyses, with patients grouped according to the highest dose of ozanimod received

Figure 1. SUNBEAM Study Design



Expanded Disability Status Scale: Every 3 months and at time of relapse.
All magnetic resonance imaging (MRI) analyses performed by a blinded central imaging facility.

IFN β-1a, interferon β-1a.

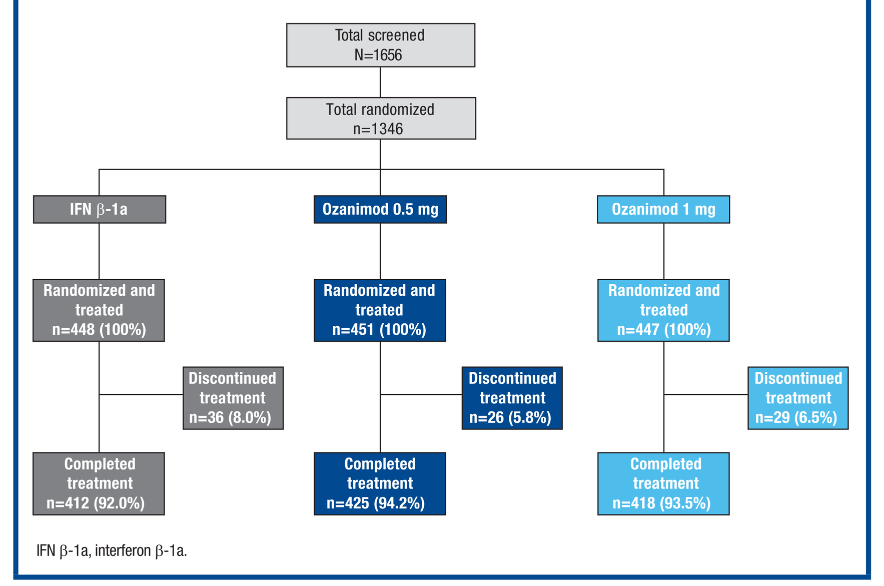
RESULTS

Baseline Demographics and Patient Disposition

- A total of 1346 RMS patients were randomized (Figure 2), with similar baseline characteristics across treatment groups (Table 1)
- Mean treatment duration was 13.6 months

RESULTS

Figure 2. Patient Disposition



IFN β-1a, interferon β-1a.

Table 1. Demographics and Baseline Characteristics

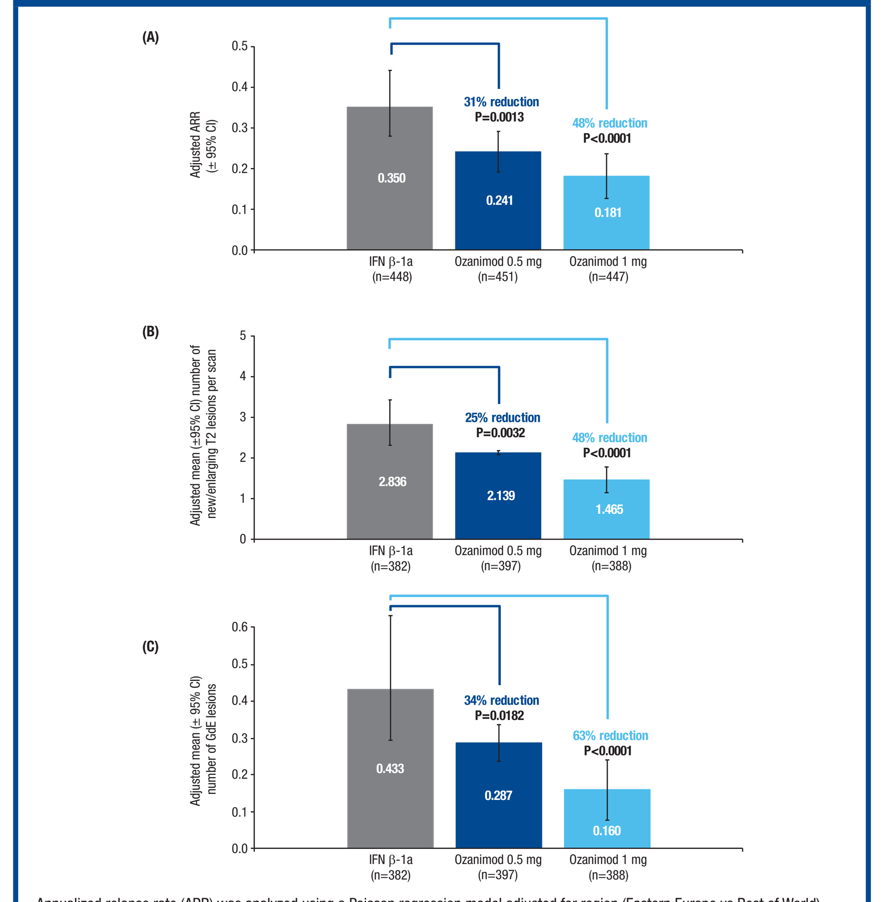
	IFN β-1a (n=448)	Ozanimod 0.5 mg (n=451)	Ozanimod 1 mg (n=447)
Age, mean years (SD)	35.9 (9.11)	36.0 (9.43)	34.8 (9.24)
Female, n (%)	300 (67.0)	311 (69.0)	283 (63.3)
Time since diagnosis, mean years (SD)	3.7 (4.36)	3.7 (4.52)	3.6 (4.19)
EDSS score, mean (SD)	2.6 (1.14)	2.7 (1.14)	2.6 (1.16)
Number of 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 cm³	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 mg and 0.5 mg reduced ARR by 48% (0.181, P<0.0001) and 31% (0.241, P=0.0013), respectively, versus IFN β-1a (0.350) (Figure 3A)
- Adjusted mean number of new/enlarging T2 lesions per scan over 12 months was reduced by 48% for ozanimod 1 mg (1.465; P<0.0001) and 25% for ozanimod 0.5 mg (2.139; P=0.0032) versus IFN β-1a (2.836) (Figure 3B)
- Adjusted mean number of GdE lesions at 1 year was reduced by 63% for ozanimod 1 mg (0.160; P<0.0001) and 34% for ozanimod 0.5 mg (0.287; P=0.0182) versus IFN β-1a (0.433) (Figure 3C)
- Ozanimod 1 mg and 0.5 mg reduced the risk of 3-month confirmed disability progression by 31% and 11%, respectively, versus IFN β-1a, with a low rate of progression across all groups (Figure 4)

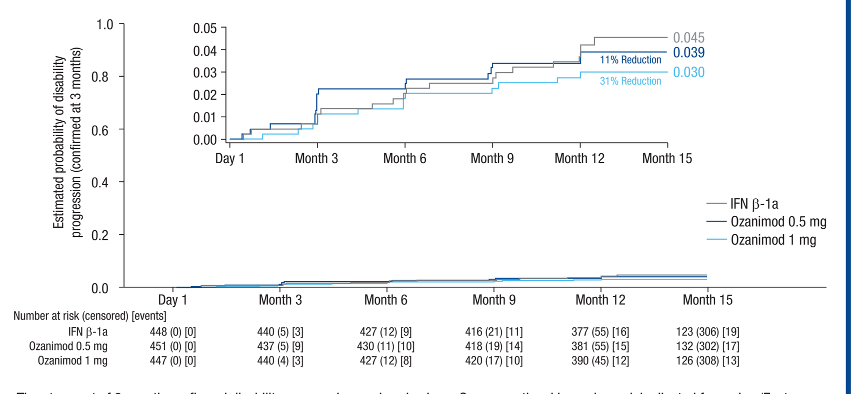
Figure 3. (A) Primary Endpoint: ARR During Treatment Period (B) Secondary Endpoint: Number of New/Enlarging T2 Lesions Over 1 Year (C) Secondary Endpoint: Number of GdE Lesions at 1 Year



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 gadolinium-enhancing (GdE) lesions, with the 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 the natural log transformation of number of available scans over 12 months as an offset term.

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

Figure 4. Time to Onset of 3-Month Confirmed Disability Progression



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 Expanded Disability Status Scale score. 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).

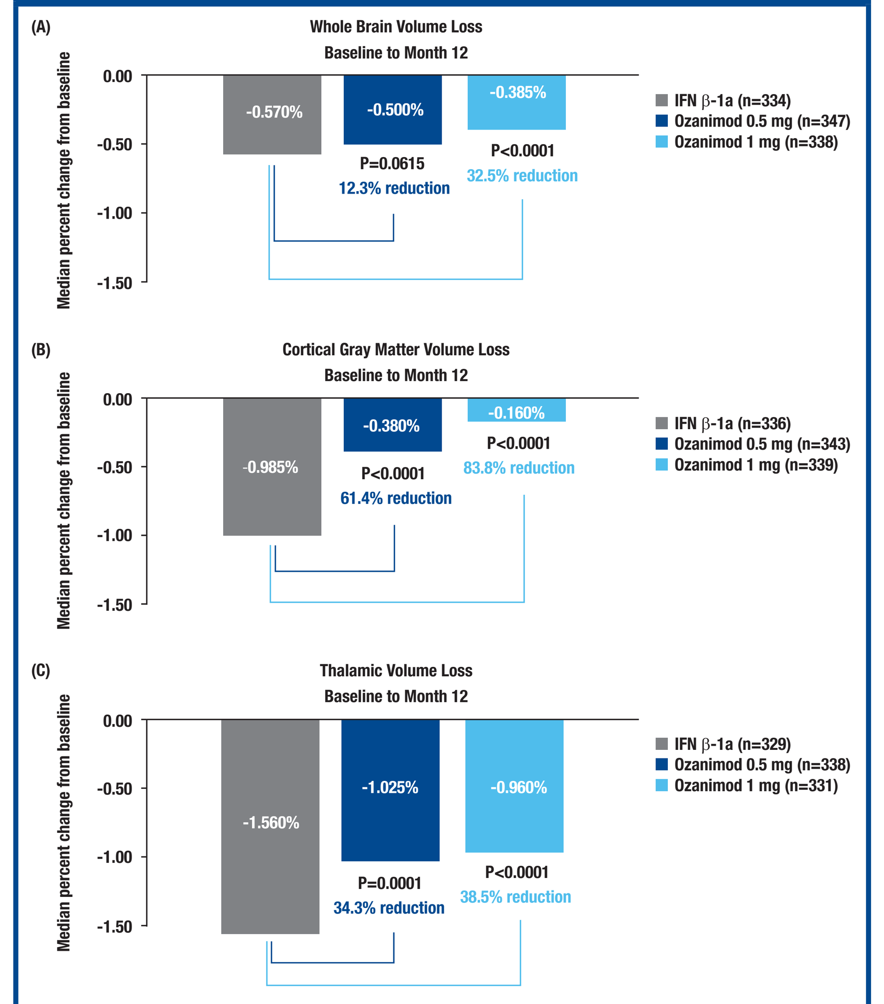
IFN β-1a, interferon β-1a.

- Following 1 year of treatment, patients in the ozanimod 1-mg group had slowing of whole brain volume loss versus IFN β-1a (P<0.0001; 32.5% reduction in median relative to IFN β-1a; median percent change from baseline: -0.385% [ozanimod 1 mg], -0.570% [IFN β-1a]). Patients in the ozanimod 0.5-mg group demonstrated a trend toward slowing brain volume loss (P=0.0615; 12.3% reduction in median relative to IFN β-1a; median percent change from baseline: -0.500%) (Figure 5A)
- Patients in both the ozanimod 1-mg and 0.5-mg groups demonstrated slowing of cortical gray matter loss: P<0.0001; 83.8% reduction in median; median percent change from baseline: -0.160% and P<0.0001; 61.4% reduction in median; median percent change from baseline: -0.380%, respectively, relative to IFN β-1a (-0.985%) (Figure 5B)
- Patients in both the ozanimod 1-mg and 0.5-mg groups demonstrated slowing of thalamic volume loss: P<0.0001; 38.5% reduction in median; median percent change from baseline: -0.960% and P=0.0001; 34.3% reduction in median; median percent change from baseline: -1.025%, respectively, relative to IFN β-1a (-1.560%) (Figure 5C)

Safety

- Treatment-emergent adverse events (AEs) and AEs leading to discontinuation were more frequent in the IFN β-1a group. Serious AEs 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
- 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 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
- Alanine aminotransferase (ALT) elevations ≥3 times the upper level of normal were reported in 4.3% (19/447) of patients treated with ozanimod 1 mg, 1.8% (8/453) treated with ozanimod 0.5 mg, and 2.2% (10/445) treated with IFN β-1a. AEs of elevated ALT were transient and generally resolved without study drug discontinuation

Figure 5. (A) Whole Brain Volume Loss, (B) Cortical Gray Matter Volume Loss, and (C) Thalamic Volume Loss at Year 1 Relative to Baseline (Observed, ITT Population)



Brain volume loss was evaluated using the Jacobian integration method to assess changes in normalized whole brain, cortical gray matter, and thalamic volumes. P-values are based on rank analysis of covariance, adjusted for region (Eastern Europe vs Rest of World) and Expanded Disability Status Scale score randomization category (≤3.5 vs >3.5), with the residual of the rank of (A) whole brain volume, (B) cortical gray matter volume, and (C) thalamic volume at baseline as the dependent variable regressed on rank of percent change from baseline. Treatment effects are reported as percent reductions in median percent change from baseline in each ozanimod treatment group relative to interferon (IFN) β-1a.

ITT, intent-to-treat.

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)
Any moderate or severe AE[a], n (%)	182 (40.9)	113 (24.9)	138 (30.8)
Any 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.

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Table 3. Adverse Events in ≥5% of Patients in Either Ozanimod Treatment Group With ≥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)

Highest incidences are denoted by red boxes. Adverse events are sorted by decreasing incidence in all ozanimod-treated patients (not shown).
IFN β-1a, interferon β-1a.

Table 4. Minimum Supine Heart Rate on Day 1, Hours 1–6

Minimum supine heart rate (day 1, hours 1–6), bpm	IFN β-1a (n=445)	Ozanimod 0.5 mg[a] (n=453)	Ozanimod 1 mg[a] (n=448)
Patients with ≥1 assessment, n	442	443	441
≥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 Adverse Events

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.

CONCLUSIONS

- Both ozanimod doses demonstrated superiority to IFN β-1a on ARR
- Adjusted mean numbers of new/enlarging T2 lesions per scan and GdE lesions at 1 year were significantly lower for both doses of ozanimod versus IFN β-1a
- Whole brain volume loss, cortical gray matter volume loss, and thalamic volume loss were reduced compared with IFN β-1a
- A dose response was consistently demonstrated across ARR and MRI efficacy endpoints
- Overall, ozanimod was well tolerated with an acceptable safety profile
- These efficacy and safety results demonstrate a favorable benefit-risk profile for ozanimod in RMS

Disclosures

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