Ozanimod Demonstrates Preservation of Brain Volume at 1 and 2 Years in Two Phase 3 Trials of Relapsing Multiple Sclerosis (SUNBEAM and RADIANCE)

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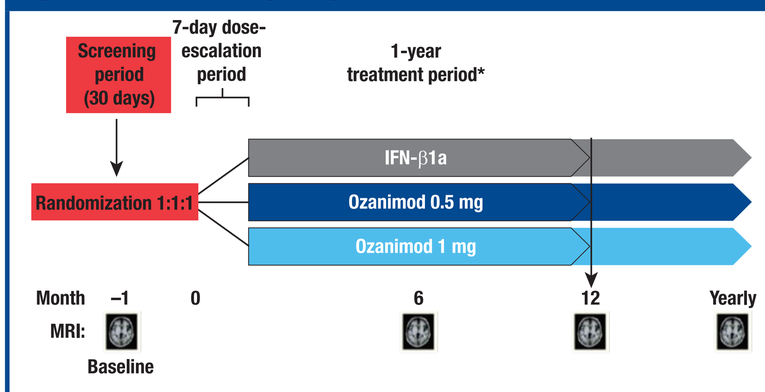
INTRODUCTION

- Ozanimod HCl (RPC1063), an oral, once-daily immunomodulator that selectively targets sphingosine 1-phosphate receptors 1 and 5, is in clinical development for treatment of relapsing multiple sclerosis (RMS)
- Recent results show that ozanimod significantly reduces annualized relapse rate and magnetic resonance imaging (MRI) lesion activity in two phase 3 RMS studies, SUNBEAM[1] and RADIANCE Part B[2]
- Brain atrophy, as measured by whole brain, cortical gray matter, and thalamic brain volume loss (BVL), has been demonstrated to correlate with cognitive dysfunction and disability accrual in patients with RMS[3–5]
- Reducing BVL is therefore an important treatment goal

METHODS

- SUNBEAM (NCT02294058; Figure 1) and RADIANCE Part B (NCT02047734; Figure 2) were two randomized, double-blind, double-dummy, active-controlled, parallel-group, phase 3 studies
  - Adult patients with RMS were randomized (1:1:1) to once-daily ozanimod 1 mg, once-daily ozanimod 0.5 mg, or weekly intramuscular interferon beta-1a (IFN-β1a) 30 µg for ≥12 months in SUNBEAM and 24 months in RADIANCE Part B
- Whole BVL was a secondary endpoint; cortical gray matter and thalamic volumes were exploratory endpoints
  - BVL was evaluated using the Jacobian integration method to assess changes in normalized whole brain, cortical gray matter, and thalamic volumes
  - Percent change in brain volume from baseline was compared between each ozanimod group and the IFN-β1a group using rank analysis of covariance, adjusted for region and Expanded Disability Status Score category, using observed data
  - Treatment effects are reported as percent reductions in median percent change from baseline in each ozanimod group relative to IFN-β1a

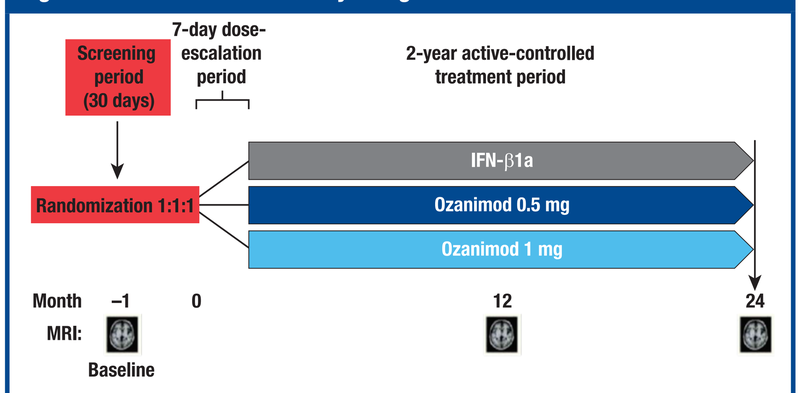
Figure 1. SUNBEAM Study Design



*Patients received randomized, blinded treatment until the last active patients were treated for at least 12 months, or discontinued.

IFN-β1a, interferon beta-1a; MRI, magnetic resonance imaging.

Figure 2. RADIANCE Part B Study Design



IFN-β1a, interferon beta-1a; MRI, magnetic resonance imaging.

DISCUSSION

- Ozanimod treatment resulted in significant effects in limiting BVL compared with IFN-β1a at both 12 months (SUNBEAM) and 24 months (RADIANCE). These results complement the ozanimod treatment effects demonstrated for gadolinium-enhancing and T2 lesion rates[4,5]
- This effect of ozanimod limiting BVL in both of these studies may suggest a favorable long-term impact on disability and cognition in patients with RMS

RESULTS

SUNBEAM

RADIANCE PART B

- Baseline MRI characteristics, including brain volumes, were similar across all treatment groups for both trials (Table 1, Table 2)

Table 1. Baseline Characteristics in SUNBEAM (ITT Population)

	IFN-β1a (n=448)	Ozanimod 0.5 mg (n=451)	Ozanimod 1 mg (n=447)
Mean (SD) age, years	35.9 (9.11)	36.0 (9.43)	34.8 (9.24)
Sex, female, n (%)	300 (67.0)	311 (69.0)	283 (63.3)
Race, White, n (%)	447 (99.8)	447 (99.1)	446 (99.8)
Region, Eastern Europe[a], n (%)	419 (93.5)	419 (92.9)	415 (92.8)
EDSS score ≤3.5, n (%)	370 (82.6)	360 (79.8)	360 (80.5)
GdE lesion presence, n (%)	216 (48.2)	202 (44.8)	214 (47.9)
Mean (SD) number of GdE lesions	1.7 (3.22)	1.6 (2.95)	1.8 (3.41)
Mean (SD) number of T2 lesions	53.7 (37.80)	53.6 (35.56)	54.5 (39.48)
Median normalized brain volume (cm^3)	1445.5	1453.0	1458.3
Median normalized cortical gray matter volume (cm^3)	523.5	527.3	525.1
Median normalized thalamic volume (cm^3)	15.4	15.4	15.4

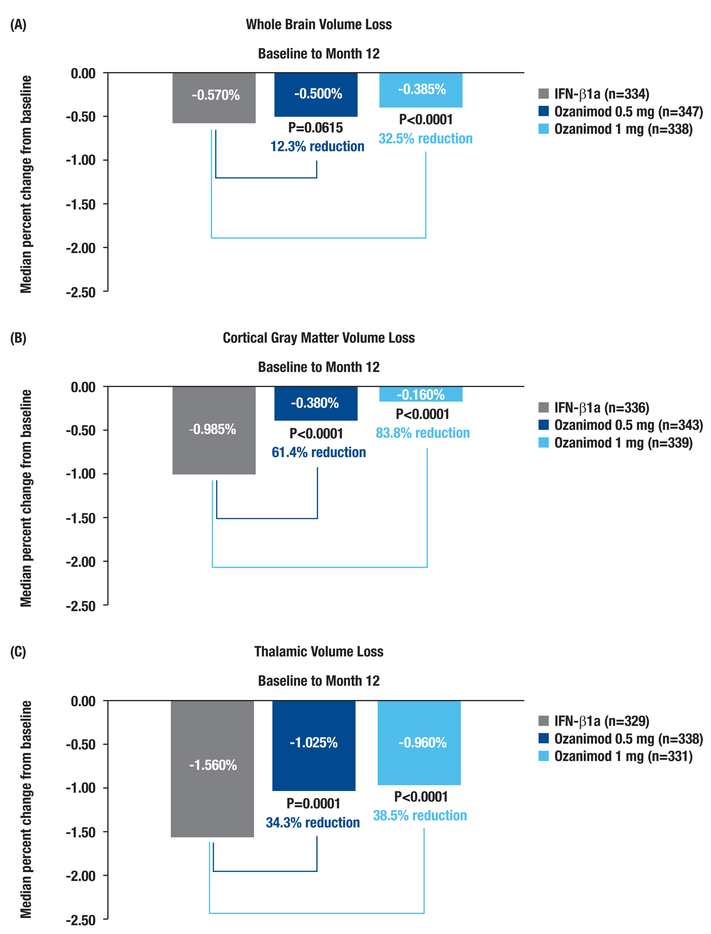
Table 2. Baseline Characteristics in RADIANCE Part B (ITT Population)

	IFN-β1a (n=441)	Ozanimod 0.5 mg (n=439)	Ozanimod 1 mg (n=433)
Mean (SD) age, years	35.1 (9.07)	35.4 (8.82)	36.0 (8.89)
Sex, female, n (%)	304 (68.9)	287 (65.4)	291 (67.2)
Race, White, n (%)	432 (98.0)	431 (98.2)	428 (98.8)
Region, Eastern Europe[a], n (%)	379 (85.9)	378 (86.1)	374 (86.4)
EDSS score ≤3.5, n (%)	377 (85.5)	368 (83.8)	366 (84.5)
GdE lesion presence, n (%)	196 (44.4)	190 (43.3)	178 (41.1)
Mean (SD) number of GdE lesions	1.8 (3.54)	1.8 (3.62)	1.6 (3.78)
Mean (SD) number of T2 lesions	48.7 (32.62)	48.7 (36.27)	47.9 (32.37)
Median normalized brain volume (cm^3)	1455.7	1452.9	1446.0
Median normalized cortical gray matter volume (cm^3)	533.4	534.3	529.7
Median normalized thalamic volume (cm^3)	15.8	15.9	15.6

[a]Eastern Europe consists of patients at sites in Belarus, Bosnia and Herzegovina, Bulgaria, Croatia, Estonia, Georgia, Latvia, Lithuania, Moldova, Poland, Romania, Russia, Serbia, and Ukraine.
EDSS, Expanded Disability Status Scale; GdE, gadolinium-enhancing; IFN-β1a, interferon beta-1a; ITT, intent-to-treat; SD, standard deviation.

- Following 12 months of treatment, patients in the ozanimod 1 mg group had significant slowing of whole BVL versus IFN-β1a (P<0.0001; 32.5% reduction in median relative to IFN-β1a; median percent change from baseline: -0.385% [ozanimod 1 mg], -0.570% [IFN-β1a]). Patients in the ozanimod 0.5 mg group demonstrated a trend toward slowing BVL (P=0.0615; 12.3% reduction in median relative to IFN-β1a; median percent change from baseline: -0.500%) (Figure 3A)
  - Patients in both the ozanimod 1 mg and 0.5 mg groups demonstrated significant 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-β1a (-0.985%) (Figure 3B)
  - Patients in both the ozanimod 1 mg and 0.5 mg groups demonstrated significant slowing of thalamic BVL: 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-β1a (-1.560%) (Figure 3C)
- Following 24 months of treatment, patients in both the ozanimod 1 mg and 0.5 mg groups demonstrated significant slowing of whole BVL versus IFN-β1a: P<0.0001; 26.6% reduction in median; median percent change from baseline: -0.690% and P<0.0001; 24.5% reduction in median; median percent change from baseline: -0.710%, respectively, relative to IFN-β1a (-0.940%) (Figure 4A)
  - Patients in the ozanimod 1 mg and 0.5 mg groups demonstrated significant slowing of cortical gray matter loss: P<0.0001; 58.3% reduction in median; median percent change from baseline: -0.530% and P<0.0001; 56.7% reduction in median; median percent change from baseline: -0.550%, respectively, relative to IFN-β1a (-1.270%) (Figure 4B)
  - Patients in the ozanimod 1 mg and 0.5 mg groups demonstrated significant slowing of thalamic BVL: P<0.0001; 31.9% reduction in median; median percent change from baseline: -1.280% and P=0.0012; 29.5% reduction in median; median percent change from baseline: -1.325%, respectively, relative to IFN-β1a (-1.880%) (Figure 4C)

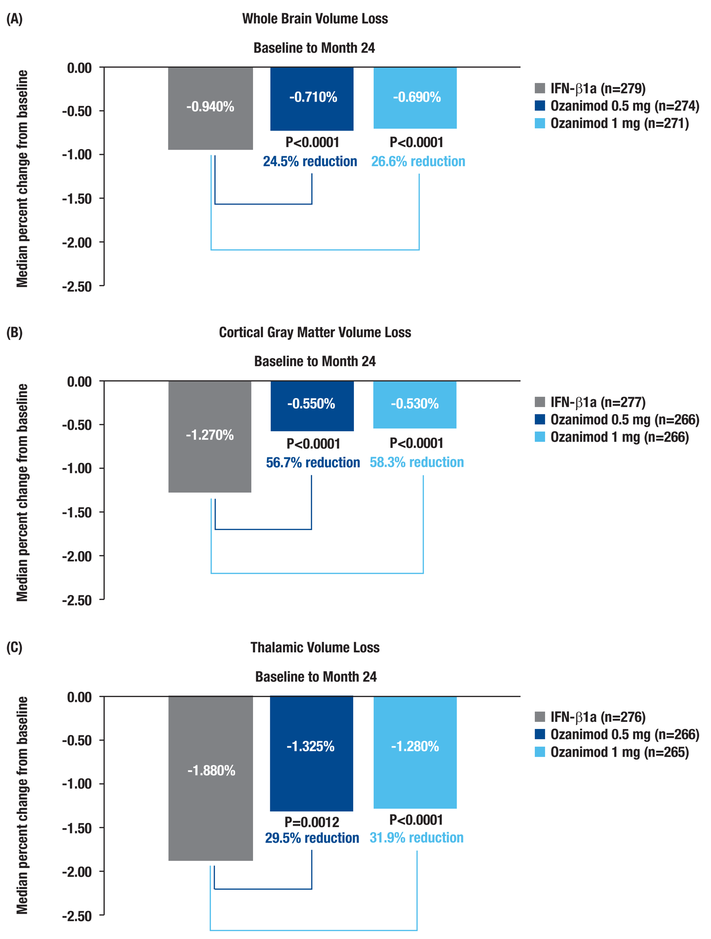
Figure 3. (A) Whole Brain Volume Loss, (B) Cortical Gray Matter Volume Loss, and (C) Thalamic Volume Loss at Month 12 Relative to Baseline in SUNBEAM (Observed, ITT Population)



P-values are based on rank analysis of covariance, adjusted for region (Eastern Europe vs rest of world) and Expanded Disability Status Scale 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.

IFN-β1a, interferon beta-1a; ITT, intent-to-treat.

Figure 4. (A) Whole Brain Volume Loss, (B) Cortical Gray Matter Volume Loss, and (C) Thalamic Volume Loss at Month 24 Relative to Baseline in RADIANCE Part B (Observed, ITT Population)



P-values are based on rank analysis of covariance, adjusted for region (Eastern Europe vs rest of world) and Expanded Disability Status Scale 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.

IFN-β1a, interferon beta-1a; ITT, intent-to-treat.

DISCLOSURES

Douglas L. Arnold reports personal fees for consulting from Acorda, Biogen, MedImmune, Mitsubishi Pharma, Novartis, Receptos, Roche, and Sanofi; grant support from Biogen and Novartis; and equity interest in NeuroRx Research. Jeffrey A. Cohen reports personal compensation for consulting for Adamas and Celgene, and as a co-editor of Multiple Sclerosis Journal – Experimental, Translational and Clinical. Giancarlo Comi reports compensation for consulting and/or speaking activities from Almirall, Biogen, Celgene/Receptos, EXCEMED, Forward Pharm, Genzyme, Merck, Novartis, Roche, Sanofi, and Teva, in the past year. Krzysztof W. Selmaj reports consulting for Biogen, Genzyme, Merck, Novartis, Ono Pharma, Receptos, Roche, Synthon, and Teva. Amit Bar-Or reports personal compensation for consulting for Biogen, Celgene/Receptos, EMD Serono, Genzyme, Medimmune, Novartis, and Roche. Lawrence Steinman reports consulting for Abbvie, Atreca, Celgene/Receptos, Novartis, Teva, Tolerion, and EMD Serono, and research support from Atara, Biogen, and Celgene. Hans-Peter Hartung reports personal fees for consulting, serving on steering committees and speaking from Bayer, Biogen, Geneuro, Genzyme, Merck, Medimmune, Novartis, Octapharma, Opexa, Roche, Sanofi, and Teva. Xavier Montalbán has received speaking honoraria and travel expenses for scientific meetings or has participated in steering committees or in advisory boards for clinical trials with Almirall, Bayer Schering Pharma, Biogen, Genentech, Genzyme, GSK, Merck Serono, MS International Federation, National Multiple Sclerosis Society, Novartis, Roche, Sanofi-Aventis, and Teva; he is an editor for Clinical Cases for MSJ. Eva K. Havrdová reports personal compensation for consulting and speaking for Actelion, Biogen, Celgene, Merck, Novartis, Roche, Sanofi, and Teva, and is supported by Czech Ministry of Education, project PROGRES Q27/LF1. Bruce A. C. Cree reports personal compensation for consulting for Abbvie, Biogen, EMD Serono, Genzyme, Novartis, and Shire. James K. Sheffield and Ning Ding are employees of Receptos, a wholly owned subsidiary of Celgene Corporation. Ludwig Kappos's institution (University Hospital Basel) has received and used exclusively for research support: steering committee, advisory board, and consultancy fees (Actelion, Addex, Bayer, Biogen, Biotica, Genzyme, Lilly, Merck, Mitsubishi, Novartis, Ono Pharma, Pfizer, Receptos, Sanofi, Santhera, Siemens, Teva, UCB, and Xenoport); speaker fees (Bayer, Biogen, Merck, Novartis, Sanofi, and Teva); support of educational activities (Bayer, Biogen, CSL Behring, Genzyme, Merck, Novartis, Sanofi, and Teva); license fees for Neurostatus products; and grants (Bayer, Biogen, European Union, Merck, Novartis, Roche, Swiss MS Society, and Swiss National Research Foundation).

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