ORAL PRESENTATION 4938

Efficacy and Safety of Ozanimod in the Blinded Extension (120 weeks) of RADIANCE Part A, a Phase 2 Trial in Relapsing Multiple Sclerosis

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DISCLOSURES

- ***Giancarlo Comi*** has received, in the past year, compensation for consulting services and/or speaking activities from Almirall, Biogen, Celgene Corporation, EXCEMED, Forward Pharm, Genzyme, Merck, Novartis, Receptos, Roche, Sanofi, and Teva
- ***Douglas L. Arnold*** has received personal fees for consulting from Acorda, Biogen, Hoffmann-LaRoche, MedImmune, Mitsubishi Pharma, Novartis, Receptos, and Sanofi-Aventis; grants from Biogen and Novartis; and an equity interest in NeuroRx Research
- ***Amit Bar-Or*** has consulted for Amplimmune, Aventis, Bayhill Therapeutics, Berlex/Bayer, Biogen Idec, BioMS, DioGenix, Eli Lilly, EMD Serono, Genentech, Genzyme, GlaxoSmithKline, Guthy-Jackson/GGF, MedImmune, Mitsubishi Pharma, Novartis, Ono Pharma, Receptos, Roche, Sanofi-Aventis, Teva, and Wyeth
- ***Krzysztof Selmaj*** has consulted for Biogen Idec, Genzyme, Merck, Novartis, Ono Pharma, Roche, Synthon, Teva, Receptos
- ***Lawrence Steinman*** reports grants and personal fees from Receptos and Celgene, outside the submitted work
- ***Eva Havrdova*** has received speaker fees and research grant support from Biogen, Genzyme, Merck Serono, Novartis, and Teva; compensation for advisory boards from Actelion, Biogen, Celgene, Sanofi, Genzyme, Merck Serono, Novartis, and Teva; and has been supported by PRVOUKP26/LF1/4, project of Czech Ministry of Education
- ***Bruce Cree*** has received, in the past 24 months, personal compensation for consulting from Abbvie, Biogen, EMD Serono, Novartis, Sanofi Genzyme and Shire
- ***Hans-Peter Hartung*** has received fees for consulting, serving in steering committees, and speaking at symposia from Bayer, Biogen, GeNeuro, Genzyme, Medimmune, Merck, Novartis, Receptos/Celgene, Roche, and Teva with approval by the Rector of Heinrich-Heine-University
- ***Ludwig Kappos***'s institution (University Hospital Basel) has received in the last 3 years (and used exclusively for research support) steering committee, advisory board, and consultancy fees from Actelion, Addex, Bayer Health Care, Biogen, Biotica, Genzyme, Lilly, Merck, Mitsubishi Tanabe Pharma, Novartis, Ono Pharma, Pfizer, Receptos, Sanofi-Aventis, Santhera, Siemens, Teva, UCB, and Xenoport; speaker fees from Bayer Health Care, Biogen, Merck, Novartis, Sanofi-Aventis, and Teva; support of educational activities from Bayer Health Care, Biogen, CSL Behring, Genzyme, Merck, Novartis, Sanofi, and Teva; royalties from Neurostatus Systems; and grants from Bayer Health Care, Biogen, Merck, Novartis, Roche, Swiss MS Society, the Swiss National Research Foundation, the European Union, and Roche Research Foundations
- ***Brett E. Skolnick*** is an employee of Receptos, a wholly owned subsidiary of Celgene Corporation
- ***Jeffrey A. Cohen*** has consulted for Genentech, Genzyme, Merck, Novartis, and Receptos, and is editor of Multiple Sclerosis Journal – Experimental, Translational and Clinical

- This study was sponsored by Receptos, a wholly owned subsidiary of Celgene Corporation

LEARNING OBJECTIVE

- To review the long-term efficacy and safety data from the phase 2 RADIANCE Part A trial of ozanimod 0.5 mg and 1.0 mg in adult patients with RMS

RMS, relapsing multiple sclerosis.

INTRODUCTION

- Ozanimod is an oral, once-daily immunomodulator selectively targeting $S1P_{1R}$ and $S1P_{5R}$[1]
- Ozanimod down-regulates $S1P_{1R}$, resulting in the retention of autoreactive T cells and B cells in lymphoid tissues while maintaining immune surveillance[1]
- RADIANCE Part A* is the first part of a phase 2/3 clinical trial of ozanimod in adults with RMS
- Results of the 24-week, placebo-controlled, phase 2 core treatment period demonstrated the efficacy of ozanimod 0.5 mg and 1 mg, with a favorable safety/tolerability profile[2]

*NCT01628393.
RMS, relapsing multiple sclerosis; $S1P_{1R}$, sphingosine 1-phosphate receptor 1; $S1P_{5R}$, sphingosine 1-phosphate receptor 5.
[1]Scott FL, et al. *Br J Pharmacol*. 2016;173:1778–1792.
[2]Cohen JA, et al. *Lancet Neurol*. 2016;15:373–381.

STUDY OBJECTIVES

- To evaluate the long-term efficacy and safety of ozanimod (0.5 mg and 1 mg) in adult patients with RMS (up to 2.5 years)

- The presentation includes data from the blinded extension portion of the phase 2 RADIANCE **Part A** trial:
  - Patients initially randomized to placebo in the 24-week core treatment period were re-randomized to ozanimod (0.5 mg or 1 mg)
  - Ozanimod-treated patients continued their initial dose assignment
  - All dose groups participated in the dose escalation upon entry to the Blinded Extension

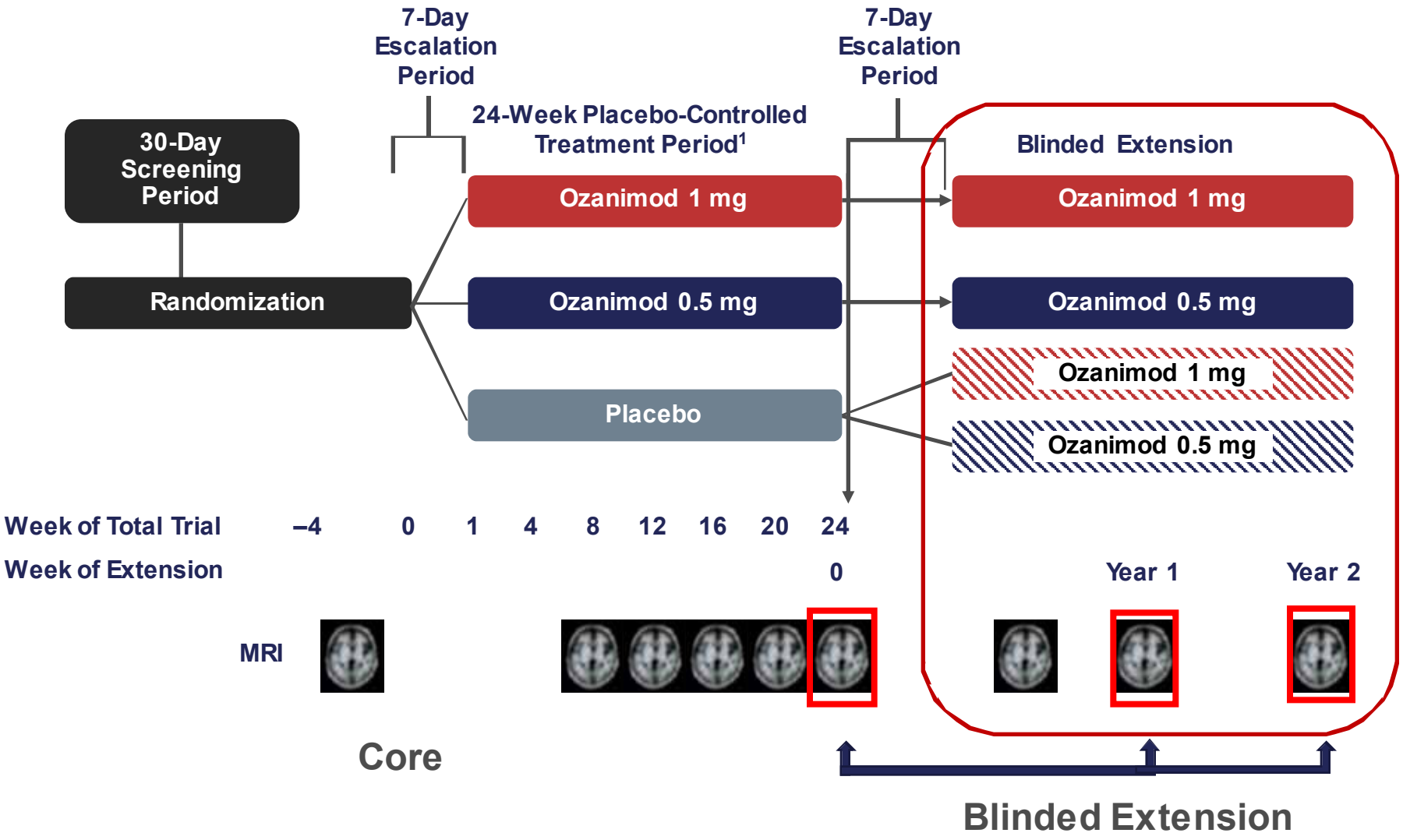
RMS, relapsing multiple sclerosis.

METHODS

Key inclusion criteria*	Key exclusion criteria
• Relapsing MS fulfilling the revised 2010 McDonald criteria[1] • 18–55 year of age • EDSS score of 0–5.0 • Brain lesions on MRI consistent with MS • ≥1 relapse in the past 12 months, or ≥1 relapse in the past 24 months and ≥1 GdE lesion in the past 12 months • Positive varicella zoster virus serology or vaccination	• Primary progressive course • Clinically relevant cardiovascular disease, resting heart rate of <55 beats per min, or treatment with drugs known to alter heart rate or cardiac conduction • Any history of Type 1 or Type 2 diabetes mellitus, history of uveitis, or other clinically significant medical illnesses or laboratory abnormalities • Not meeting appropriate washout periods for DMTs in core treatment period

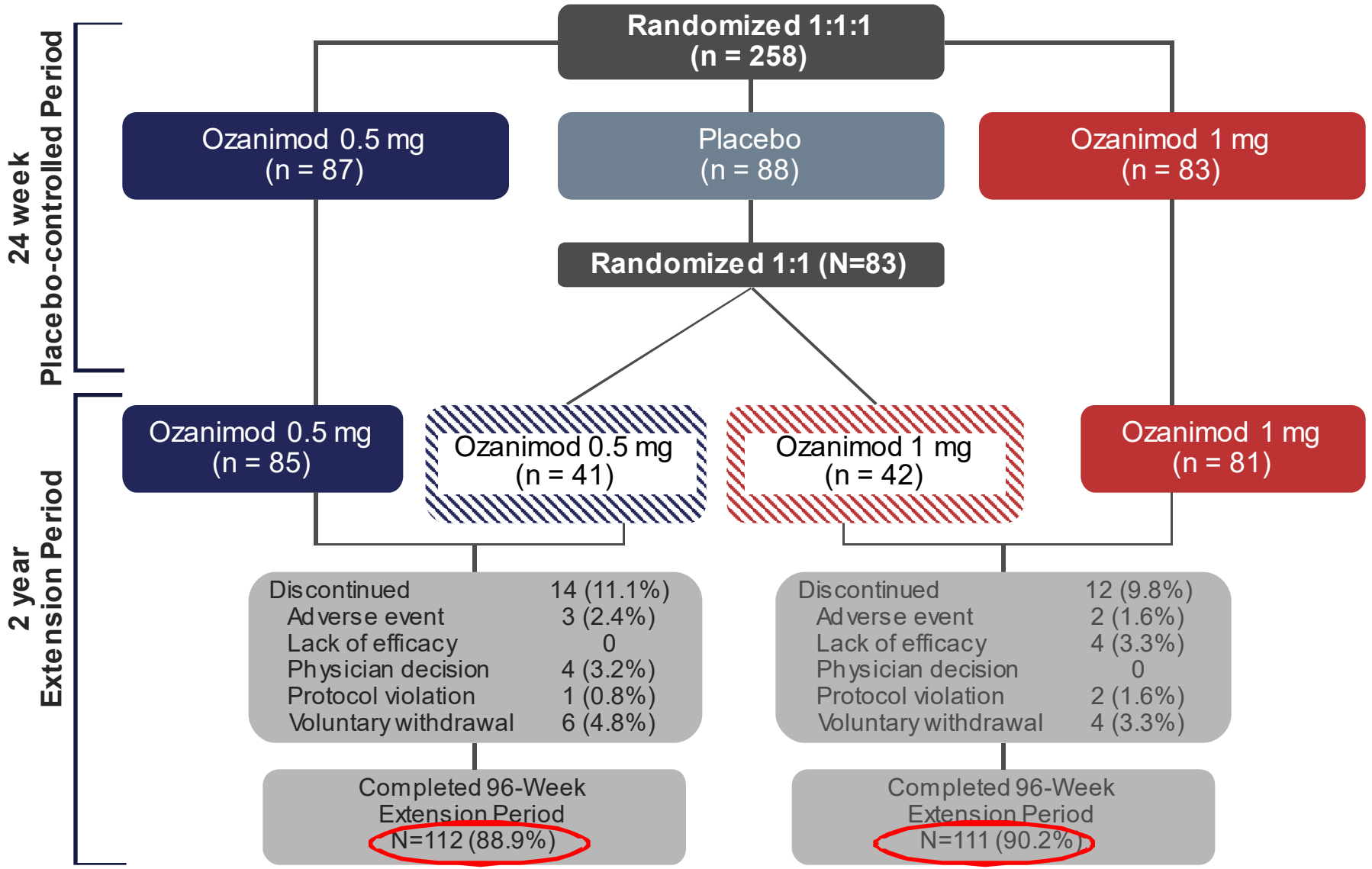
*Full inclusion and exclusion criteria can be found at clinicaltrials.gov: NCT01628393.
DMT, disease-modifying treatment; EDSS, Expanded Disability Status Scale; GdE, gadolinium-enhancing; MRI, magnetic resonance image; MS, multiple sclerosis; S1P, sphingosine 1-phosphate.
[1]Polman CH, et al. *Ann Neurol*. 2011;69:292–302.

RADIANCE PART A TRIAL DESIGN



All images were analyzed by NeuroRx, Montreal, Canada.
GdE, gadolinium-enhancing; MRI, magnetic resonance imaging.
[1]Cohen JA, et al. *Lancet Neurol*. 2016;15:373–381.

STUDY POPULATION DISPOSITION

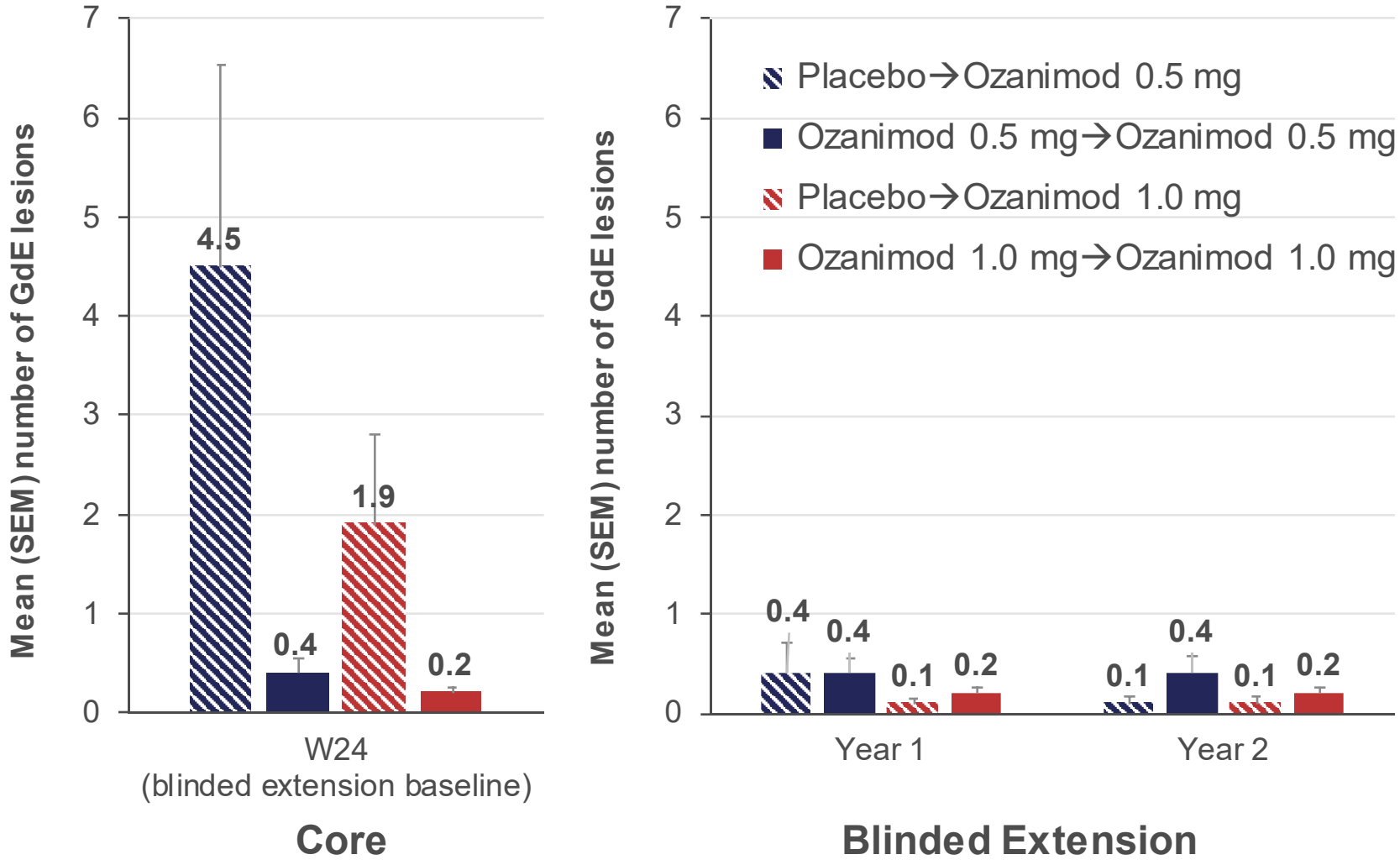


DEMOGRAPHIC AND DISEASE CHARACTERISTICS
AT ORIGINAL RANDOMIZATION, FOR PATIENTS ENTERING THE BLINDED EXTENSION

	Ozanimod 0.5 mg			Ozanimod 1.0 mg		
	Core Study Treatment			Core Study Treatment		
	Placebo (n = 41)	Ozanimod (n = 85)	Total (n = 126)	Placebo (n = 42)	Ozanimod (n = 81)	Total (n = 123)
Age, years	41.0 (8.0)	38.1 (9.3)	39.0 (8.9)	36.9 (8.7)	38.5 (9.9)	38.0 (9.5)
Female, %	73.2	68.2	69.8	71.4	70.4	70.7
White, %	100.0	97.6	98.4	100.0	100.0	100.0
Years since MS diagnosis	5.3 (5.2)	2.8 (5.0)	3.6 (5.2)	3.7 (5.1)	3.6 (4.5)	3.7 (4.7)
EDSS score	2.7 (1.2)	2.9 (1.3)	2.8 (1.3)	2.9 (1.4)	2.8 (1.2)	2.9 (1.3)
Relapses in previous 24 months	2.0 (1.2)	2.0 (1.7)	2.0 (1.6)	1.7 (0.8)	1.8 (1.1)	1.8 (1.0)
GdE lesion(s)	1.8 (3.7)	0.9 (1.4)	1.2 (2.5)	0.6 (1.4)	1.4 (2.8)	1.1 (2.4)
Free of GdE lesions, n (%)	28 (68.3)	51 (60.0)	79 (62.7)	30 (71.4)	51 (63.0)	81 (65.9)
Number of patients who took prior MS medication, n (%)	18 (43.9)	19 (22.4)	37 (29.4)	12 (28.6)	18 (22.2)	30 (24.4)

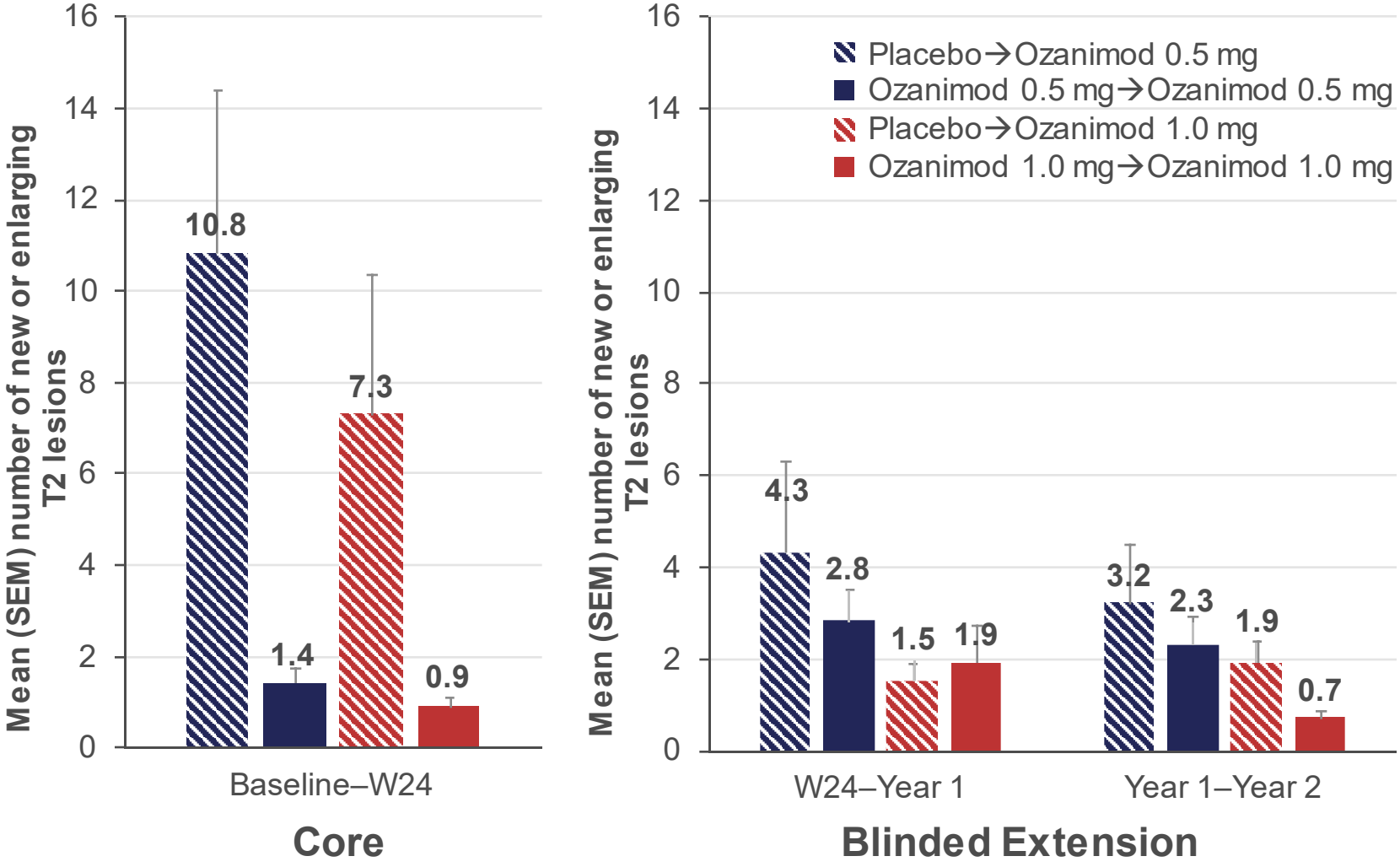
Data are expressed as mean (SD) unless otherwise indicated.
EDSS, Expanded Disability Status Scale; GdE, gadolinium-enhancing; MS, multiple sclerosis.

MEAN NUMBER OF GdE LESIONS



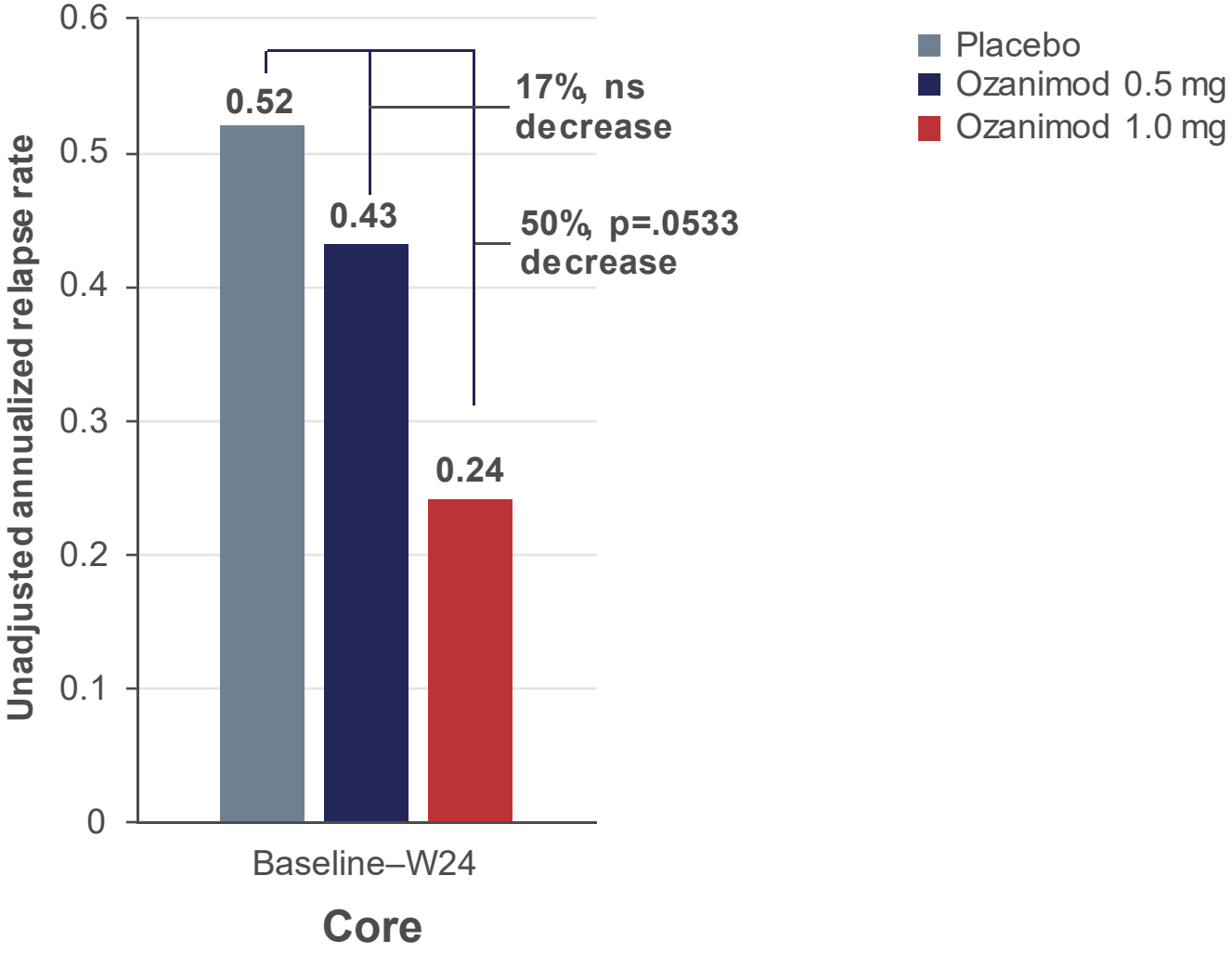
GdE, gadolinium-enhancing; SEM, standard error of the mean.

NUMBER OF NEW OR ENLARGING T2 LESIONS



SEM, standard error of the mean.

UNADJUSTED ANNUALIZED RELAPSE RATE



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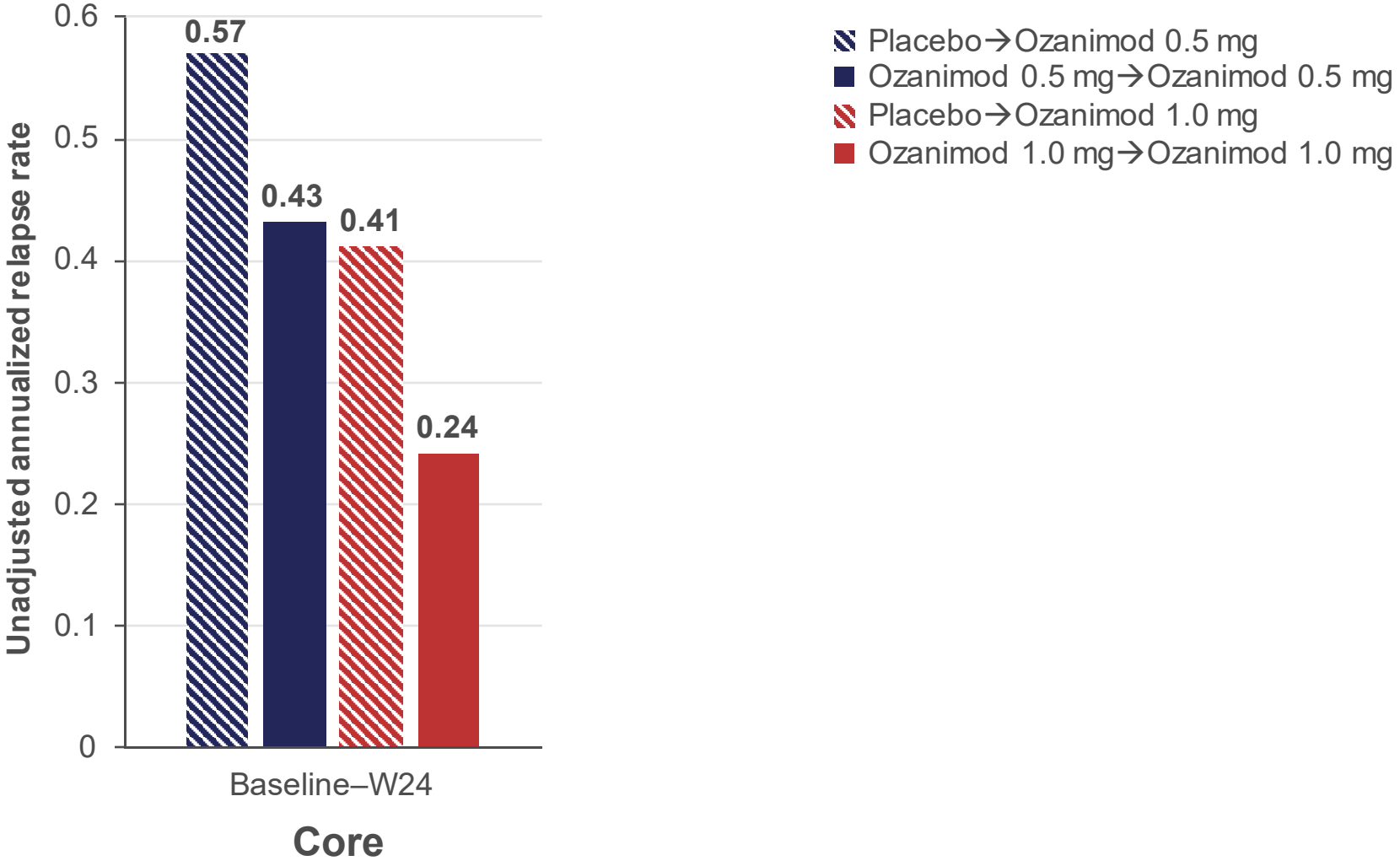

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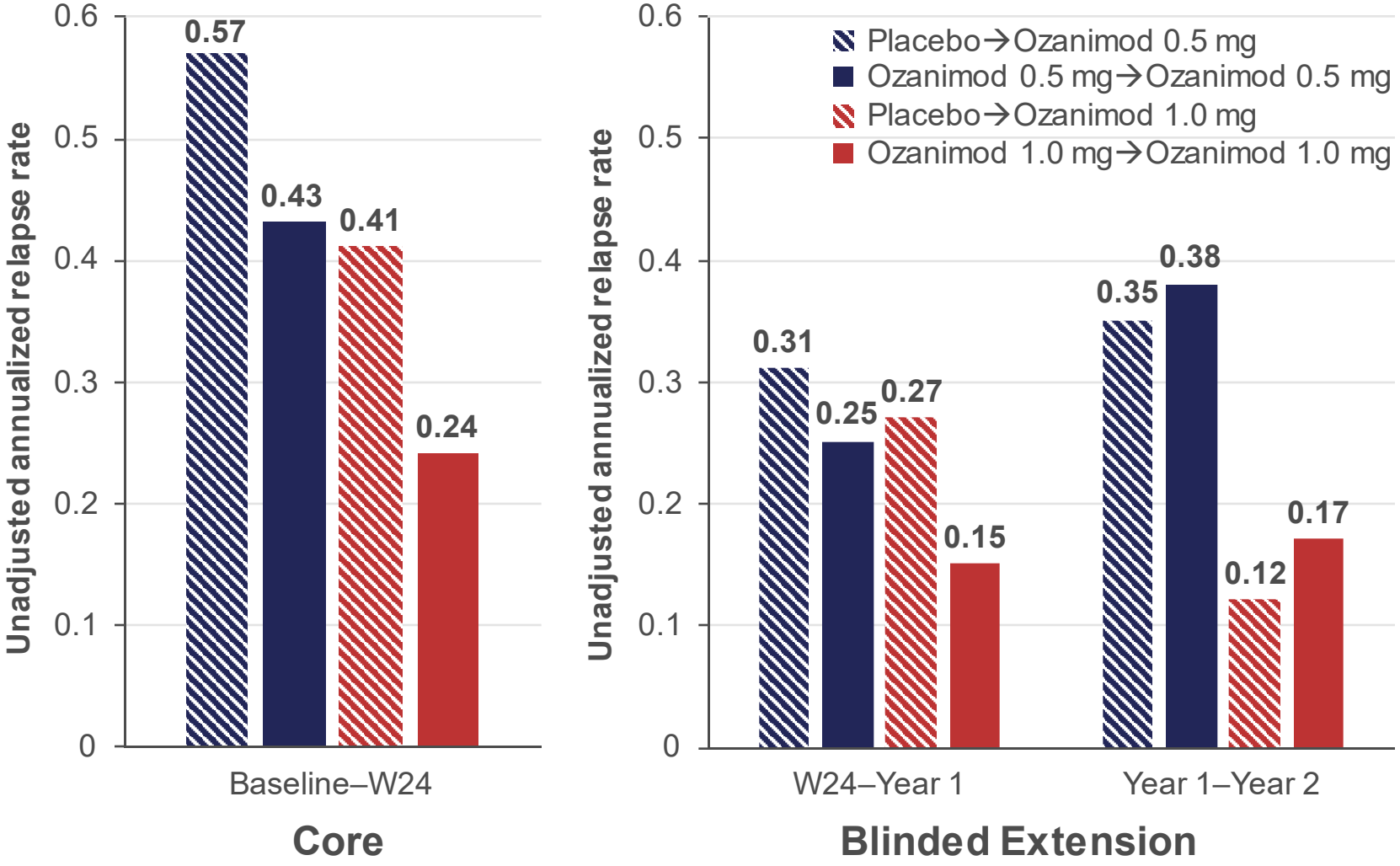

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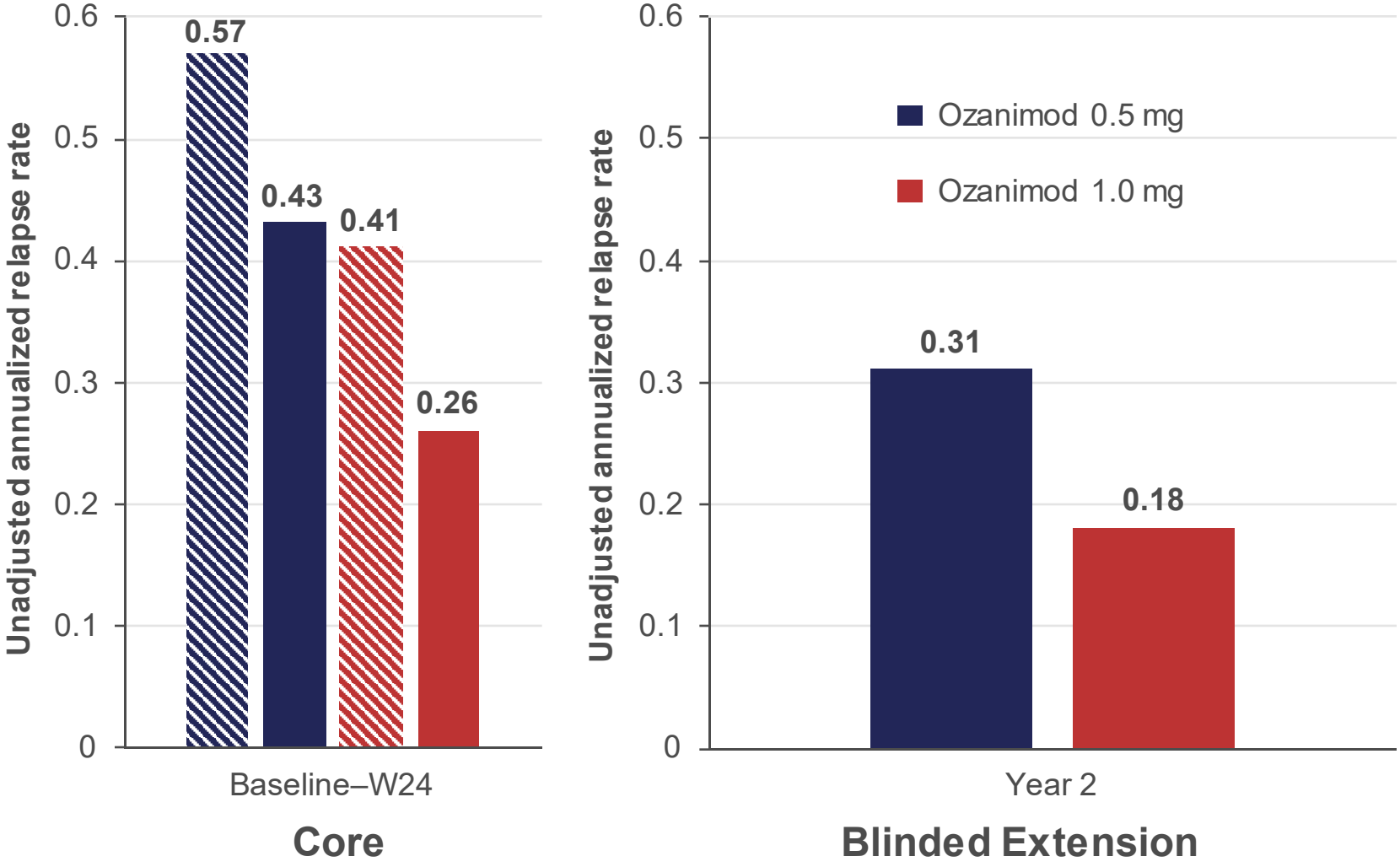

OVERVIEW OF TEAEs DURING 2-YEAR BLINDED EXTENSION

	Ozanimod 0.5 mg (n = 126)	Ozanimod 1 mg (n = 123)
≥1 TEAE	99 (78.6%)	93 (75.6%)
≥1 Severe TEAE	6 (4.8%)	3 (2.4%)
≥1 Drug-Related TEAE	5 (4.0%)	4 (3.3%)
≥1 Serious TEAE	12 (9.5%)	9 (7.3%)
≥1 TEAE leading to study drug discontinuation	3 (2.4%)	1 (0.8%)
Treatment-related deaths	0	0

- None of the serious TEAEs was considered related to treatment with ozanimod. No specific serious TEAEs occurred in >1 patient
- The most common TEAEs, similar to the 24-week placebo-controlled period, were minor infections (eg, nasopharyngitis, respiratory tract, urinary tract) and headache
- No cases of macular edema were reported
- No serious opportunistic infections, malignancy, or clinically significant pulmonary TEAEs reported

TEAE, treatment-emergent adverse event.

CARDIAC MONITORING

- Dose re-escalation during blinded extension:

Assigned Treatment	Days 1 to 4	Days 5 to 7	From Day 8 On
Ozanimod	0.25 mg	0.5 mg	0.5 mg or 1 mg

- During Day 1 or Day 1 of blinded extension:
  - No first-dose TEAE bradycardia
  - No atrioventricular block of ≥2nd degree

Incidence of Minimum Heart Rates During Day 1 of the Extension

Minimum Heart Rate (bpm)	Ozanimod 0.5 mg			Ozanimod 1.0 mg		
	Core Study Treatment			Core Study Treatment		
	Placebo (n = 41)	Ozanimod (n = 85)	Total (n = 126)	Placebo (n = 42)	Ozanimod (n = 81)	Total (n = 123)
≥65	12 (29.3%)	45 (52.9%)	57 (45.2%)	23 (54.8%)	48 (59.3%)	71 (57.7%)
60–64	23 (56.1%)	24 (28.2%)	47 (37.3%)	13 (31.0%)	24 (29.6%)	37 (30.1%)
55–59	4 (9.8%)	12 (14.1%)	16 (12.7%)	4 (9.5%)	7 (8.6%)	11 (8.9%)
50–54	2 (4.9%)	4 (4.7%)	6 (4.8%)	1 (2.4%)	2 (2.5%)	3 (2.4%)
45–49	0	0	0	0	0	0
40–44	0	0	0	1 (2.4%)*	0	1 (0.8%)*
<40	0	0	0	0	0	0

*Heart rate 44 bpm at 4 hours post-dose with pre-dose heart rate of 55 bpm.
TEAE, treatment-emergent adverse event.

INCIDENCE OF LIVER TRANSAMINASE ELEVATION IN THE EXTENSION PERIOD SAFETY POPULATION

	Placebo→ Ozanimod 0.5 mg	Ozanimod 0.5 mg→ Ozanimod 0.5 mg	Placebo→ Ozanimod 1.0 mg	Ozanimod 1.0 mg→ Ozanimod 1.0 mg
	(n = 41)	(n = 84)	(n = 41)	(n = 81)
ALT, n (%)				
>1 ULN	16 (39.0)	43 (51.2)	15 (36.6)	32 (39.5)
≥2 ULN	3 (7.3)	13 (15.5)	7 (17.1)	12 (14.8)
≥3 ULN	2 (4.9)	2 (2.4)	5 (12.2)	3 (3.7)
≥4 ULN	2 (4.9)	1 (1.2)	2 (4.9)	1 (1.2)
≥5 ULN	2 (4.9)	1 (1.2)	2 (4.9)	0
AST, n (%)				
>1 ULN	8 (19.5)	12 (14.3)	7 (17.1)	14 (17.3)
≥2 ULN	2 (4.9)	0	2 (4.9)	2 (2.5)
≥3 ULN	1 (2.4)	0	1 (2.4)	1 (1.2)
≥4 ULN	1 (2.4)	0	0	0
≥5 ULN	0	0	0	0

- ALT ≥3x ULN occurred in 12 (4.9%) patients in the extension period safety population
- 5 patients discontinued from the study according to protocol requirements for ALT ≥5x ULN; all improved or recovered after drug discontinuation

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal.

CONCLUSIONS

- Ozanimod (0.5 mg and 1 mg) demonstrated continued efficacy on MRI and clinical measures of MS disease activity over 2.5 years
- Ozanimod 1 mg provides greater efficacy over 0.5 mg
- TEAEs associated with ozanimod treatment over the ≥ 2 years of the blinded extension were consistent with the Core Period with no apparent differences between 0.5 and 1 mg ozanimod
- The safety and tolerability results suggest a favorable benefit:risk profile for ozanimod that awaits confirmation in the ongoing phase 3 trials (SUNBEAM* and RADIANCE-Part B†)

*NCT02294058. †NCT02047734.
MRI, magnetic resonance imaging; MS, multiple sclerosis; TEAE, treatment-emergent adverse event.

BACKUP

INCIDENCE OF LYMPHOCYTE COUNT <200 CELLS/µL

Core Study Period	Placebo	Ozanimod 0.5 mg	Ozanimod 1 mg
	(n = 88)	(n = 87)	(n = 83)
Baseline	0	0	0
Week 24	0	0	0
Last available	0	0	0

Extension Period	Ozanimod 0.5 mg	Ozanimod 1 mg
	(n = 126)	(n = 123)
Week 24 (blinded extension baseline)	0	0
Week 36	0	1 (0.8)
Week 48	0	1 (0.8)
Week 60	0	0
Week 72	0	1 (0.9)
Week 84	0	0
Week 96	0	2 (1.8)
Week 108	0	0
Week 120	0	0
Week 132	0	0
Week 144	0	0
Week 168/Early termination	0	0

CARDIAC PROFILE, SUBJECT 4011003
HEART RATE ON DAY 1 OF EXTENSION PERIOD

Timepoint	Heart Rate (bpm)*
Pre-dose/Baseline	55
Hour 1	49
Hour 2	48
Hour 3	48
Hour 4	44
Hour 5	60
Hour 6	48

*The corresponding values during the original dose-escalation period were: pre-dose/baseline, 60 bpm; hour 1, 56 bpm; hour 2, 64 bpm; hour 3, 59 bpm; hour 4, 53 bpm; hour 5, 50 bpm; hour 6, 68 bpm.