SUPPLEMENTARY APPENDIX

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: K Selmaj et al. Ozanimod in Relapsing Multiple Sclerosis: Pooled Safety Results From the Clinical Development Program

Table A.1 Schedule of safety assessments in ozanimod clinical trials for RMS

	Phase 1 (NCT02797015)	**Phase 2 RADIANCE (NCT01628393)**	**Phase 2 RADIANCE Blinded Extension Period**[a]	**Phase 3 RADIANCE (NCT02047734)**	**Phase 3 SUNBEAM (NCT02294058)**	**Open-label Extension Study DAYBREAK (NCT02576717)**
Monitoring of TEAEs and Serious TEAEs	Throughout each study (each study visit)					
Vital signs[d]	Screening; days 1, 5, 8, 28, 56, 85; early termination or EOS[b]	Screening; days 1, 5[e], 29, 57, 85, 113, 141; EOT-day 169[e]	Day 183[f], Q12 wk, EOS, unscheduled relapse visit, early termination, F/U visit	Screening; days 1, 15, 92, 183, 274, 365, 456, 547, 638, 729; unscheduled relapse visit; early termination; F/U visit	Screening; days 1[g], 15, 92, 183, 274; EOT-day 365; unscheduled relapse visit; early termination; F/U visit	Day 1[c], Q3 mo, unscheduled relapse visit, early termination or EOS, safety F/U visit
Physical examination	Screening, early termination or EOS[b]	Screening, EOT-day 169	EOS, early termination	Screening, day 365, day 729, early termination	Screening, day 365, early termination	Day 1[c], Q12 mo, early termination or EOS
12-lead ECG[h]	Screening; days 1, 5, 8, 28, 56, 85	Screening; days 1, 5[e], 29, 85, EOT-day 169[e]	Day 183[f], Q12 wk, EOS, early termination, F/U visit	Screening; days 1, 15, 365, 729; early termination; F/U visit	Screening; day 1[g], day 15, EOT-day 365 (unless done within previous 6 mo), early termination, F/U visit	Day 1, Q12 mo, early termination or EOS, safety F/U visit

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Complete blood count	Screening; predose on days 1, 5, 8, 28, 56, 85; postdose on days 1, 2, 3, and 4-6; early termination or EOS[b]	Screening; days 1, 29, 85; EOT-day 169	Q12 wk; EOS; unscheduled relapse visit; early termination; F/U visit	Screening; days 1, 92, 183, 274, 365, 456, 547, 638, 729; unscheduled relapse visit; early termination; F/U visit	Screening; days 1, 92, 183, 274; EOT-day 36; unscheduled relapse visit; early termination; F/U visit	Day 1[c], Q3 mo, early termination or EOS, ALC F/U visit (Q14 d after last dose); safety F/U visit
Chemistry	Screening; predose on days 1, 28, 85; and early termination or EOS[b]	Screening; days 1, 29, 85; EOT-day 169	Q12 wk, EOS, unscheduled relapse visit, early termination; F/U visit	Screening; days 1, 92, 183, 274, 365, 456, 547, 638, 729; unscheduled relapse visit; early termination; F/U visit	Screening; days 1, 92, 183, 274; EOT-day 365; unscheduled relapse visit; early termination; F/U visit	Day 1[c], Q3 mo, early termination or EOS, ALC F/U visit (Q14 d after last dose); safety F/U visit
Liver function tests	Screening; predose on days 1, 28, 85; early termination or EOS[b]	Screening; days 1, 29, 85; EOT-day 169	Q12 wk, EOS, unscheduled relapse visit; early termination, F/U visit	Screening; days 1, 92, 183, 274, 365, 456, 547, 638, 729; unscheduled relapse visit; early termination; F/U visit	Screening; days 1, 15, 92, 183, 274; EOT-day 365; unscheduled relapse visit; early termination F/U visit	Day 1[c], Q3 mo, early termination or EOS, ALC follow-up visit (Q14 d after last dose); safety F/U visit
Urinalysis	Screening, early termination or EOS[b]	Screening, EOT-day 169	Q12 wk, EOS, unscheduled relapse visit, early termination, F/U visit	Screening; days 1, 92, 183, 274, 365, 456, 547, 638, 729; unscheduled relapse visit; early termination F/U visit	Screening; days 1, 92, 183, 274; EOT-day 365; unscheduled relapse visit; early termination; F/U visit	Day 1[c], Q3 mo, early termination or EOS, ALC F/U visit (Q14d after last dose); safety F/U visit
Pulmonary function tests[j]		Screening, day 85, EOT-day 169	Q12 wk, EOS, early termination	Screening; days 92,183, 365, 729; early termination	Screening, day 92, day 183, EOT-day 365, (unless done within previous 6 mo), early termination	Day 1[c], Q12 mo, early termination or EOS
Optical		Screening, EOT-	EOS, early	Screening; days	Screening, day	Day 1[c], Q12 mo,

	Phase 1 (NCT02797015)	Phase 2 RADIANCE (NCT01628393)	Phase 2 RADIANCE Blinded Extension Period[a]	Phase 3 RADIANCE (NCT02047734)	Phase 3 SUNBEAM (NCT02294058)	Open-label Extension Study DAYBREAK (NCT02576717)
coherence tomography (OCT)[k]		day 169	termination	183, 365, 729; early termination	183, EOT-day 365 (unless done within previous 6 mo), early termination	early termination or EOS
Skin examination		Screening, day 169		Screening, day 365, day 729, early termination	Screening; EOT-day 365 (unless done within previous 6 mo) early termination	Day 1[c], Q12 mo, early termination or EOS
Serum/urine pregnancy test (WOCBP only)	Screening; days 1, 28, 56, 85; early termination or EOS[b]	Screening; days 1, 29, 57, 85, 113, 141; EOT-day 169	Q12 wk, EOS, early termination, F/U visit	Screening; days 1, 92, 183, 274, 365, 456, 547, 638, 729; early termination, F/U visit	Screening; days 1, 92, 183, 274; EOT-day 365; early termination; F/U visit	Day 1[c], Q3 mo, early termination or EOS, safety F/U visits (28 and 75 day after last dose)

ECG: electrocardiogram; **EOS**: end of study; **EOT**: end of treatment; **F/U**: follow-up (~4 weeks after last dose); **ME**: macular edema; **OCT**: optical coherence tomography; **PE**: physical examination; **Q**: every; **TEAEs**: treatment-emergent adverse events; **WOCBP**: women of childbearing potential.

[a]At week 24 of the phase 2 trial, participants could enter a 2-year dose-blinded extension period.

[b]An EOS evaluation was performed for participants who completed the study; this evaluation occurred at least 7 days after the last dose for participants enrolling in DAYBREAK, or 28 days after the last dose for those not enrolling in DAYBREAK. For participants who withdrew from treatment prior to study completion for any reason, an EOS evaluation was performed as soon as possible after the decision to permanently discontinue treatment was made.

[c]Only if not performed at the EOT visit of the parent trial or not within the timeframe prior to the EOT visit specified by the parent trial protocol.

[d]Vital signs were collected predose and every hour for 6 hours after the initial dose with the exception of participants entering DAYBREAK from phase 1 or phase 2 RADIANCE who did not require dose escalation. For these participants, the EOT vital signs from phase 2 RADIANCE or EOS vital signs from phase 1 were used as the baseline vital signs for DAYBREAK.

[e]In phase 2 RADIANCE, 6-hour postdose monitoring was performed on day 5 only for the first 75 participants. At the week 24 visit (day 169), cardiac monitoring procedures were performed for participants who continued in the extension period following the first dose of that period.

[f]A visit for safety assessments was performed 14 days after the first dose of study medication.

[g]The first-dose cardiac monitoring strategy was repeated at day 5 or at day 8 if any cardiac safety issues were observed at the prior day of dose escalation.

[h]ECG was performed predose and 6 hours postdose, with the exceptions of participants who entered DAYBREAK from phase 1 or phase 2 RADIANCE who did not require dose escalation.

[i]Began 15 min before dosing and continued for 24 hours after dosing.

[j]Pulmonary function tests include forced expiratory volume in 1 second and forced vital capacity measurements at all the above indicated visits.

[k]If abnormal OCT findings or visual signs or symptoms of ME were observed, a general ophthalmologic examination including eye history, visual acuity, and dilated ophthalmoscopy was also performed.

Table A.2 Change from baseline in supine/sitting systolic and diastolic blood pressure during treatment with ozanimod 0.92 mg: overall RMS population

Time of Assessment	n	Systolic Blood Pressure, Change From Baseline, mm Hg			Diastolic Blood Pressure, Change From Baseline, mm Hg		
		Mean	SD	SE	Mean	SD	SE
Day 1							
Hour 1	1752	1.9	7.93	0.19	0.1	6.84	0.16
Hour 2	1752	1.8	8.62	0.21	-0.7	7.54	0.18
Hour 3	1752	1.4	9.13	0.22	-1.0	7.60	0.18
Hour 4	1752	1.5	9.31	0.22	-1.1	7.82	0.19
Hour 5	1751	2.0	9.26	0.22	-0.9	7.54	0.18
Hour 6	1750	3.0	8.75	0.21	-0.1	7.37	0.18
Month							
3	1742	4.0	11.02	0.26	1.5	8.72	0.21
6	1722	4.7	11.17	0.27	1.5	9.21	0.22
12	1680	4.0	11.29	0.28	1.3	8.99	0.22

18	1987	4.8	11.83	0.27	2.3	9.47	0.21
24	1885	5.0	11.84	0.27	2.5	9.93	0.23
30	1677	5.6	12.56	0.31	3.3	9.82	0.24
36	1655	5.6	11.97	0.29	3.3	9.47	0.23
42	1107	5.7	12.67	0.38	3.4	9.97	0.30

RMS: relapsing multiple sclerosis; **SD**: standard deviation; **SE**: standard error.

Table A.3 Hypertension, bradycardia, cardiac conduction abnormalities, and ischemic heart conditions during long-term treatment with ozanimod 0.92 mg

	Phase 3 Study Population (N=882)		**Overall RMS Population (N=2631)**	
	Incidence, n (%)	**IR/1000 PY[a] (95% CI)**	**Incidence, n (%)**	**IR/1000 PY[a] (95% CI)**
Hypertension-related AEs	40 (4.5)	30.6 (21.8–41.6)	167 (6.3)	24.7 (21.1–28.7)
Hypertension	30 (3.4)	22.8 (15.4–32.5)	141 (5.4)	20.7 (17.4–24.4)
Hypertensive crisis	2 (0.2)	1.5 (0.2–5.4)	6 (0.2)[b]	0.9 (0.3–1.9)
Essential hypertension	1 (0.1)	0.7 (0.0–4.1)	1 (<0.1)	0.1 (0.0–0.8)
Blood pressure increased	7 (0.8)	5.2 (2.1–10.8)	22 (0.8)	3.1 (2.0–4.7)
Blood pressure fluctuation	0	0 (0.0–2.7)	2 (0.1)	0.3 (0.0–1.0)
Bradycardias	14 (1.6)	10.5 (5.8–17.7)	33 (1.3)	4.7 (3.2–6.6)
Syncope	2 (0.2)[c]	1.5 (0.2–5.4)	16 (0.6)[c]	2.3 (1.3–3.7)
Bradycardia	7 (0.8)	5.2 (2.1–10.8)	10 (0.4)[d]	1.4 (0.7–2.6)

Sinus bradycardia	5 (0.6)	3.7 (1.2–8.7)	7 (0.3)[d]	1.0 (0.4–2.0)
Cardiac conduction abnormalities in ≥3 (0.2%) participants				
Palpitations	7 (0.8)	5.2 (2.1–10.8)	11 (0.4)	1.6 (0.8–2.8)
Atrioventricular block, first degree	5 (0.6)	3.7 (1.2–8.7)	12 (0.5)	1.7 (0.9–1.9)
Bundle branch block, right	1 (0.1)	0.7 (0.0–4.1)	6 (0.2)	0.9 (0.3–1.9)
Tachycardia	2 (0.2)	1.5 (0.2–5.4)	5 (0.2)	0.7 (0.2–1.7)
Heart rate increased	1 (0.1)	0.7 (0.0–4.1)	4 (0.2)	0.6 (0.2–1.5)
Atrial fibrillation	0	0 (0.0–2.7)	3 (0.1)	0.4 (0.1–1.2)
Ischemic heart conditions	0	0 (0.0–2.7)	11 (0.4)	1.6 (0.8–2.8)
Angina pectoris	0	0 (0.0–2.7)	6 (0.2)	0.9 (0.3–1.9)
Myocardial ischemia	0	0 (0.0–2.7)	3 (0.1)	0.4 (0.1–1.2)
Myocardial infarction	0	0 (0.0–2.7)	2 (<0.1)[e]	0.3 (0.0–1.0)
Angina unstable	0	0 (0.0–2.7)	1 (<0.1)	0.1 (0.0–0.8)

CI: confidence interval; **IR**: incidence rate; **PY**: person-years; **RMS**: relapsing multiple sclerosis; **TEAE**: treatment-emergent adverse effect.

[a]IR/1000 PY, study duration–adjusted incidence rate per 1000 person-years, calculated as number of participants with a TEAE of interest/PY x 1000 where PY was calculated as (date of first TEAE of interest – date of first dose of study drug + 1)/365.25; for participants without a TEAE of interest, time on study was the study duration (last date on study – date of first dose of study drug + 1)/365.25.

[b]None of the reports of hypertensive crisis were classified as serious.

[c]One case of syncope (which occurred during a phase 3 trial) was considered serious.

[d]Five of the 10 participants with bradycardia and 3 of the 7 with sinus bradycardia experienced these events on day 1, following their initial dose of ozanimod.

[e]Both participants who experienced myocardial infarction had a history of hypertension, and 1 also had hyperlipidemia and the other had chronic obstructive pulmonary disease. Both participants continued in the study with no change in ozanimod dosing.

Table A.4 Confirmed Cases of ME in All RMS Patients Treated With Ozanimod

Case	Study	Treatment Group	Time of Onset Relative to Ozanimod Initiation, Days	Pre-existing Risk Factor or Confounding Factor	Action Taken With Study Drug	Status
1	RADIANCE Phase 3	Ozanimod 0.46 mg	211	History of ME	Ozanimod withdrawn permanently	Resolved
2	RADIANCE Phase 3	Ozanimod 0.46 mg	366	Central serous choroidopathy	Ozanimod withdrawn permanently	Resolved
3	SUNBEAM	Ozanimod 0.46 mg	182	ME secondary to ocular trauma	Ozanimod withdrawn permanently	Resolved
4	SUNBEAM	Ozanimod 0.46 mg	183	Prior unreported uveitis (intraocular inflammation)	Ozanimod withdrawn	Resolved

					permanently	
5	DAYBREAK	Ozanimod 0.92 mg	366	Pigment epithelial detachment with possible choroidal neovascularization	No action taken	Resolving[a]
6	DAYBREAK	Ozanimod 0.92 mg	15	Uveitis	Ozanimod withdrawn permanently	Resolved
7	DAYBREAK	Ozanimod 0.92 mg	279	History of retinopathy and optic neuritis	Ozanimod withdrawn permanently	Resolved

ME, macular edema; RMS, relapsing multiple sclerosis.

[a]As of March 2020.

Table A.5 Serious infections

	Phase 3 Study Population (N=882)		Overall RMS Population (N=2631)	
	Incidence, n (%)	**IR/1000 PY[a] (95% CI)**	**Incidence, n (%)**	**IR/1000 PY[a] (95% CI)**
Any serious infection	9 (1.0)	6.7 (3.1–12.8)	44 (1.7)	6.3 (4.6–8.4)
Appendicitis	3 (0.3)	2.2 (0.5–6.5)	8 (0.3)	1.1 (0.5–2.2)
Pyelonephritis acute	1 (0.1)	0.7 (0.0–4.1)	7 (0.3)	1.0 (0.4–2.0)
Pneumonia	0	0 (0.0–2.7)	4 (0.2)	0.6 (0.2–1.5)
Bronchitis	0	0 (0.0–2.7)	2 (0.08)	0.3 (0.0–1.0)
Subcutaneous abscess	1 (0.1)	0.7 (0.0–4.1)	2 (0.08)	0.3 (0.0–1.0)
Lyme disease	0	0 (0.0–2.7)	2 (0.08)	0.3 (0.0–1.0)
Tonsillitis	1 (0.1)	0.7 (0.0–4.1)	2 (0.08)	0.3 (0.0–1.0)
UTI	1 (0.1)	0.7 (0.0–4.1)	2 (0.08)	0.3 (0.0–1.0)
Gastroenteritis	1 (0.1)	0.7 (0.0–4.1)	1 (0.04)	0.1 (0.0–0.8)
Postoperative abscess	1 (0.1)	0.7 (0.0–4.1)	1 (0.04)	0.1 (0.0–0.8)

Escherichia UTI	0	0 (0.0–2.7)	1 (0.04)	0.1 (0.0–0.8)
Acute sinusitis	0	0 (0.0–2.7)	1 (0.04)	0.1 (0.0–0.8)
Chronic hepatitis B	0	0 (0.0–2.7)	1 (0.04)	0.1 (0.0–0.8)
Dacryocystitis	0	0 (0.0–2.7)	1 (0.04)	0.1 (0.0–0.8)
HIV infection	0	0 (0.0–2.7)	1 (0.04)	0.1 (0.0–0.8)
Hepatitis A	0	0 (0.0–2.7)	1 (0.04)	0.1 (0.0–0.8)
Measles	0	0 (0.0–2.7)	1 (0.04)	0.1 (0.0–0.8)
Peritonitis	0	0 (0.0–2.7)	1 (0.04)	0.1 (0.0–0.8)
Pyelonephritis	0	0 (0.0–2.7)	1 (0.04)	0.1 (0.0–0.8)
Pyelonephritis chronic	0	0 (0.0–2.7)	1 (0.04)	0.1 (0.0–0.8)
Salpingitis	0	0 (0.0–2.7)	1 (0.04)	0.1 (0.0–0.8)
Toxic shock syndrome	0	0 (0.0–2.7)	1 (0.04)	0.1 (0.0–0.8)
URTI	0	0 (0.0–2.7)	1 (0.04)	0.1 (0.0–0.8)
Vestibular neuronitis	0	0 (0.0–2.7)	1 (0.04)	0.1 (0.0–0.8)
Chronic sinusitis	0	0 (0.0–2.7)	1 (0.04)	0.1 (0.0–0.8)

Diverticulitis	0	0 (0.0–2.7)	1 (0.04)	0.1 (0.0–0.8)

CI: confidence interval; **HIV**: human immunodeficiency virus; **IR**: incidence rate; **PY**: person-years; **RMS**: relapsing multiple sclerosis; **TEAE**: treatment-emergent adverse event; **URTI**: upper respiratory tract infection; **UTI**: urinary tract infection.

[a]IR/1000 PY, study duration–adjusted incidence rate per 1000 person-years, calculated as number of participants with a TEAE of interest/PY x 1000 where PY was calculated as (date of first TEAE of interest – date of first dose of study drug + 1)/365.25; for participants without a TEAE of interest, time on study was the study duration (last date on study – date of first dose of study drug + 1)/365.25.