Eight-Year Analyses of Repeated Confirmed Disability Progressions in the OPERA I/II and ORATORIO Studies and Their Open-Label Extensions

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ORATORIO (NCT01194570), OPERA I (NCT01247324) and OPERA II (NCT01412333)

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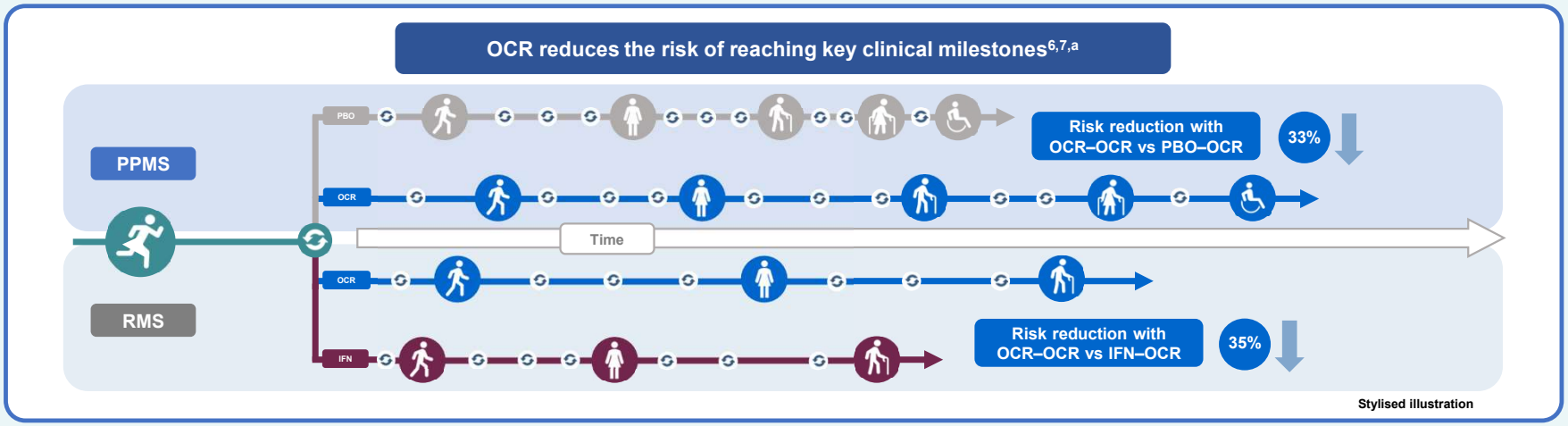
Poster presentation number P050

Supplemental Material

Background

- Long-term disability is an important outcome for patients with MS[1] and delaying; the time to reach disability milestones is a significant treatment goal
- In both RMS and PPMS, Phase III data showed significant benefit of OCR on measures of disability progression,[2,3] with sustained efficacy in the OLEs[4,5]
  - Patients initiating OCR earlier had significantly reduced risk of disability progression vs those switching from comparator[6,7]
- In addition, OCR reduced the risk of reaching key disability milestones vs comparator in RMS and PPMS[a,6–9]
  - Using extrapolation analysis, OCR delayed the time to requiring a wheelchair by 7 years in patients with PPMS, vs comparator[9]



OCR reduces the risk of reaching key clinical milestones

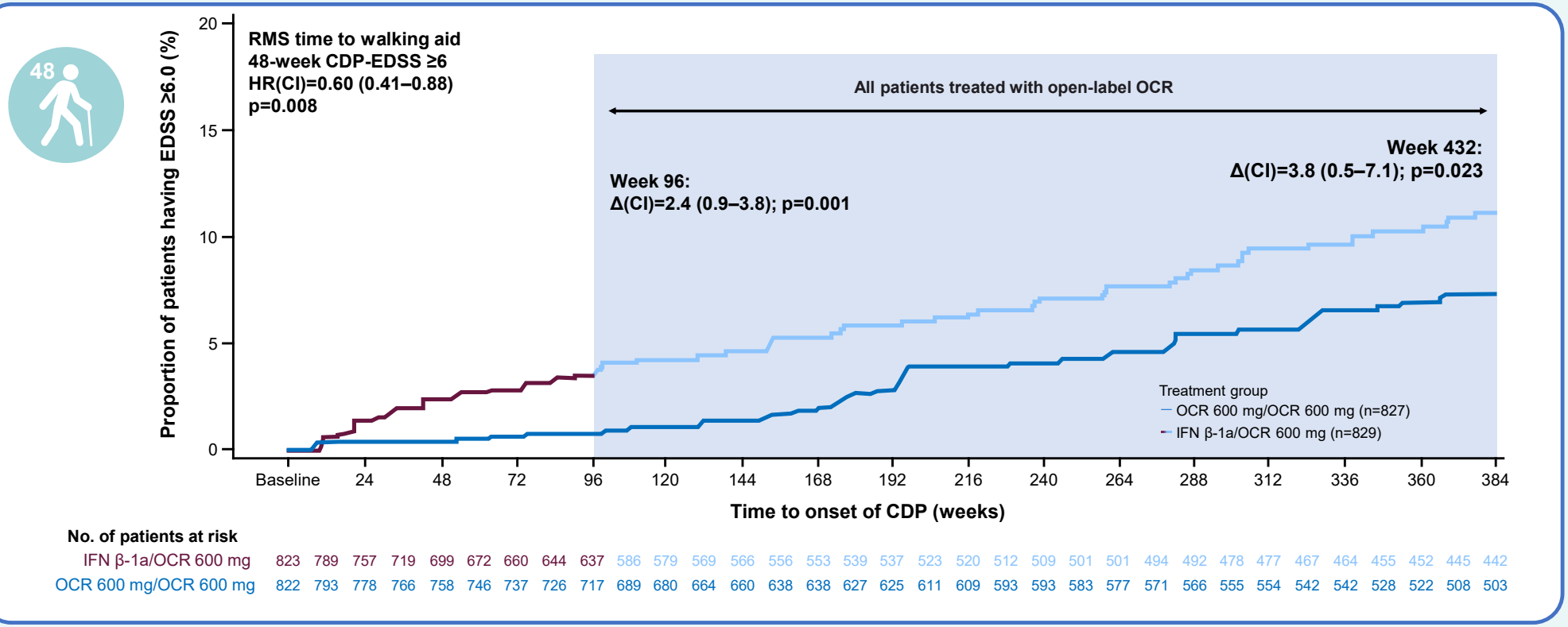
[a]See also slides 4 and 5.

IFN, interferon; MS, multiple sclerosis; OCR, ocrelizumab; OLE, open-label extension; PBO, placebo; PPMS, primary progressive multiple sclerosis; RMS, relapsing multiple sclerosis.

1. Wilson LS, *et al. Int J MS Care* 2015;17:74–82; 2. Montalban X, *et al. N Engl J Med* 2017;376:209–220; 3. Hauser SL, *et al. N Engl J Med* 2017:376:221–234; 4. Hauser SL, *et al. Neurology* 2020;95:e1854–e1867; 5. Wolinsky J, *et al. Lancet Neurol* 2020;19:998–1009; 6. Wolinsky J, *et al. ECTRIMS* 2021; Platform Presentation 158; 7. Giovannoni G, *et al. ECTRIMS* 2021; Poster 723. 8. Giovannoni G, *et al. Eur J Neurol* 2021;29:1238–1242; 9. Butzkueven H, *et al. Eur J Neurol* 2021;29:1082–1090.

OPERA I/II OLE: Time to walking aid (EDSS ≥6.0) confirmed for ≥48 weeks

Over 8 years of the DBP+OLE, the risk of requiring a walking aid confirmed for ≥48 weeks was 40% lower among those who initiated OCR earlier vs delayed treatment (average HR DBP+OLE [95% CI]: 0.60 [0.41–0.88]; p=0.008)



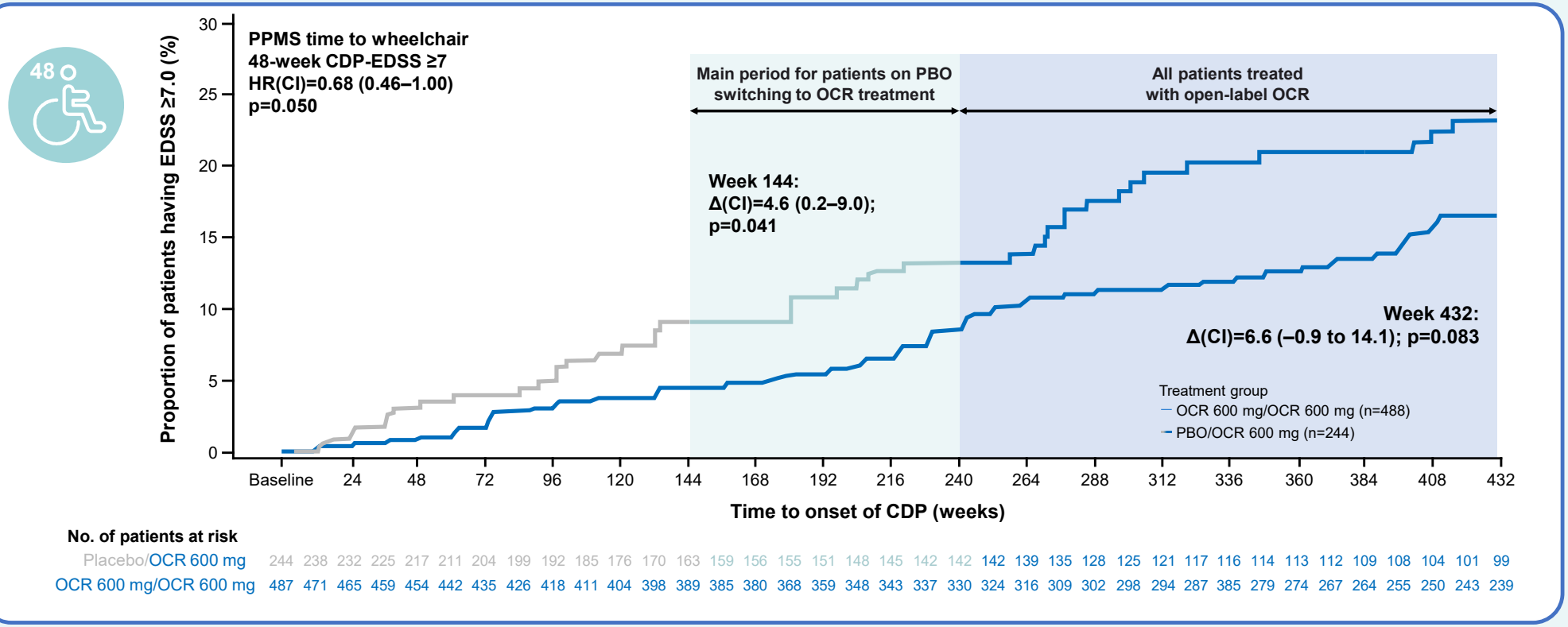
No. of patients at risk

IFN β-1a/OCR 600 mg	823	789	757	719	699	672	660	644	637	586	579	569	566	556	553	539	537	523	520	512	509	501	501	494	492	478	477	467	464	455	452	445	442
OCR 600 mg/OCR 600 mg	822	793	778	766	758	746	737	726	717	689	680	664	660	638	638	627	625	611	609	593	593	583	577	571	566	555	554	542	542	528	522	508	503

HRs were estimated by Cox regression stratified by study, geographical region (USA vs ROW), and baseline EDSS score (<4.0 vs ≥4.0). Comparison of the survival distributions used the log-rank test. Clinical data cut-off: 26 November 2021.
CDP, confirmed disability progression; CI, confidence interval; DBP, double-blind period; EDSS, Expanded Disability Status Scale; HR, hazard ratio; IFN, interferon; OCR, ocrelizumab; OLE, open-label extension; ROW, rest of world.

ORATORIO OLE: Time to wheelchair (EDSS ≥7.0) confirmed for ≥48 weeks

Over 8 years of the DBP+OLE, the risk of requiring a wheelchair confirmed for ≥48 weeks was 32% lower among those who initiated OCR earlier vs delayed treatment (average HR DBP+OLE [95% CI]: 0.68 [0.46–1.00]; p=0.050)



No. of patients at risk

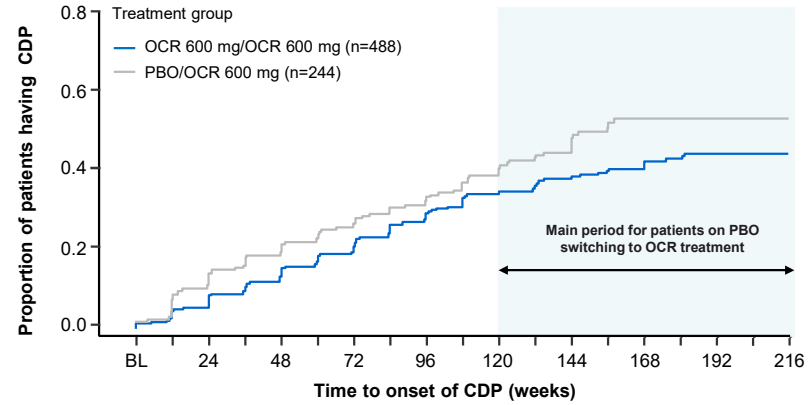
Placebo/OCR 600 mg	244	238	232	225	217	211	204	199	192	185	176	170	163	159	156	155	151	148	145	142	142	142	139	135	128	125	121	117	116	114	113	112	109	108	104	101	99
OCR 600 mg/OCR 600 mg	487	471	465	459	454	442	435	426	418	411	404	398	389	385	380	368	359	348	343	337	330	324	316	309	302	298	294	287	385	279	274	267	264	255	250	243	239

HRs were estimated by Cox regression stratified by geographical region (USA vs ROW), and age (≤45 vs >45 years). Comparison of the survival distributions used the log-rank test. Clinical data cut-off: 26 November 2021.
CDP, confirmed disability progression; CI, confidence interval; DBP, double-blind period; EDSS, Expanded Disability Status Scale; HR, hazard ratio; OCR, ocrelizumab; OLE, open-label extension; PBO, placebo; PPMS, primary progressive multiple sclerosis; ROW, rest of world.

Methods: Statistical analysis

- A rate-based method, the Negative Binomial model, was used for the analysis of repeated CDP events[1]
  - The treatment effect estimate can be interpreted as a RR
- Repeated events over time were visualised by estimates of the MCF
  - The MCF represents the estimated average number of progression events, per patient, over time
- RRs and CIs of annualised repeated events were visualised using forest plots

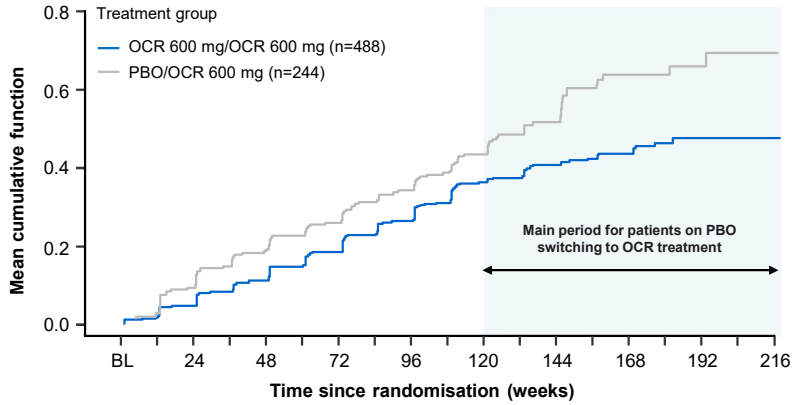
Example of time to first event Kaplan–Meier plot[2]



No. of patients at risk:

	BL	24	48	72	96	120	144	168	192	216
Placebo	244	232	212	199	189	180	172	162	153	145	136	120	85	66	46	30	20	7	2
OCR 600 mg	487	462	450	431	414	391	376	355	338	319	304	281	207	166	136	80	47	20	7

Example of repeated event mean cumulative function plot[2]



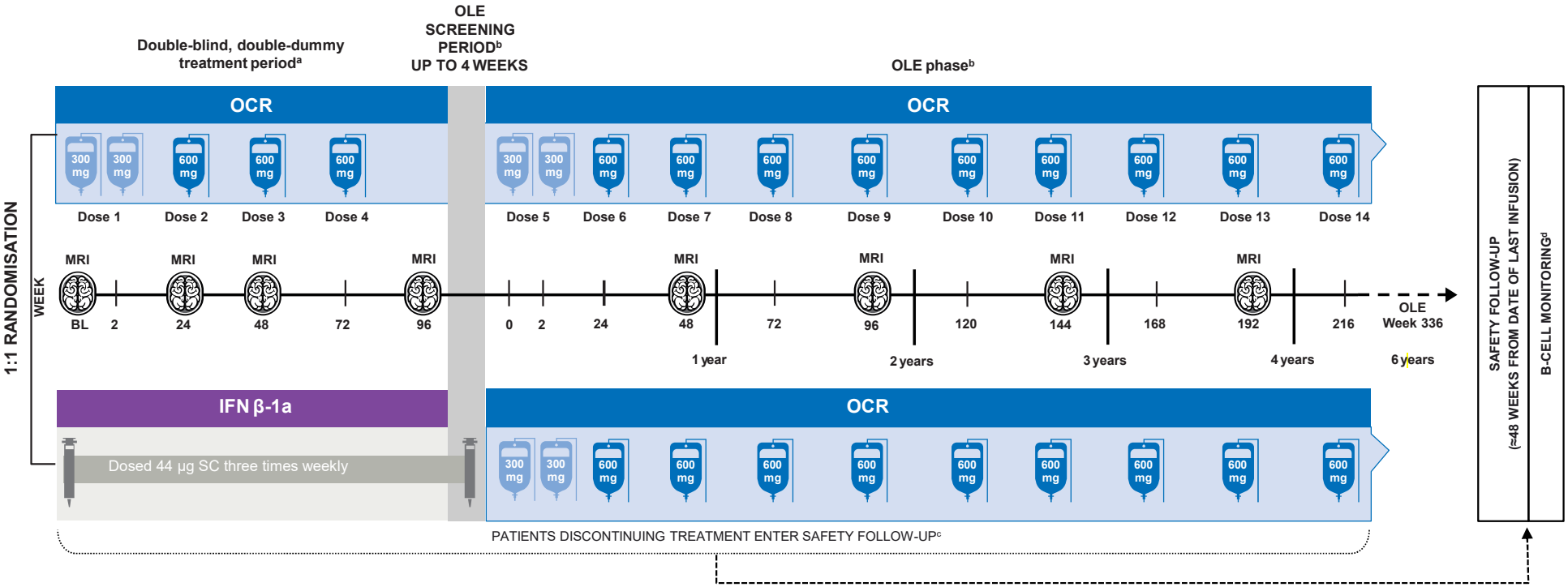
No. of patients at risk:

	BL	24	48	72	96	120	144	168	192	216
Placebo	244	238	234	229	223	215	210	204	197	191	182	165	123	95	69	46	29	9	2
OCR 600 mg	487	473	466	461	455	443	438	434	426	420	412	365	293	231	175	109	63	25	7

At Week 120, the start of the main switching period in the ORATORIO study, 494 patients were available for analysis using repeated CDP events vs 404 patients using the Kaplan–Meier approach.
BL, baseline; CDP, confirmed disability progression; CI, confidence interval; MCF, mean cumulative function; OCR, ocrelizumab; PBO, placebo; RR, rate ratio.

1. Bühler A, *et al. MSJ.* 2022. doi: 10.1177/13524585221125382.

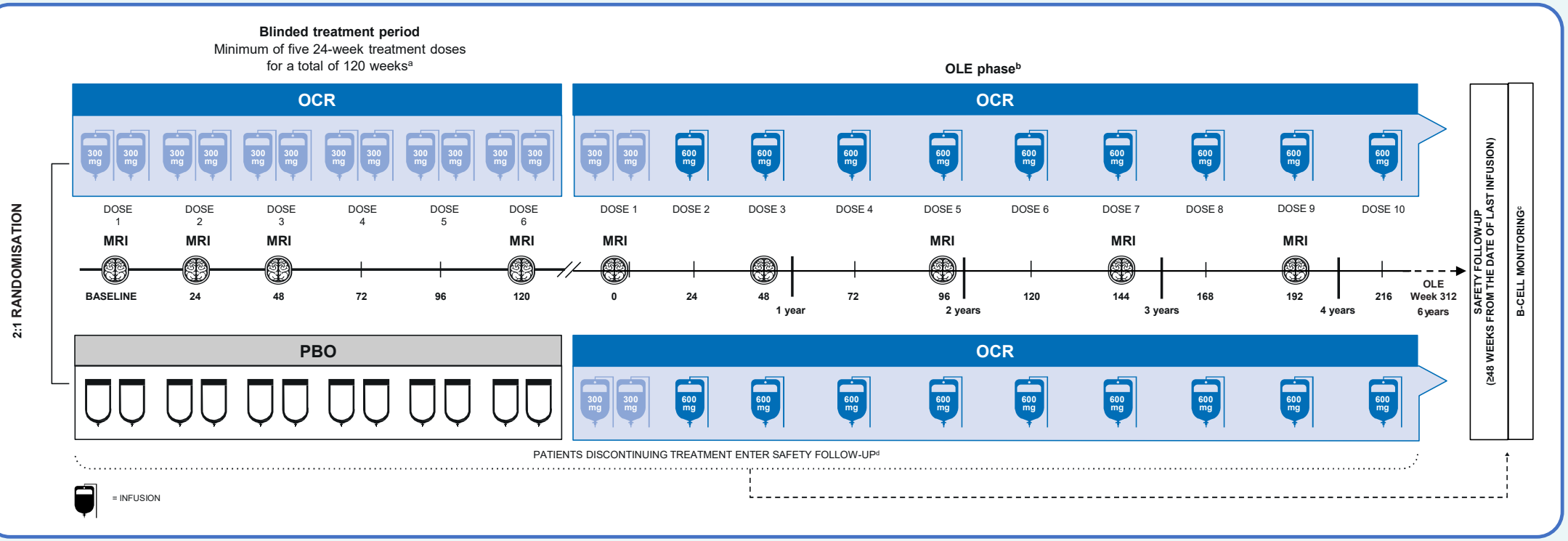
Methods: OPERA I/OPERA II study design



In the DBP, patients were randomised to OCR or comparator (IFN β-1a).
At OLE initiation, patients continued OCR or switched from IFN β-1a to OCR

[a]Patients in the OCR group received placebo injections three times weekly, while patients in the IFN β-1a group received placebo infusions on Days 1 and 15 and at Weeks 24, 48 and 72;
[b]During OLE screening, patients received IFN β-1a or placebo until first infusion of Dose 5; [c]OLE was not mandatory – patients who declined to participate in the OLE entered safety follow-up;
[d]Continued monitoring occurs if B cells are not repleted. Data cut-off: 26 November 2021.
BL, baseline; DBP, double-blind period; IFN, interferon; OCR, ocrelizumab; OLE, open-label extension; SC, subcutaneous.

Methods: ORATORIO study design



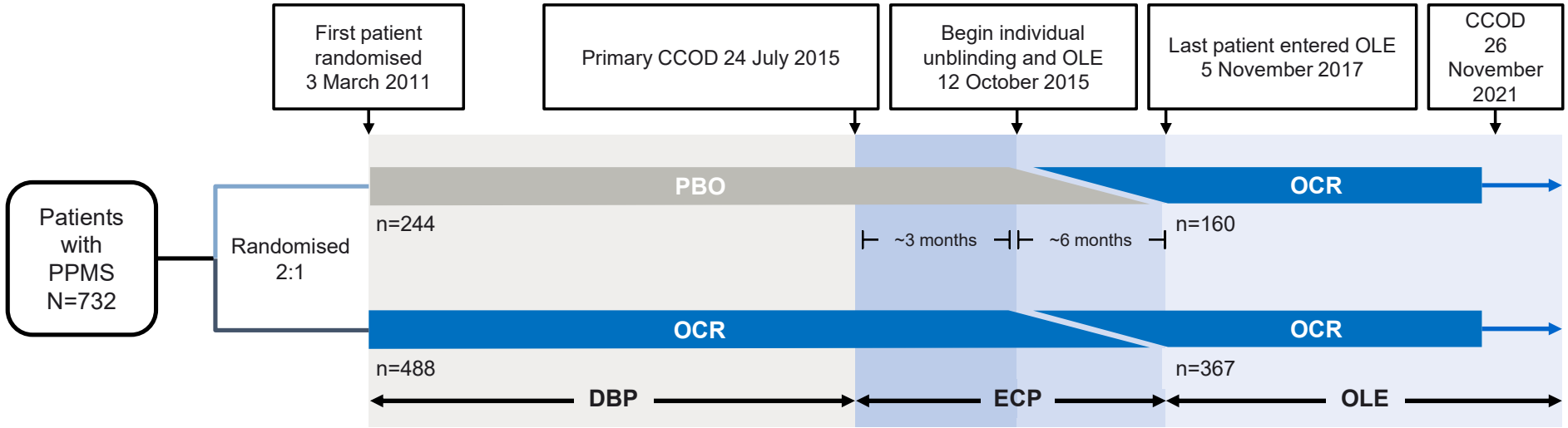
In the DBP, patients were randomised to OCR or PBO.
At OLE initiation, patients continued OCR or switched from PBO to OCR

[a]The blinded treatment period continued until the last patient completed 120 weeks and a target of 253 CDP events was reached; [b]OLE was not mandatory – patients who declined to participate in the OLE entered safety follow-up; [c]Continued monitoring occurs if B cells are not repleted. Data cut-off: 26 November 2021.
CDP, confirmed disability progression; DBP, double-blind period; OCR, ocrelizumab; OLE, open-label extension; PBO, placebo.

Methods: ORATORIO study periods

DBP (cut-off date: 24 July 2015)

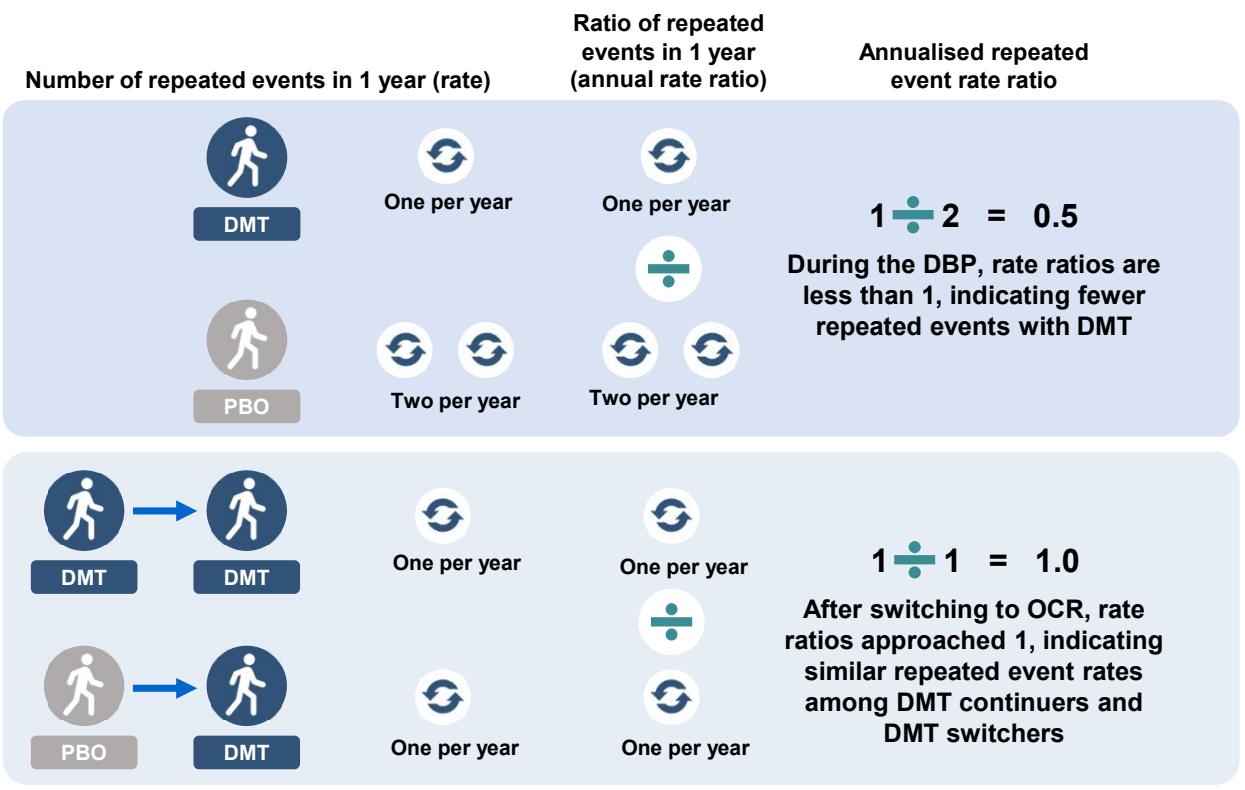
- Patients with PPMS received treatment for ≥120 weeks until a prespecified number of CDP events occurred in the study:
  - Patients (N=732) received OCR 600 mg IV infusions or matching PBO every 24 weeks (randomised 2:1)
  - Upon completion of the DBP, patients remained on blinded treatment as randomised until the outcome of the trial was evaluated
  - When the study was determined to be positive, sites were unblinded and patients could enter the OLE phase

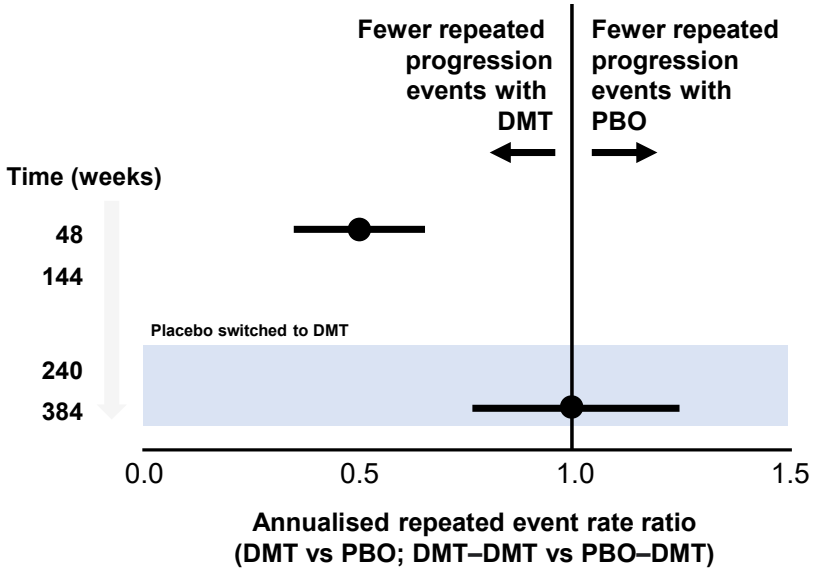


CCOD, clinical cut-off date; CDP, confirmed disability progression; DBP, double-blind period; ECP, extended controlled period; IV, intravenous; OCR, ocrelizumab; OLE, open-label extension; PBO, placebo; PPMS, primary progressive multiple sclerosis.

Methods: Annualised repeated event rate ratios

How annualised repeated event rate ratios were calculated: Illustrative example





Stylised illustration

DBP, double-blind period; DMT, disease-modifying therapy; OCR, ocrelizumab; PBO, placebo.

Methods: Statistical analysis

- A rate-based method, the NB model, was used for the analysis of repeated CDP events[1]
  - The method retains the beneficial aspects of randomisation and is, therefore, recommended for the analysis of a RCT with repeated CDP events[2,3]
  - It assumes that the rate function is constant over time and heterogeneity between subjects is modelled via gamma-distributed frailties[4]
  - The model included a subject's number of CDP events as the response variable, and their (log-transformed) follow-up duration as an offset, and was adjusted for the randomisation stratification factors of the respective studies
  - The treatment effect estimate can be interpreted as a RR. RRs and CIs of annualised repeated events were visualised using forest plots
- Repeated events over time were visualised by Nelson–Aalen type estimates of the cumulative mean function[a]

[a]Mean cumulative number of repeated CDP events.

CDP, confirmed disability progression; CI, confidence interval; NB, Negative Binomial; RCT, randomised clinical trial; RR, rate ratio.

1. Bühler A, *et al. MSJ* 2022. DOI: 10.1177/13524585221125382. 2. Cook RJ, Lawless J. The statistical analysis of repeated events. New York: Springer Science & Business Media, 2007:128–133.
3. Bühler A. Comparison of time-to-first-event and repeated event methods in multiple sclerosis trials. Masters Thesis, Ulm University, Germany, 2019. http://arxiv.org/abs/2111.01937. 4. Wang YC, *et al. J Neurol Sci* 2009;285:206–211.

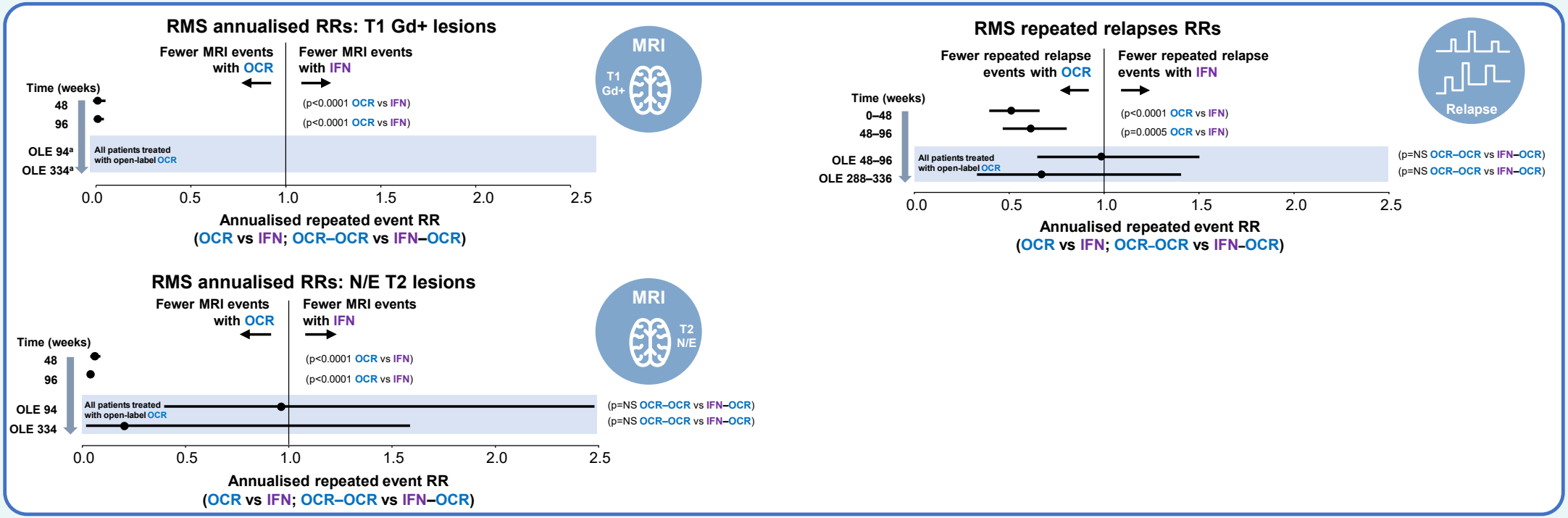
Methods: Study endpoints

RMS: Additional efficacy assessments presented to OLE Week 288

- **Disease activity**: Defined as having at least one the following events (binary within each year):
  - Repeated 48-week EDSS-CDP
  - Protocol-defined relapse
  - Gadolinium-enhancing T1 lesion
  - New or enlarging T2 lesion

CDP, confirmed disability progression; EDSS, Expanded Disability Status Scale; OLE, open-label extension; RMS, relapsing multiple sclerosis.

Results: RMS – ARR and MRI lesions



After switching to OCR, disease activity rates (assessed by repeated relapses and new MRI lesion activity) were similar between continuous OCR and PBO–OCR switch groups

CCOD: 26 November 2021.
RR was estimated by GEE Poisson regression model with repeated measurements using unstructured covariance matrix, adjusted by randomised treatment, geographical region (USA vs ROW), baseline age (>45 vs ≤45 years), year and treatment-by-year interaction.
ARR, annualised relapse rate; CCOD, clinical cut-off date; CI, confidence interval; GEE, generalised estimating equation; IFN, interferon; N/E T2, new/enlarging T2 lesion; NS, not significant; OCR, ocrelizumab; OLE, open-label extension; PBO, placebo; RMS, relapsing multiple sclerosis: ROW, rest of world; RR, rate ratio; T1 Gd+, T1 gadolinium-enhancing lesion.

Poster Results figure footnotes

PPMS: 48-Week, Repeated CDP-EDSS and cCDP

CCOD, 26 November 2021. [a]cCDP (binary, within each year) was defined as having at least one of the following events: 48W-CDP-EDSS; 48W-CDP-9HPT; 48W-CDP-T25FW. Week 240 is shown, as it is the first visit when all patients had switched to OCR in the OLE. Overall RR was estimated using the Negative Binomial model adjusted for geographical region (USA vs ROW) and baseline age (>45 vs ≤45 years). Annualised RR was estimated using a GEE Poisson regression model with repeated measurements, adjusted by randomised treatment, geographical region (USA vs ROW), baseline age (>45 vs ≤45 years), year and treatment-by-year interaction. Patients with missing baseline EDSS score were excluded from analysis. Patients with an initial disability progression during the ECP or OLE treatment period who discontinue the extended controlled or OLE treatment early and do not have a subsequent visit with EDSS measurement are imputed as having a CDP event. Similar findings were observed when using a 24-week confirmation window for disability progression events.
9HPT, Nine-Hole Peg Test; cCDP, composite confirmed disability progression; CCOD, clinical cut-off date; CDP, confirmed disability progression; DBP, double-blind period; ECP, extended controlled period; EDSS, Expanded Disability Status Scale; GEE, generalised estimating equation; NS, not significant; OCR, ocrelizumab; OLE, open-label extension; PBO, placebo; PPMS, primary progressive multiple sclerosis; ROW, rest of world; RR, rate ratio; T25FW, Timed 25-Foot Walk; W, week.

PPMS: 48-Week, Repeated CDP-9HPT and CDP-T25FW

CCOD, 26 November 2021. Week 240 is shown, as it is the first visit when all patients had switched to OCR in the OLE. Overall RR was estimated using the Negative Binomial model adjusted for geographical region (USA vs ROW) and baseline age (>45 vs ≤45 years). Annualised RR was estimated using a GEE Poisson regression model with repeated measurements, adjusted by randomised treatment, geographical region (USA vs ROW), baseline age (>45 vs ≤45 years), year and treatment-by-year interaction. Patients with missing baseline EDSS scores were excluded from analysis. Patients with an initial disability progression during the ECP or OLE treatment period who discontinue the extended controlled or OLE treatment early and do not have a subsequent visit with EDSS measurement are imputed as having a CDP event. Similar findings were observed when using a 24-week confirmation window for disability progression events.
9HPT, Nine-Hole Peg Test; CDP, confirmed disability progression; CCOD, clinical cut-off date; DBP, double-blind period; ECP, extended controlled period; EDSS, Expanded Disability Status Scale; GEE, generalised estimating equation; NS, not significant; OCR, ocrelizumab; OLE, open-label extension; PBO, placebo; PPMS, primary progressive multiple sclerosis; ROW, rest of world; RR, rate ratio; T25FW, Timed 25-Foot Walk; W, week.

RMS: 48-Week, Repeated CDP-EDSS and Disease Activity

CCOD, 26 November 2021. [a]Disease activity (binary within each year) was defined as having at least one of the following events: Repeated, 48W-CDP-EDSS; protocol-defined relapse; T1 Gd+ lesion; N/E T2 lesion. Overall RR was estimated using the Negative Binomial model adjusted for geographical region (USA vs ROW) and baseline age (>45 vs ≤45 years). Annualised RR was estimated using a GEE Poisson regression model with repeated measurements, adjusted by randomised treatment, geographical region (USA vs ROW), baseline age (>45 vs ≤45 years), year and treatment-by-year interaction. Patients with missing baseline EDSS scores were excluded from analysis. Patients with an initial disability progression during the OLE treatment period who discontinue the OLE treatment early and do not have a subsequent visit with EDSS measurement are imputed as having a CDP event. Similar findings were observed when using a 24-week confirmation window for disability progression events.
CDP, confirmed disability progression; CCOD, clinical cut-off date; DBP, double-blind period; EDSS, Expanded Disability Status Scale; GEE, generalised estimating equation; N/E T2, new/enlarging T2 lesion; NS, not significant; OCR, ocrelizumab; OLE, open-label extension; PBO, placebo; RMS, relapsing multiple sclerosis; ROW, rest of world; RR, rate ratio; T1 Gd+, T1 gadolinium-enhancing lesion; W, week.