Sustained Reduction in 48-Week Confirmed Disability Progression in Patients With PPMS Treated With Ocrelizumab in the ORATORIO OLE: 7-Year Follow-up

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ORATORIO study (NCT01194570)

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K Coutant is an employee of F. Hoffmann-La Roche Ltd.

H Koendgen is an employee and shareholder of F. Hoffmann-La Roche Ltd.

HM Schneble is an employee and a shareholder of F. Hoffmann-La Roche Ltd.

J Overell is currently an employee and shareholder of F. Hoffmann-La Roche Ltd. During his previous employment he received personal compensation for consulting, serving on a scientific advisory board, speaking, or other activities with Teva, Biogen, Celgene, EMD Serono, MedDay, Novartis, Roche, Sanofi Genzyme, WebMD Global, and Allergan. His research and department were supported by grants from Sanofi Genzyme, Biogen, Novartis, and Roche.

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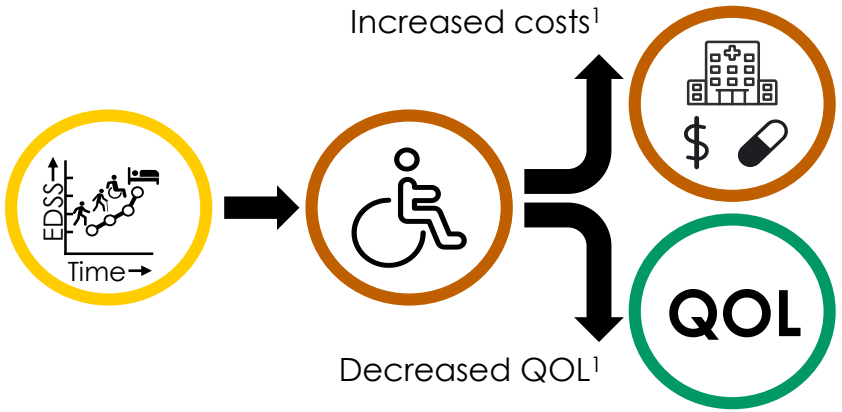
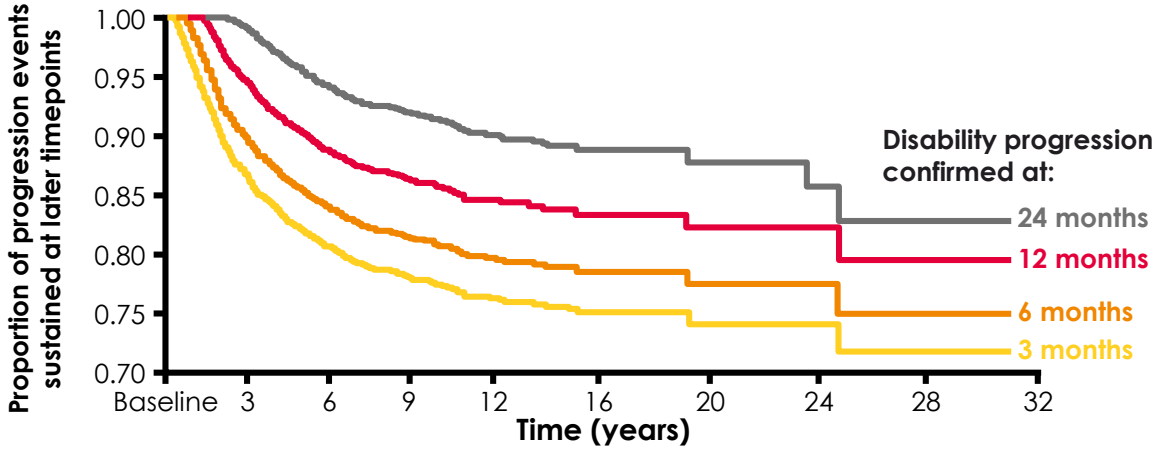
Key EDSS milestones and relevance to both patients and society

- Reaching EDSS score ≥7.0, a key clinical disability milestone representing wheelchair confinement, has a major impact on patients' quality of life and associated treatment costs[1]

Upper extremity functional impairment, as assessed using 9HPT, is prevalent in patients with PPMS, and adversely impacts patient independence and quality of life[2,3]



Longer confirmation periods for CDP more likely reflect permanent disability[4]



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- OCR was the first anti-CD20 monoclonal antibody approved at a dose of 600 mg IV twice yearly, for the treatment of RMS and PPMS; it remains the only approved treatment for PPMS[5,6]
- OCR had significant benefit on 12/24W-CDP, ARR, and MRI measures in pivotal Phase III studies in patients with RMS[7] and PPMS,[8] with sustained efficacy in the respective open-label extension periods[9,10]

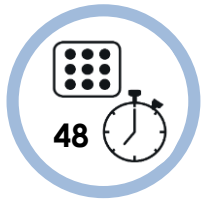
In the MSBase prospective cohort of 16,636 patients, with a follow-up duration of 6.8 years, the most important determinant of progression stability was the length of the confirmation period.[4]
9HPT, 9-Hole Peg Test; ARR, annualized relapse rate; CDP, confirmed disability progression; EDSS, Expanded Disability Status Scale; IV, intravenous; OCR, ocrelizumab; PPMS, primary progressive multiple sclerosis; RMS, relapsing multiple sclerosis; QOL, quality of life.
1. Kobelt G, *et al. Mult Scler* 2017;23:1123–1136; 2. Holper L, *et al. J Neurol* 2010;257:103–113; 3. Lamers I, Feys P. *Mult Scler* 2014;20:775–784; 4. Kalincik T, *et al. Brain* 2015;138:3287–3298; 5. OCREVUS [ocrelizumab] Full Prescribing Information. Genentech, Inc., 2020; 6. OCREVUS [ocrelizumab] Summary of Product Characteristics. Roche Pharma AG, 2020; 7. Hauser SL, *et al. N Engl J Med* 2017:376:221–234; 8. Montalban X, *et al. N Engl J Med* 2017;376:209–220 9. Hauser SL, *et al. Neurology* 2020; ePub ahead of print: PMID: 32690791; 10. Wolinsky J, *et al. ECTRIMS* 2019: Presentation no. 159.

Objective and methods: CDP, 9HPT, and time-to-wheelchair

Objective: To assess the efficacy of switching to or maintaining OCR therapy on measures of 48-week CDP, including **time-to-wheelchair**, in the OLE of ORATORIO

- **Methods:**
  - In the DBP, 732 patients were randomized to OCR or PBO and followed for ≥120 weeks until a prespecified number of CDP events occurred
  - At DBP completion, patients remained on blinded treatment until the trial outcome was determined (ECP)
  - At OLE start, patients continued OCR (OCR-OCR) or switched from PBO to OCR (PBO-OCR)
- **Outcomes:**

CDP-EDSS: Increase in EDSS score from baseline



CDP-9HPT: ≥20% increase in 9HPT from baseline

CDP-T25FW: ≥20% increase in T25FW from baseline

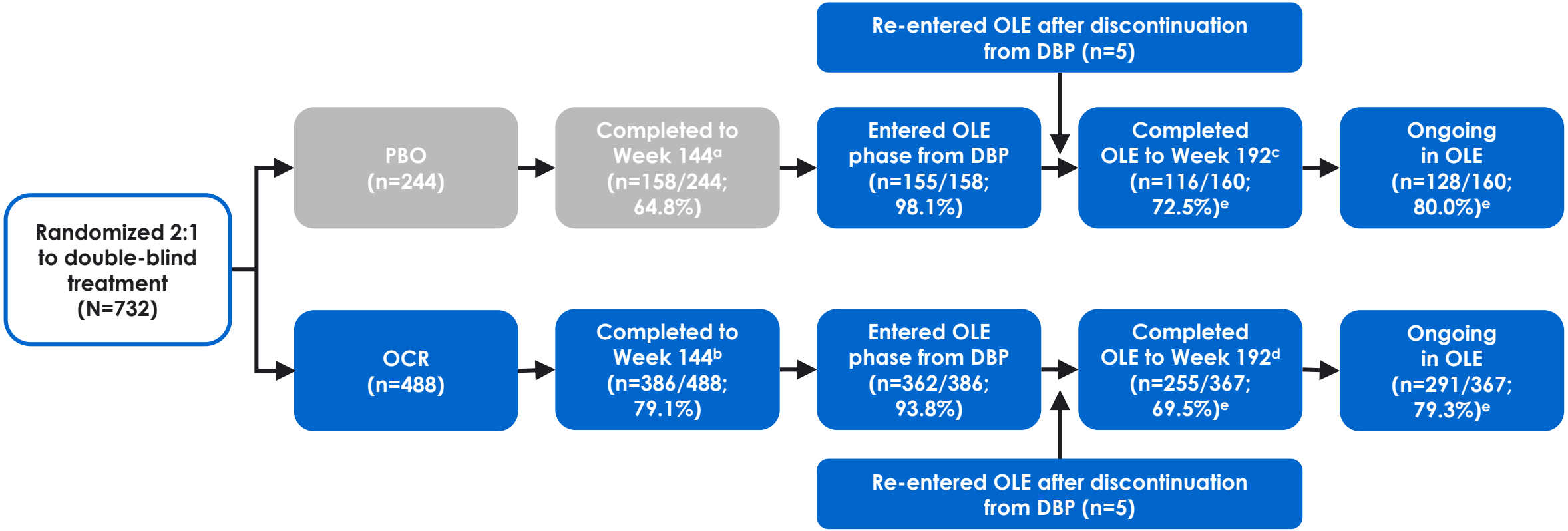
cCDP: Time to first onset of either CDP, or ≥20% increases in T25FW or 9HPT

Time-to-wheelchair: Time to confirmed EDSS ≥7.0

9HPT, 9-Hole Peg Test; cCDP, composite CDP; CDP, confirmed disability progression; DBP, double-blind period; ECP, extended controlled period; EDSS, Expanded Disability Status Scale; OCR, ocrelizumab; OLE, open-label extension; PBO, placebo; T25FW, Timed 25-Foot Walk.

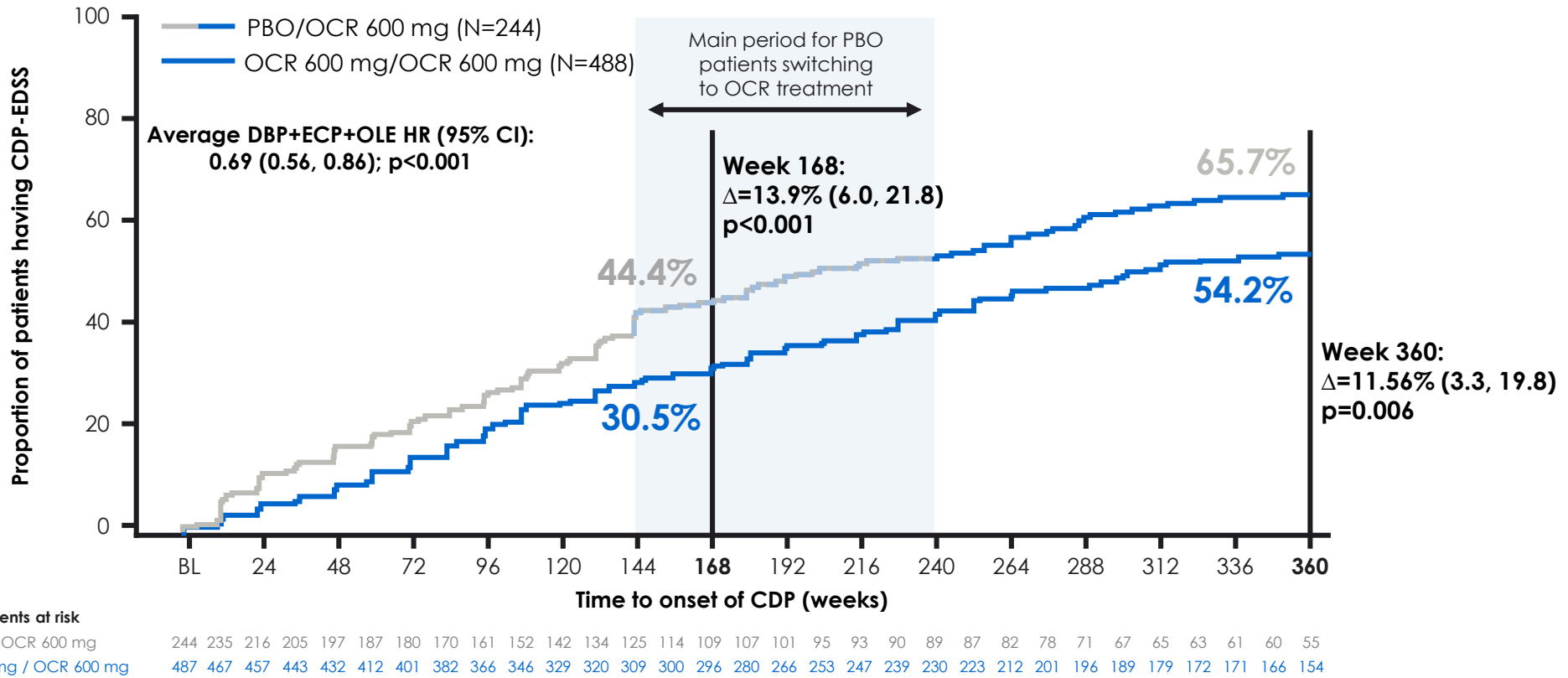
ORATORIO OLE: Patient disposition after 7 years of follow-up

- Overall, 95% of patients who completed to Week 144 entered the OLE period of the ORATORIO study; this represents 71% of those initially randomized



Percentages in parentheses are of the ITT population. Clinical cut-off date: January 3, 2020.
[a]47 (19.3%) patients entered safety follow-up from DBP; [b]75 (15.4%) patients entered safety follow-up from DBP; [c]10 (6.3%) patients entered safety follow-up from OLE; [d]28 (7.6%) patients entered safety follow-up from OLE; [e]Percentages in parentheses are of the OLE population.
DBP, double-blind period; ITT, intention-to-treat; OCR, ocrelizumab; OLE, open-label extension; PBO, placebo.

Results: Time to 48-week CDP-EDSS



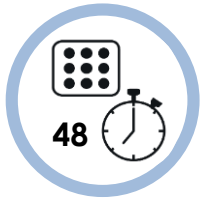
No. of patients at risk

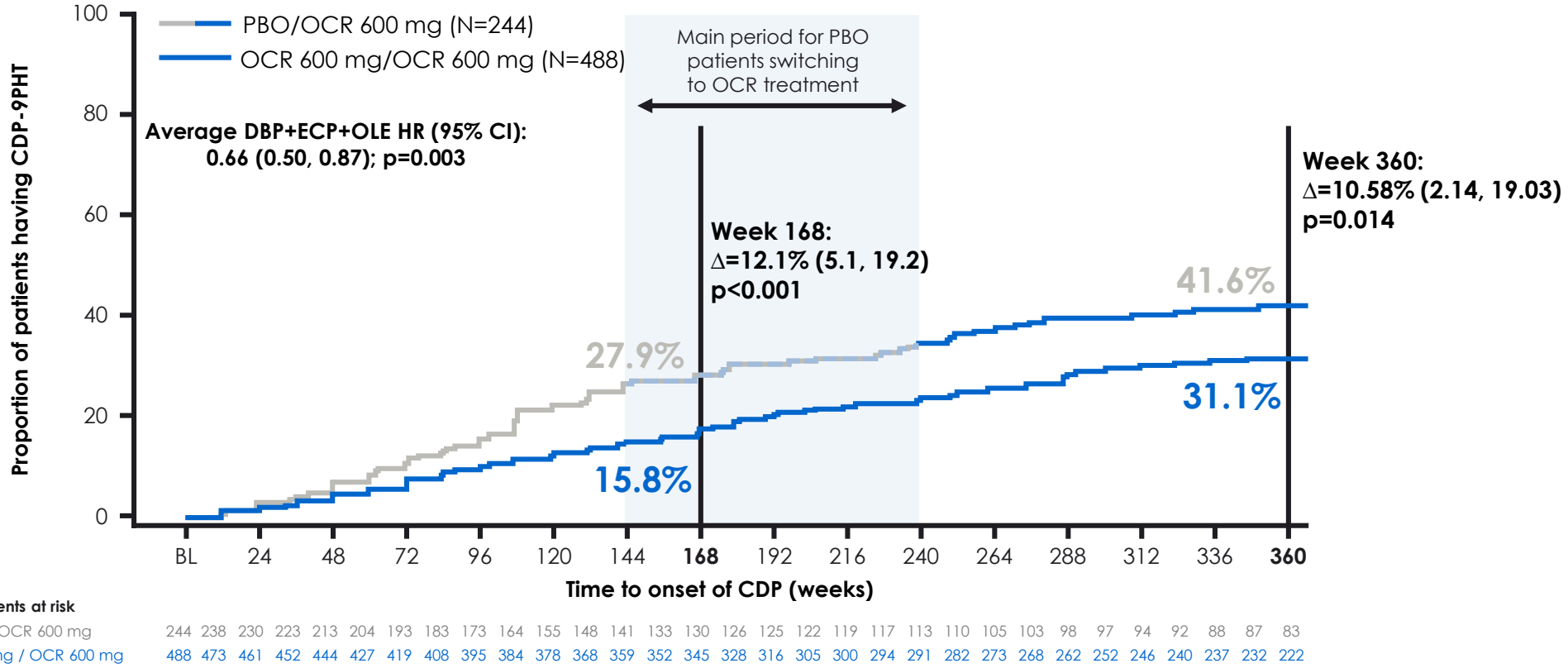
Placebo / OCR 600 mg	244	235	216	205	197	187	180	170	161	152	142	134	125	114	109	107	101	95	93	90	89	87	82	78	71	67	65	63	61	60	55
OCR 600 mg / OCR 600 mg	487	467	457	443	432	412	401	382	366	346	329	320	309	300	296	280	266	253	247	239	230	223	212	201	196	189	179	172	171	166	154

Over 7 years of the DBP+ECP+OLE, the risk of reaching 48-week CDP-EDSS was significantly lower (31%) in those who initiated OCR earlier vs delayed treatment

Over 7 years of the DBP+ECP+OLE, for T25FW the HR (95% CI) was: 0.79 (0.64, 0.96); see supplemental slides. Week 168 is shown, as it is the first visit when most patients had switched to OCR in the OLE. Hazard ratios were estimated by Cox regression stratified by study, geographical region (US vs ROW), and age (≤45 years vs >45 years). Comparison of the survival distributions used the log-rank test. Patients with missing baseline EDSS were excluded from analysis. Patients with an initial disability progression during the extended controlled treatment period 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.
BL, baseline; CDP, confirmed disability progression; DBP, double-blind period; ECP, extended controlled period; EDSS, Expanded Disability Status Scale; HR, hazard ratio; OCR, ocrelizumab; OLE, open-label extension; ROW, rest of the world; T25FW, Timed 25-Foot Walk.

Results: Time to 48-week CDP-9HPT





No. of patients at risk

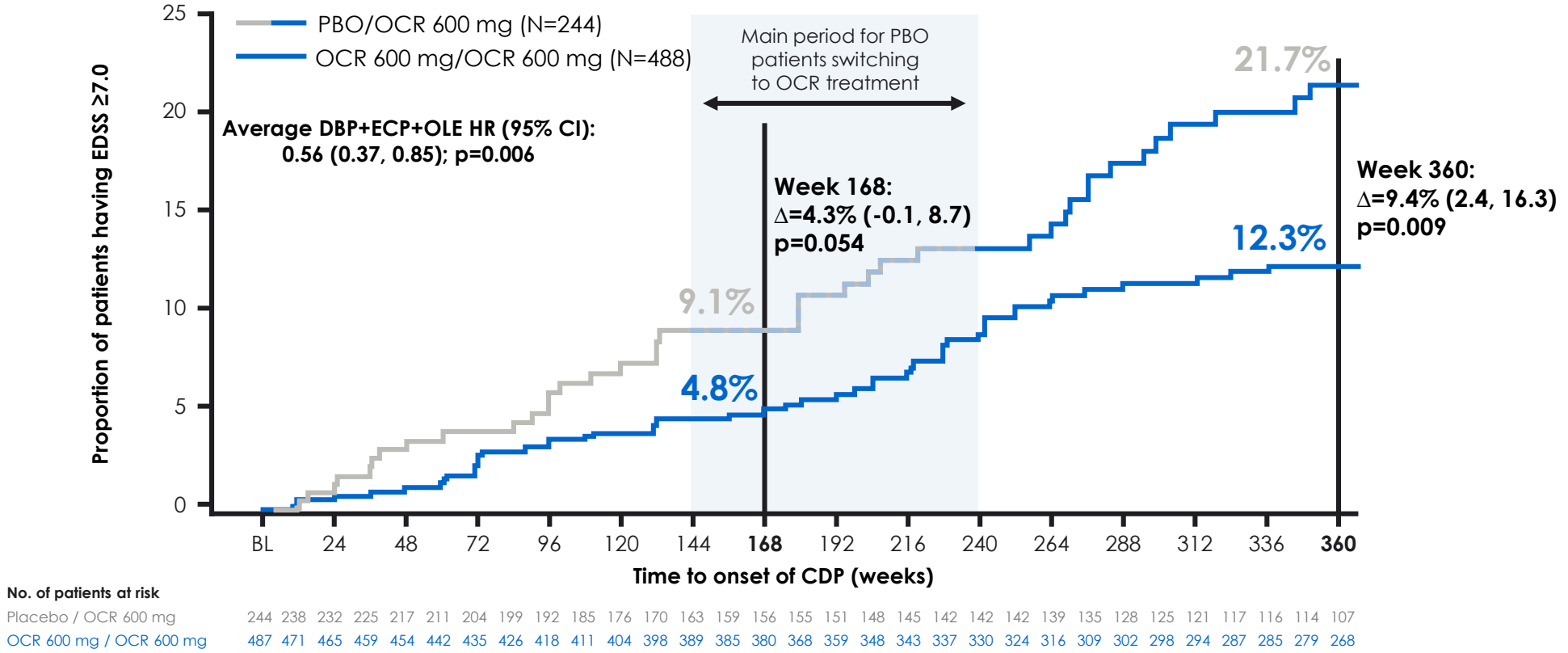
Placebo / OCR 600 mg	244	238	230	223	213	204	193	183	173	164	155	148	141	133	130	126	125	122	119	117	113	110	105	103	98	97	94	92	88	87	83
OCR 600 mg / OCR 600 mg	488	473	461	452	444	427	419	408	395	384	378	368	359	352	345	328	316	305	300	294	291	282	273	268	262	252	246	240	237	232	222

Over 7 years of the DBP+ECP+OLE, the risk of reaching 48-week CDP-9HPT was significantly lower (34%) in those who initiated OCR earlier vs delayed treatment

Over 7 years of the DBP+ECP+OLE, for cCDP the HR (95% CI) was: 0.73 (0.61, 0.88); see supplemental slides. Week 168 is shown, as it is the first visit when most patients had switched to OCR in the OLE. Hazard ratios were estimated by Cox regression stratified by study, geographical region (US vs ROW), and age (≤45 years vs >45 years). Comparison of the survival distributions used the log-rank test. Patients with an initial disability progression during the extended controlled treatment period or OLE treatment period who discontinue the Extended Controlled or OLE treatment early and do not have a subsequent visit with are imputed as having a CDP event.

9HPT, 9-Hole Peg Test; BL, baseline; CDP, confirmed disability progression; DBP, double-blind period; ECP, extended controlled period; HR, hazard ratio; OCR, ocrelizumab; OLE, open-label extension; ROW, rest of the world.

Results: Time-to-wheelchair (EDSS ≥7.0) confirmed for ≥48 weeks



Over 7 years of the DBP+ECP+OLE, the risk of requiring a wheelchair confirmed for ≥48 weeks was significantly lower (44%) in those who initiated OCR earlier vs delayed treatment

Week 168 is shown, as it is the first visit when most patients had switched to OCR in the OLE. Hazard ratios were estimated by Cox regression stratified by study, geographical region (US vs ROW), and age (≤45 years vs >45 years). Comparison of the survival distributions used the log-rank test. Patients with missing baseline EDSS were excluded from analysis. Patients with an EDSS score ≥7.0 the time of treatment discontinuation with no further EDSS score are imputed as having event.

BL, baseline; CDP, confirmed disability progression; DBP, double-blind period; ECP, extended controlled period; EDSS, Expanded Disability Status Scale; HR, hazard ratio; OCR, ocrelizumab; OLE, open-label extension; ROW, rest of the world.

Results: Safety after 7 years of follow-up

Event	ORATORIO controlled treatment period		ORATORIO all OCR exposure population Rate per 100 PY (95% CI)[c]
	PBO rate per 100 PY (95% CI)[a]	OCR rate per 100 PY (95% CI)[b]	
Any adverse event[d]	**259 (247–271)**	**252 (244–260)**	**237 (232–242)**
Infections and infestations[d]	**72.5 (66.5–79.0)**	**70.8 (66.8–75.0)**	**74.2 (71.4–77.1)**
Urinary tract infection	17.8 (14.9–21.2)	15.1 (13.2–17.1)	19.0 (17.6–20.5)
Nasopharyngitis	17.7 (14.8–21.0)	12.8 (11.1–14.6)	12.4 (11.3–13.6)
Upper respiratory tract infection	2.9 (1.8–4.4)	5.2 (4.2–6.5)	5.1 (4.4–5.9)
Malignancies[d,e,f]	**0.27 (0.03–0.99)**	**0.93 (0.52–1.54)**	**1.00 (0.70–1.39)**
Serious adverse events[d]	**12.1 (9.7–14.9)**	**10.2 (8.7–11.8)**	**12.9 (11.8–14.2)**
Serious infections[g]	3.02 (1.89–4.57)	2.74 (1.99–3.68)	4.41 (3.75–5.15)

- See presentation P0389 for further ocrelizumab safety data

[a]Includes patients who received PBO during the controlled treatment period of the ORATORIO study; [b]Includes patients who received any dose of OCR during the controlled treatment period of ORATORIO; [c]Includes patients who received any dose of OCR during the controlled and OLE treatment phases of ORATORIO and data from patients who were originally randomized to PBO included after switch to open-label OCR treatment. CCOD for inclusion of data in this analysis: January 03, 2020; [d]Multiple occurrences of the same adverse event (except for malignancies) in one patient are counted multiple times; Includes adverse events falling into the MedDRA versions 18.1 (ORATORIO controlled treatment period) and 22.1 (CCOD: January 03, 2020); [e]Malignancies are identified using adverse events falling into the standard MedDRA query 'Malignant tumors (narrow)'; [f]Reported as incidence rate per 100 PY of first malignancy; [g]Serious infections are defined using adverse events falling into the MedDRA SOC Infections and Infestations, and using 'Is the event non-serious or serious?' from the adverse event case report form.

CCOD, clinical cut-off date; DBP, double-blind period; IFN, interferon; MedDRA, Medical Dictionary for Regulatory Activities; OCR, ocrelizumab; OLE, open-label extension; PBO, placebo; PY, patient years; SOC, system organ class.

Conclusions

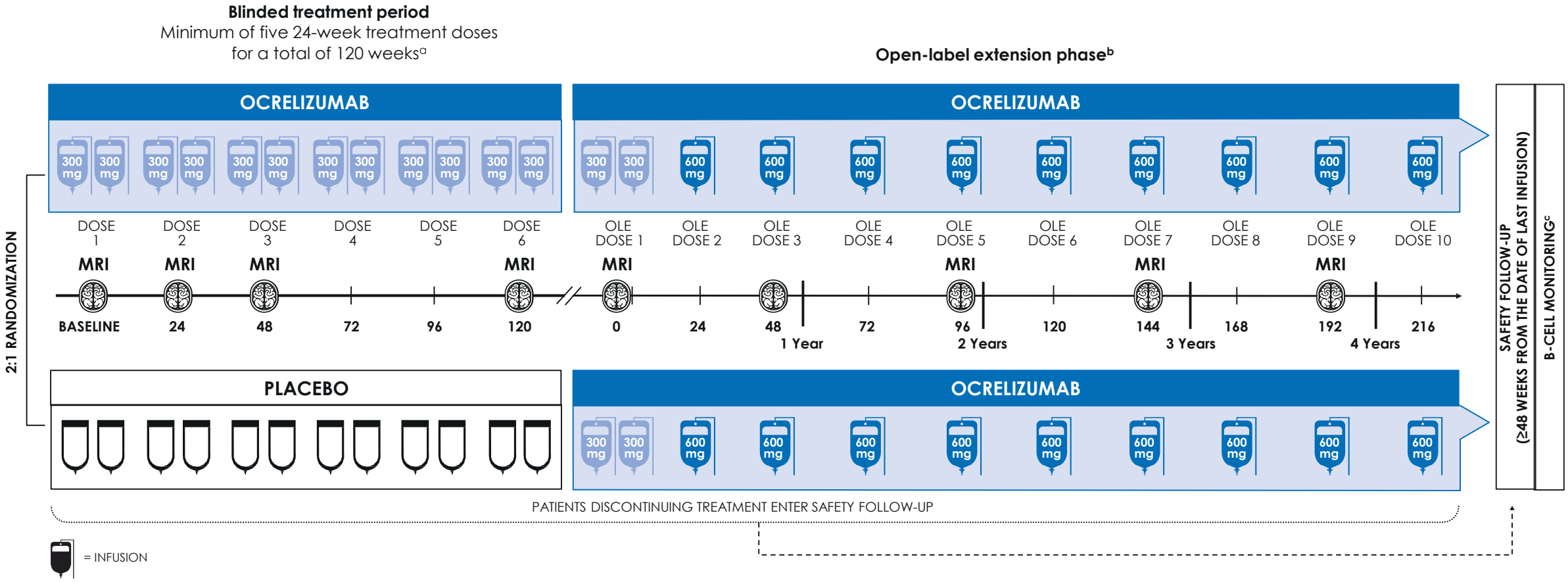
- Over 7 years of follow-up, patients initiating ocrelizumab 3–5 years earlier vs those initially receiving placebo had a significantly reduced risk (confirmed for ≥48 weeks, a period more likely reflecting permanent disability) of:
  - Confirmed disability progression on EDSS score, 9HPT, and T25FW
  - Requiring a wheelchair
- The safety profile observed in the OLE was generally consistent with that seen during the DBP and no new safety signals were detected
- The effect of ocrelizumab on lessening confirmed worsening of disability and delaying the time to meaningful disability milestones has the potential to positively impact patients' quality of life and reduce healthcare costs and burdens[1]
- See presentation P0216 for the long-term efficacy results of OCR in patients with RMS (6.5 years)

9HPT, 9-Hole Peg Test; DBP, double-blind period; EDSS, Expanded Disability Status Scale; OCR, ocrelizumab; OLE, open-label extension; T25FW, Timed 25-Foot Walk; RMS, relapsing multiple sclerosis.

1. Kobelt G, *et al. Mult Scler* 2017;23:1123–1136.

Supplemental Material

ORATORIO OLE phase: Study design

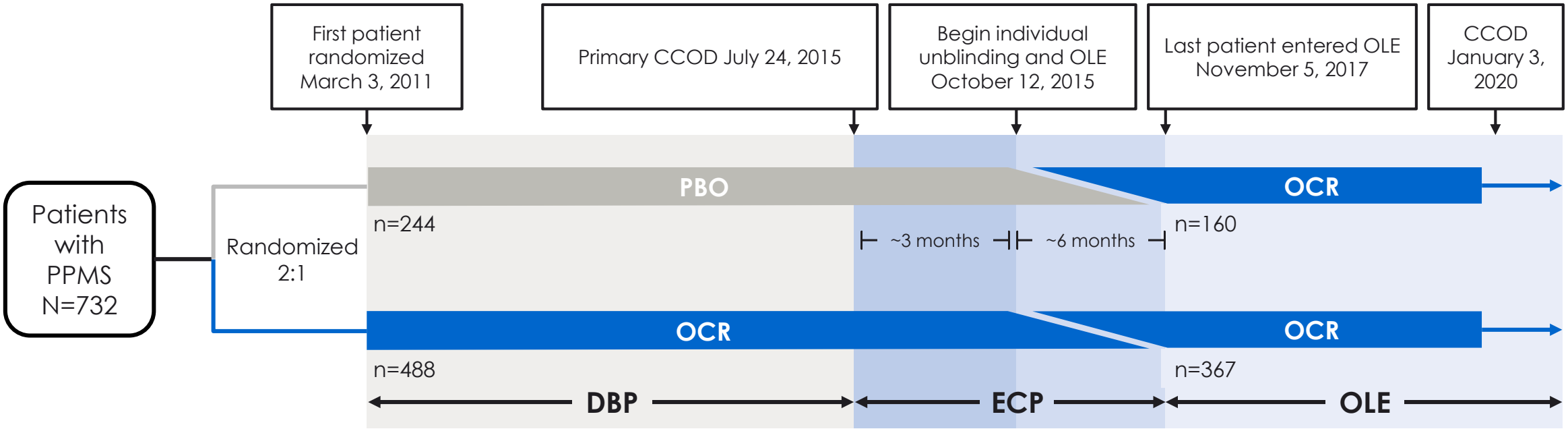


[a]The blinded treatment period continued until the last patient completed 120 weeks and a target of 253 CDP events was reached; [b]OLE was not mandatory. Patients who declined to participate in the OLE entered safety follow-up; [c]Continued monitoring occurs if B cells are not repleted.
CDP, confirmed disability progression; OLE, open-label extension.

ORATORIO study periods

Double-blind period (cut-off date: July 24, 2015)

- Patients with PPMS received treatment for ≥120 weeks until a prespecified number of CDP events occurred:
  - Patients (N=732) received OCR 600 mg IV infusions or matching PBO every 24 weeks (randomized 2:1)
  - Upon completion of the DBP, patients remained on blinded treatment as randomized 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; OCR, ocrelizumab; OLE, open-label extension; PBO, placebo; PPMS, primary progressive multiple sclerosis.

Study endpoints and statistical analysis

Efficacy assessments

- Time to onset of 24- and 48-week CDP from baseline sustained for at least 24 or 48 weeks:
  - **CDP-EDSS** was defined as an increase in the EDSS score from the baseline of the DBP of at least 1.0 point (increase of ≥0.5 points if baseline EDSS score >5.5)
  - **CDP-T25FW** was defined as a ≥20% increase in T25FW from baseline
  - **CDP-9HPT** was defined as a ≥20% increase in 9HPT from baseline
  - **Composite CDP** was defined as the time to first onset of either CDP, or ≥20% increases in T25FW or 9HPT
  - **Time-to-wheelchair analysis** (confirmed EDSS ≥7.0 for at least 24 weeks)

Statistical analysis

- CDP for at least 24 and 48 weeks was assessed using Kaplan–Meier and Cox survival analysis in the ITT population
- Hazard ratios were estimated using Cox regression stratified by region (US vs ROW) and age (≤45 vs >45 years)
- Comparison of the survival distributions used the log-rank test

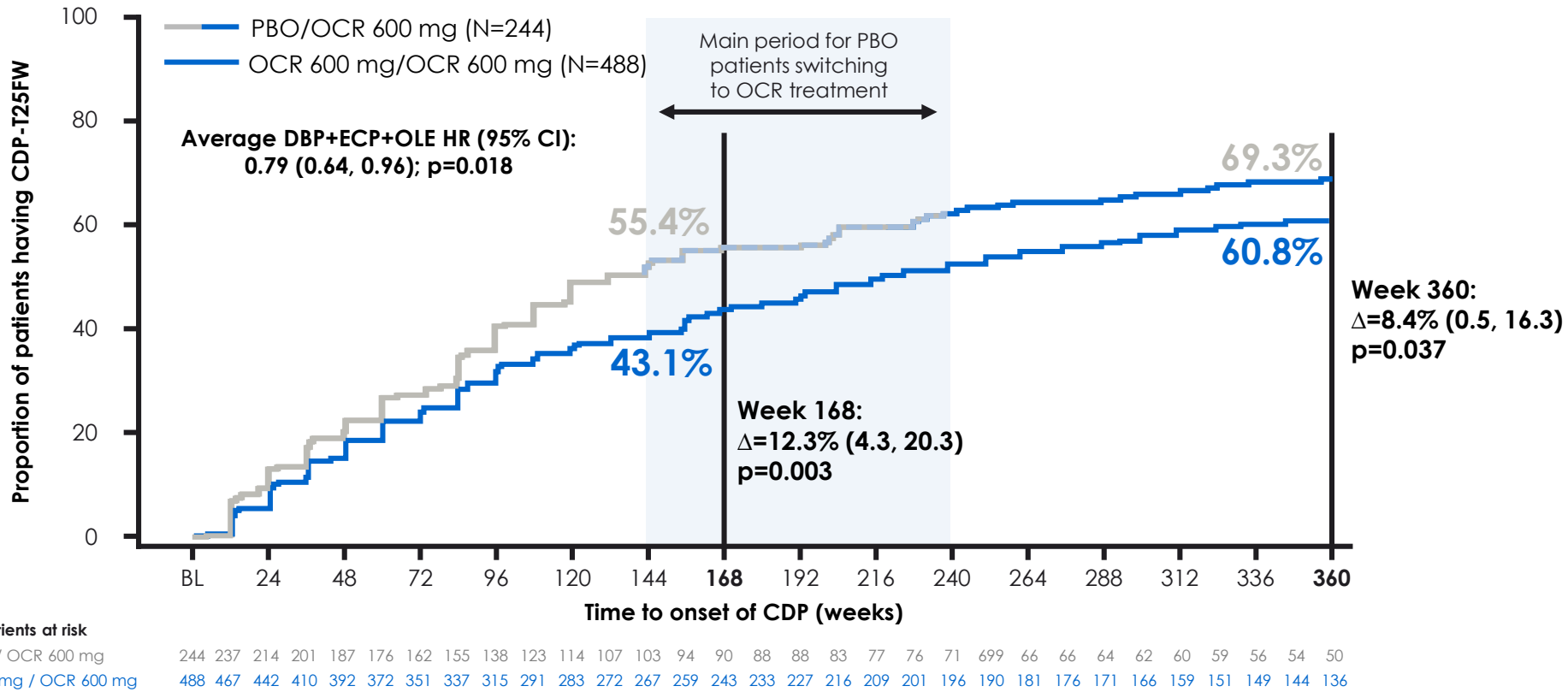
9HPT, 9-Hole Peg Test; CDP, confirmed disability progression; EDSS, Expanded Disability Status Scale; ROW, rest of world; T25FW, Timed 25-Foot Walk.

Baseline demographics and disease characteristics for the ORATORIO populations at the start of the DBP and OLE

	DBP baseline		OLE baseline	
	Placebo/ OCR 600 mg (N=244)	OCR 600 mg/ OCR 600 mg (N=488)	Placebo/ OCR 600 mg (n=160)	OCR 600 mg/ OCR 600 mg (n=367)
Age, mean (SD), years	44.4 (8.3)	44.7 (7.9)	49.2 (7.7)	48.5 (7.8)
Female, n (%)	124 (50.8)	237 (48.6)	82 (51.3)	174 (47.4)
EDSS score, mean (SD)	4.7 (1.2)	4.7 (1.2)	5.2 (1.50)	4.9 (1.52)
Pts with T1 Gd-enhancing lesions, n (%)	60 (24.7)	133 (27.5)	25 (15.8)	1 (0.3)
No. T1 Gd-enhancing lesions, mean (SD)	0.6 (1.6)	1.2 (5.1)	0.3 (1.0)	0.01(0.2)
No. T2 lesions, mean (SD)	48.2 (39.3)	48.7 (38.2)	49.5 (32.6)	50.0 (36.3)
T2 lesion volume, mean (SD), cm^3	10.9 (13.0)	12.7 (15.1)	11.2 (12.8)	12.2 (13.6)
T1 hypointense lesions, volume, mean (SD), cm^3	4.2 (6.1)	5.2 (7.9)	5.4 (7.8)	5.9 (8.3)
Normalized brain volume, mean (SD), cm^3	1,469.9 (88.7)	1,462.9 (84.0)	N/A	N/A

Demographics and disease characteristics are based on the last person entering the OLE October 30, 2017.
DBP, double-blind period; EDSS, Expanded Disability Status Scale; Gd, gadolinium; N/A, not available; OCR, ocrelizumab; OLE, open-label extension; Pts, patients.

Results: Time to 48-week CDP-T25FW



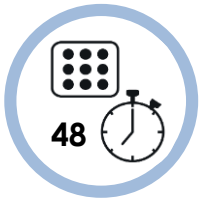
No. of patients at risk

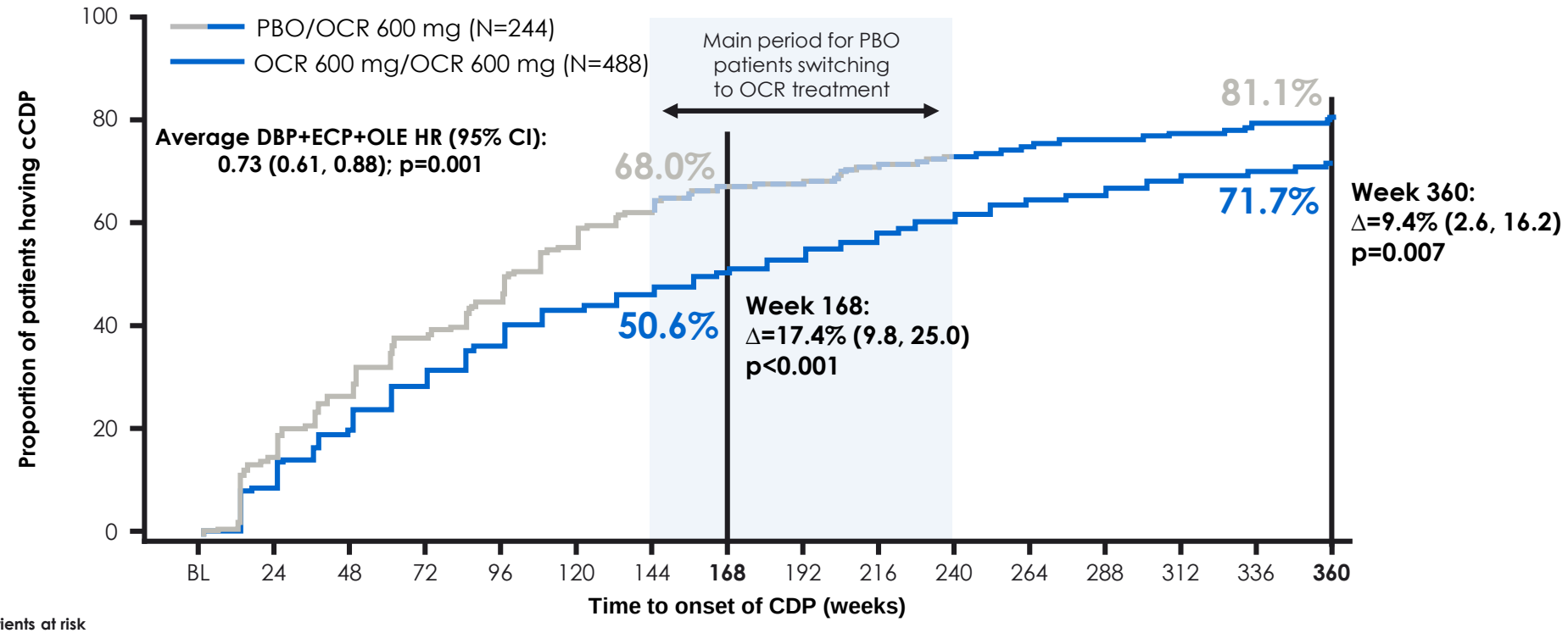
Placebo / OCR 600 mg	244	237	214	201	187	176	162	155	138	123	114	107	103	94	90	88	88	83	77	76	71	699	66	66	64	62	60	59	56	54	50
OCR 600 mg / OCR 600 mg	488	467	442	410	392	372	351	337	315	291	283	272	267	259	243	233	227	216	209	201	196	190	181	176	171	166	159	151	149	144	136

Over 7 years of the DBP+ECP+OLE, the risk of reaching 48-week CDP-T25FW was 21% lower in those who initiated OCR earlier vs delayed treatment

Week 168 is shown, as it is the first visit when most patients had switched to OCR in the OLE. Hazard ratios were estimated by Cox regression stratified by study, geographical region (US vs ROW), and age (≤45 years vs >45 years). Comparison of the survival distributions used the log-rank test. Patients with an initial disability progression during the extended controlled treatment period or OLE treatment period who discontinue the Extended Controlled or OLE treatment early and do not have a subsequent visit are imputed as having a CDP event.
BL, baseline; CDP, confirmed disability progression; DBP, double-blind period; ECP, extended controlled period; HR, hazard ratio; OCR, ocrelizumab; OLE, open-label extension; T25FW, Timed 25-Foot Walk.

Results: Time to 48-week cCDP





No. of patients at risk

Placebo / OCR 600 mg	244	234	202	183	169	155	141	134	122	105	96	88	81	72	68	67	67	62	58	56	53	52	48	47	43	43	41	41	37	35	32
OCR 600 mg / OCR 600 mg	488	462	431	396	376	350	328	311	289	266	255	248	238	230	219	208	199	187	180	168	164	156	148	141	138	130	124	118	117	114	105

Over 7 years of the DBP+ECP+OLE, the risk of reaching 48-week cCDP was 27% lower in those who initiated OCR earlier vs delayed treatment

Week 168 is shown, as it is the first visit when most patients had switched to OCR in the OLE. Hazard ratios were estimated by Cox regression stratified by study, geographical region (US vs ROW), age (≤45 years vs >45 years). Comparison of the survival distributions used the log-rank test. cCDP is defined as an increase in EDSS, or 20 percent increase in T25FW or 20% increase in 9HPT that is maintained for at least 24 weeks. The earliest event was counted.

9HPT, 9-Hole Peg Test; BL, baseline; cCDP, composite CDP; CDP, confirmed disability progression; DBP, double-blind period; ECP, extended controlled period; HR, hazard ratio; OCR, ocrelizumab; OLE, open-label extension; T25FW, Timed 25-Foot Walk.

Reasons for withdrawal from treatment in OLE treatment period

Reason, n (%)	PBO/OCR (N=160)	OCR/OCR (N=367)
Discontinued	32 (20.0)	76 (20.7)
Adverse event	6 (3.8)	8 (2.2)
Death	2 (1.2%)	7 (1.9)
Lack of efficacy	4 (2.5)	4 (1.1)
Lost to follow-up	1 (0.6)	6 (1.6)
Other	3 (1.9)	24 (6.5)
Physician decision	1 (0.6)	6 (1.6)
Protocol violation	1 (0.6)	0
Patient withdrawal	10 (6.3)	21 (5.7)

NB: patient randomization in ORATORIO was 2:1 for OCR:PBO.
OCR, ocrelizumab; OLE, open-label extension; PBO, placebo.