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Late Breaking Abstracts
26 September 2025

Efficacy and Safety of Ocrelizumab vs Placebo in Primary Progressive MS: Results of the Phase IIIb ORATORIO-HAND Study

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ORATORIO-HAND (NCT04035005)

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- **G. Giovannoni** has received personal compensation for serving as a consultant for AbbVie, Aslan, Atara Biotherapeutics, Biogen, Bristol-Myers Squibb–Celgene, F. Hoffmann-La Roche Ltd, GlaxoSmithKline, GW Pharma, Janssen/Johnson & Johnson, Japanese Tobacco, Jazz Pharmaceuticals, LifNano, Merck and Company, Merck KGaA/EMD Serono, Moderna, Novartis, Sanofi-Genzyme and Teva.
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- **R. Bove** has received research support from the California Initiative to Advance Precision Medicine, the Department of Defense, the National Institutes of Health and the National MS Society as well as Biogen, Eli Lilly, Novartis and Roche/Genentech, Inc. She has received personal compensation for consulting from Alexion, Amgen, Cadenza, EMD Serono, Sanofi-Genzyme and TG Therapeutics
- **G.R. Cutter** has received compensation for participation in data and safety monitoring boards for AI Therapeutics, AMO Pharma, Applied Therapeutics, AstraZeneca, Avexis Pharmaceuticals, Bristol-Meyers Squibb–Celgene, CSL Behring, Cynata Therapeutics, DiaMedica Therapeutics, Horizon Pharmaceuticals, Immunic, Karuna Therapeutics, Kezar Life Sciences, Mapi Pharmaceuticals Ltd, Medtronic, Merck, Mitsubishi Tanabe Pharma Holdings, Opko Biologics, Prothena Biosciences, Novartis, Pipeline Therapeutics, Regeneron, Sanofi-Aventis, Reata Pharmaceuticals, Teva Pharmaceuticals, United BioSource LLC, University of Texas Southwestern, University of Pennsylvania and Visioneering Technologies, and in consulting or advisory boards for Alexion, Antisense Therapeutics, Avotres, Biogen, Clene Nanomedicine, Clinical Trial Solutions LLC, ENDRA Life Sciences, Cognito Therapeutics, Entelexo Biotherapeutics, Inc., Genentech, Inc., Genzyme, GW Pharmaceuticals, Hoya Corporation, Immunic, Immunosis Pty Ltd, Klein-Buendel Incorporated, Linical, Merck Serono, Novartis, Perception Neurosciences, Protalix Biotherapeutics, Regeneron, Roche, SAB Biotherapeutics, Sapience Therapeutics and Scott & Scott LLP. Dr Cutter is an employee of the University of Alabama at Birmingham and President of Pythagoras, Inc., a private consulting company located in Birmingham AL, USA.
- **X. Montalban's** institution has received compensation for lecture honoraria and travel expenses, participation in scientific meetings, clinical trial steering committee membership or clinical advisory board participation in recent years from AbbVie, Actelion, Alexion, AstraZeneca, Bial PD, Biogen, Bristol-Myers Squibb–Celgene, EMD Serono, Genzyme, Hoffmann-La Roche, Immunic Therapeutics, Indivi, Janssen Pharmaceuticals, Jusivé Pharmaceutical, Lilly, MedDay, Medscape, Merck, Merz Therapeutics, Mylan-Viatris, Nervgen, Neuraxpharm, Novartis, Peervoice, Rewind Therapeutics, Samsung-Biosys, Sandoz, Sanofi-Genzyme, Teva Pharmaceutical, TG Therapeutics, Zenas Biopharma, EXCEMED, ECTRIMS, MSIF and NMSS or any of their affiliates
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- **J.S. Wolinsky** has received personal compensation for consulting, serving on scientific advisory boards or other activities with Cleveland Clinic Foundation, EMD Serono, Novartis, F. Hoffmann-La Roche Ltd/Genentech Inc., Sandoz and Zenas Pharma; his royalties for out-licensed monoclonal antibodies are received through UTHealth.
- **H-M. Schneble, A. Baldinotti, U. Bonati, C. Giacobino, Q. Wang** and **K. Yang** are employees and shareholders of F. Hoffmann-La Roche Ltd.
- **J. Oh** has received compensation for consulting or speaking from Biogen, Bristol-Myers Squibb, Eli Lilly, EMD Serono, F. Hoffmann-La Roche Ltd, Novartis and Sanofi-Genzyme and research funding from Biogen and F. Hoffmann-La Roche Ltd.

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Background

- Ocrelizumab remains the only approved treatment for PPMS
- In the ORATORIO (NCT01194570) trial, ocrelizumab showed a 24% risk reduction in EDSS progression vs placebo.[1] An even greater risk reduction (44%) was shown for worsening in hand function (9HPT)[2]
- The impact of ocrelizumab in older and more advanced patients with PPMS, particularly on worsening of hand function, is not fully understood

Objective

ORATORIO-HAND (NCT04035005) aimed to evaluate efficacy and safety of ocrelizumab in patients with PPMS, including older patients and those with more advanced disease

9HPT, 9-Hole Peg Test; EDSS, Expanded Disability Status Scale; PPMS, primary progressive multiple sclerosis.

1. Montalban X, et al. *N Eng J Med.* 2017;376:209-220. 2. Fox EJ, et al. *Mult Scler*. 2018;24:1862-1870 (Suppl. Appendix).

Methods

Inclusion and Exclusion Criteria

	ORATORIO-HAND[1,2]	ORATORIO[3,4]
McDonald criteria	2017	2005
Age, years	≤65	≤55
EDSS score	3.0-8.0	3.0-6.5
MRI	Inclusion of at least 350 patients with MRI activity[a] prior to randomisation	No specific criteria
Disease duration	<20 years for EDSS 7.0-8.0 <15 years for EDSS >5.0 <10 years for EDSS ≤5.0	<15 years for EDSS >5.0 <10 years for EDSS ≤5.0
Previous treatments	Treatment-naive for B-cell therapies Immunosuppressive medications allowed but requiring appropriate washout	Treatment-naive for B-cell therapies No other immunosuppressive medications

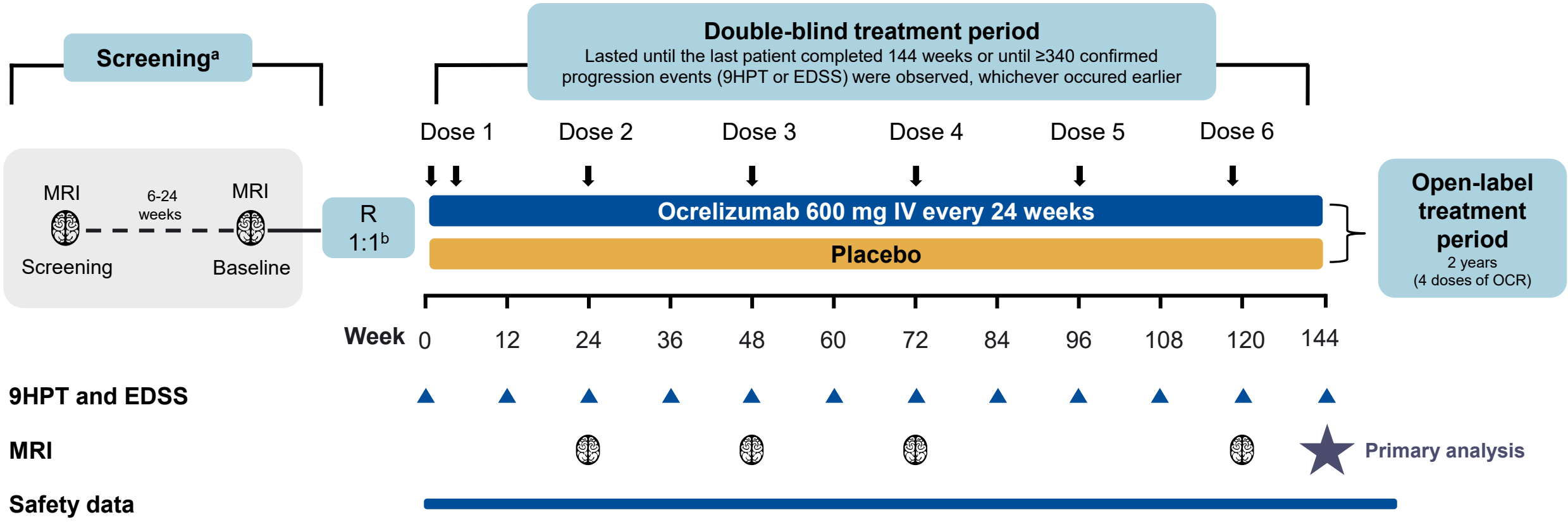
Inclusion criteria for ORATORIO-HAND were broader than for ORATORIO, allowing enrolment of older patients with longer disease duration and greater disability

EDSS, Expanded Disability Status Scale; MRI, magnetic resonance imaging.
[a]Based on one MRI scan compared with a historical MRI scan performed in the previous year, per protocol.
1. Giovannoni G, et al. Presented at ECTRIMS 2018. Poster P619. 2. ClinicalTrials.gov. NCT04035005. Accessed 10 June 2025. 3. ClinicalTrials.gov. NCT01194570. Accessed 10 June 2025. 4. Montalban X, et al. *N Engl J Med* 2017;376:209-220.

Methods

Study Design: Event-Driven, Double-Blind, Placebo-Controlled Study

Recruitment: 08/2019 to 12/2024



Full study design is available in the Supplement.

9HPT, 9-Hole Peg Test; EDSS, Expanded Disability Status Scale; IV, intravenous; MRI, magnetic resonance imaging; OCR, ocrelizumab; R, randomised.

[a]The screening phase was designed to detect MRI activity: two MRI scans ≥6 weeks apart or one MRI scan that could be compared with a historical MRI scan. [b]Stratification factors were MRI activity, defined as any T1 gadolinium-enhancing lesion(s) or new/enlarging T2 lesion(s) during the screening period (yes vs no), age (≤55 vs >55 years), EDSS score (≤6.5 vs >6.5), and region (EU, UK and Canada vs other).

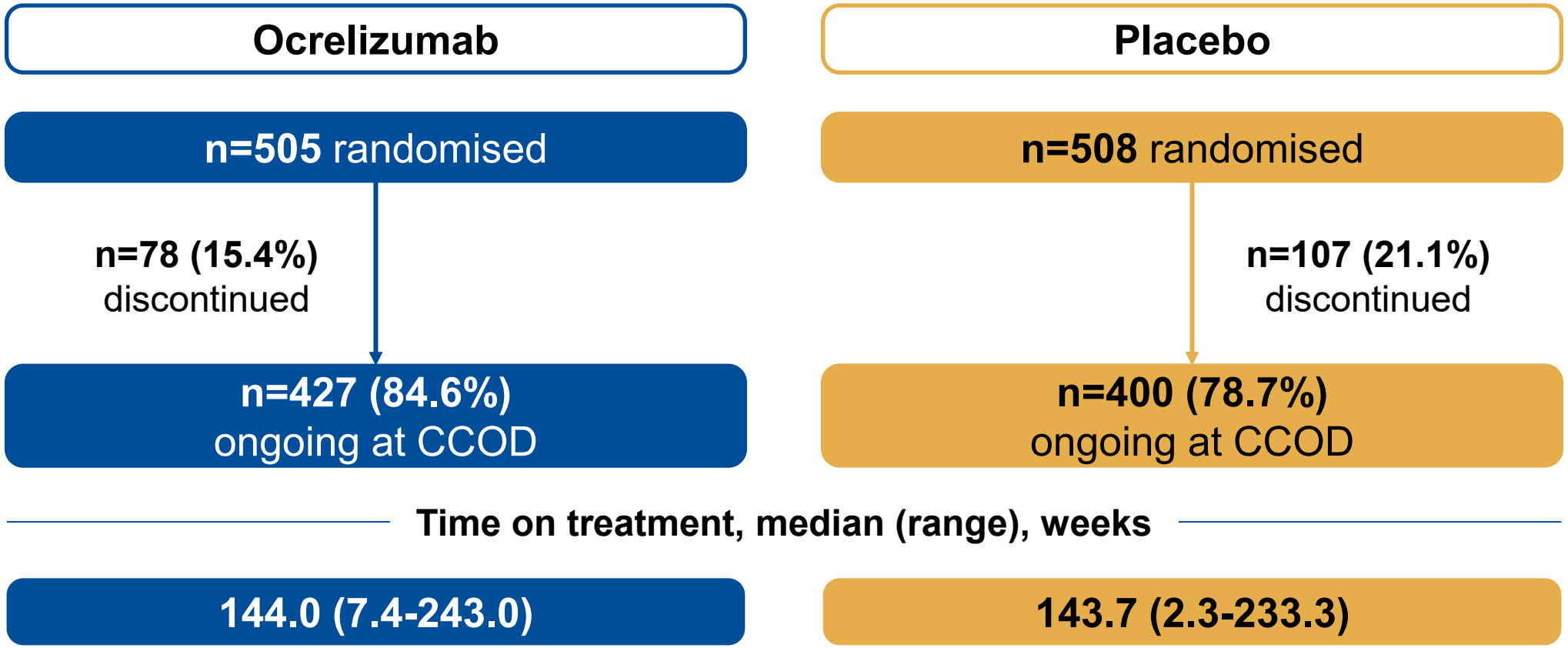
Methods

Primary and Secondary Endpoints

Primary endpoint	• Time to onset of 12-week composite CDP[a]: defined as time to onset of 20% worsening in CDP-9HPT or CDP-EDSS[b] in all randomised and MRI-active participants
Secondary endpoints	• Time to 12-week and 24-week CDP in 9HPT • Time to 12-week and 24-week CDP in EDSS • Annual rate of change from baseline in radius of total volume of T2 lesions • Annual rate of percent change in total brain volume[c]
Safety endpoints	• Adverse events and serious adverse events • Adverse events leading to study treatment withdrawal • Infusion-related reactions • Infections • Malignancies

9HPT, 9-Hole Peg Test; CDP, confirmed disability progression; EDSS, Expanded Disability Status Scale; MRI, magnetic resonance imaging; T25FWT, Timed 25-Foot Walk Test.
[a]Composite CDP is commonly EDSS + T25FW + 9HPT; however, as ORATORIO-HAND includes nonambulatory patients, T25FW was not included. [b]Defined as an increase of ≥1.0 point from baseline EDSS score in patients with a baseline EDSS score ≤5.5 or an increase of ≥0.5 point in patients with a baseline EDSS score of >5.5. [c]Measured from Week 24.

Patient Disposition and Time on Treatment



Clinical cutoff date: 15 January 2025.

Results

Patient Characteristics Were Well Balanced in Both Treatment Arms

	ORATORIO-HAND Ocrelizumab (n=505)	ORATORIO-HAND Placebo (n=508)	ORATORIO All patients (n=732)[1]
Age, median (range), years	48 (18-66)	47 (22-66)	46 (18-56)
≤55 years, n (%)	366 (72.5)	371 (73.0)	727 (99.3)
>55 years, n (%)[a]	139 (27.5)	137 (27.0)	5 (0.7%)
Female, %	57.4	54.7	49.3
EDSS score, median (range)	6.0 (3.0-8.0)	6.0 (2.5-8.0)	4.5 (2.5-7.0)
>6.5, n (%)	77 (15.2)	84 (16.5)	0
9HPT, median (range), sec	34.2 (25.1-216.9)	33.8 (24.5-221.8)	26.9 (11.1-300.0)
Presence of T1 Gd^+ lesions, %	24.0	22.2	26.4
Duration since symptom onset, median (range), years	9.4 (0.7-27.6)	9.0 (0.7-37.4)	5.9 (0.9-32.9)
Prior DMT, %	8.3	6.1	11.6

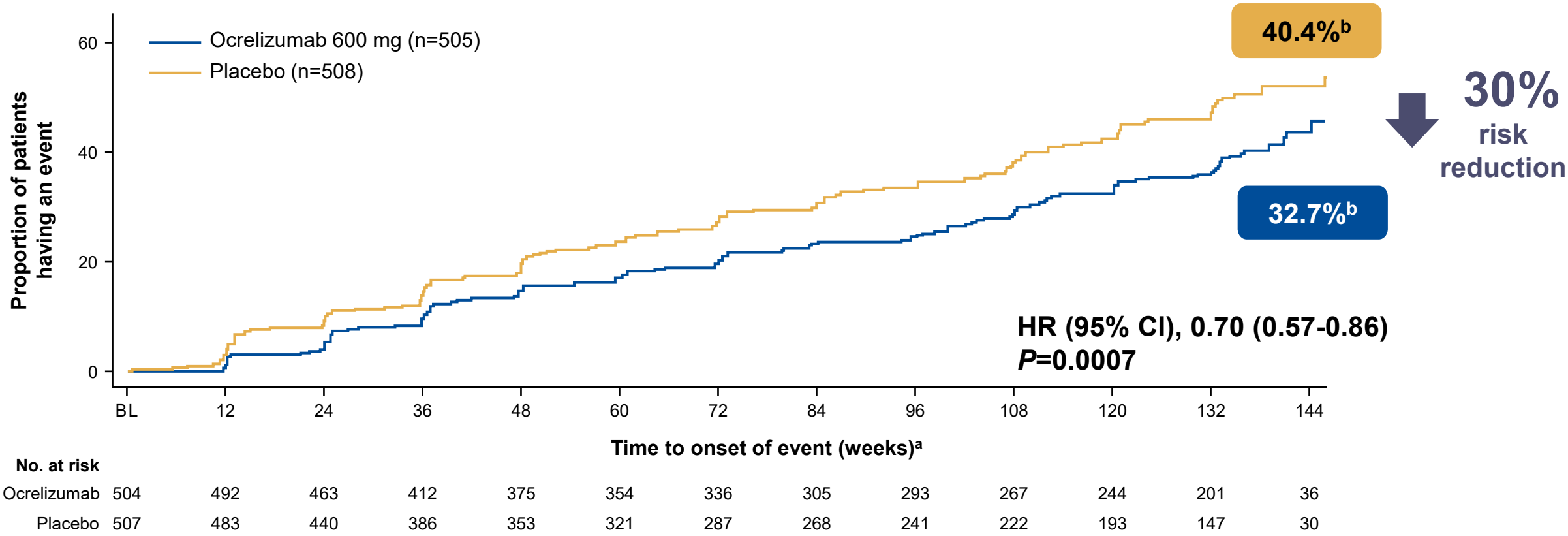
Patients in ORATORIO-HAND[b] were older, had greater disability both on EDSS and 9HPT and had longer disease duration than those in ORATORIO[1]

9HPT, 9-Hole Peg Test; DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; Gd^+, gadolinium-enhancing.

[a]All patients were aged <56 years at time of signing the informed consent form; however, 5 patients in the intention-to-treat population were 56 years at the time of randomisation. [b]Differences in baseline characteristics in ORATORIO-HAND vs ORATORIO were expected, based on the ORATORIO-HAND study inclusion criteria. 1. Montalban X, et al. *N Engl J Med* 2017;376:209-220.

Primary Endpoint in All Patients

Ocrelizumab Showed a 30% Risk Reduction on 12-Week Composite CDP on EDSS or 9HPT

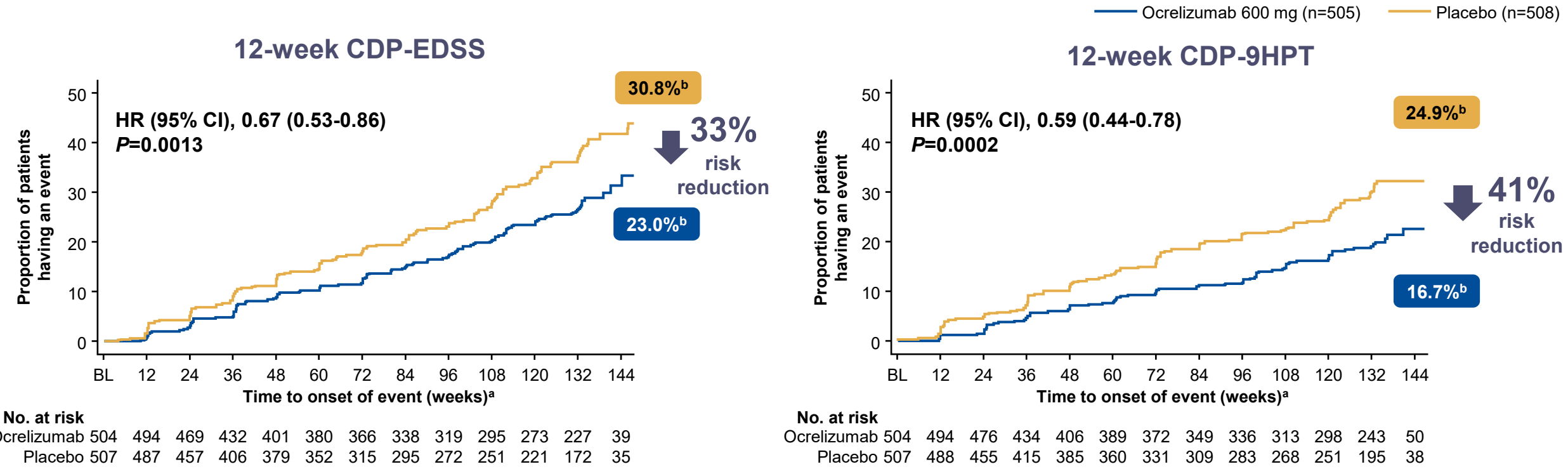


No. at risk													
Ocrelizumab	504	492	463	412	375	354	336	305	293	267	244	201	36
Placebo	507	483	440	386	353	321	287	268	241	222	193	147	30

Clinical cutoff date: 15 January 2025. 9HPT, 9-hole peg test; CDP, confirmed disability progression; EDSS, Expanded Disability Status Scale; HR, hazard ratio. [a]Data from Weeks 156 and 168 are not shown here due to low n values. Event was defined as presence of 12-week composite CDP. Baseline is the last assessment prior to or on the date of randomisation. Participants with missing verified strata were excluded from analysis. Participants without events prior to initiation of another MS DMT or commercial ocrelizumab were censored, unless they withdrew from study treatment due to lack of efficacy or had an initial disability progression prior to treatment switch, in which case an event was imputed. Participants without any prior progression events (including imputed events) during the double-blind treatment and follow-up 1 periods were censored at their last EDSS or 9-HPT assessment during these periods, whichever was earliest. [b]The percentage corresponds to the percentage of participants with an event during the double-blind treatment and follow-up 1 periods. HRs were estimated by Cox regression. HRs and log-rank test *P* values were stratified by magnetic resonance imaging activity (yes vs no), age (≤55 vs >55 years), EDSS score (≤6.5 vs >6.5), region (EU, UK and Canada vs other).

Secondary Endpoint in All Patients

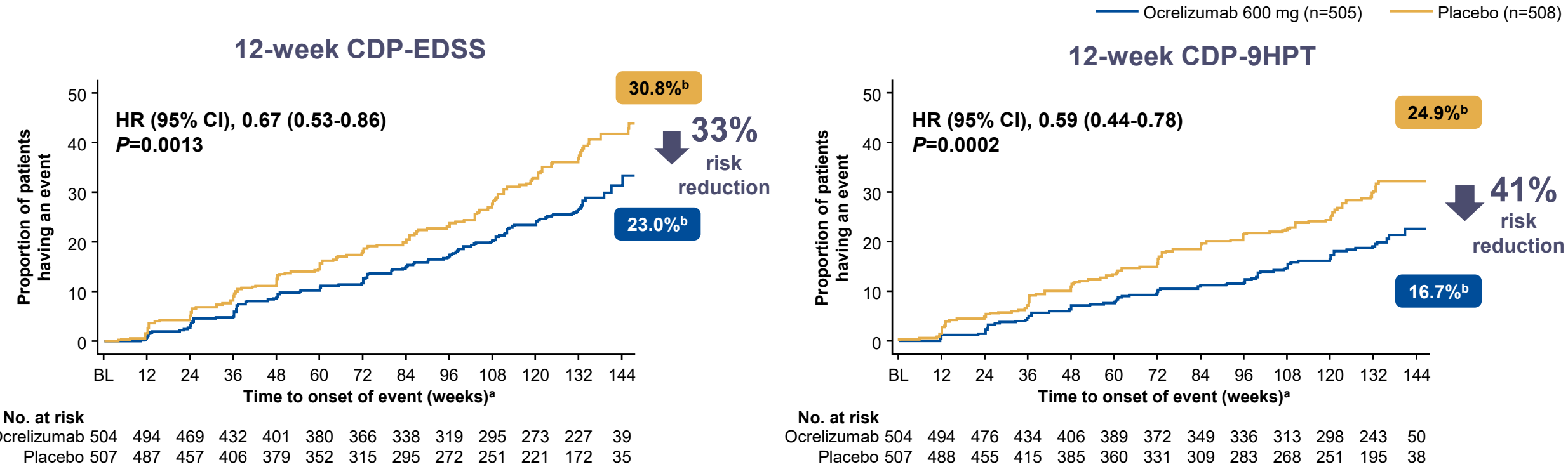
Ocrelizumab Showed Significant Risk Reductions on Individual Components of Composite CDP



Clinical cutoff date: 15 January 2025. 9HPT, 9-Hole Peg Test; BL, baseline; cCDP, composite confirmed disability progression; CDP, confirmed disability progression; EDSS, Expanded Disability Status Scale; HR, hazard ratio. [a]Data from Weeks 156 and 168 are not shown here due to low n values. Event was defined as presence of 12-week cCDP. Baseline is the last assessment prior to or on the date of randomisation. Participants with missing verified strata were excluded from analysis. Participants without events prior to initiation of another MS DMT or commercial ocrelizumab were censored, unless they withdrew from study treatment due to lack of efficacy or had an initial disability progression prior to treatment switch, in which case an event was imputed. Participants without any prior progression events (including imputed events) during the double-blind treatment and follow-up 1 periods were censored at their last EDSS or 9-HPT assessment during these periods, whichever was earliest. [b]The percentage corresponds to the percentage of participants with an event during the double-blind treatment and follow-up 1 periods.

Secondary Endpoint in All Patients

Ocrelizumab Showed Significant Risk Reductions on Individual Components of Composite CDP

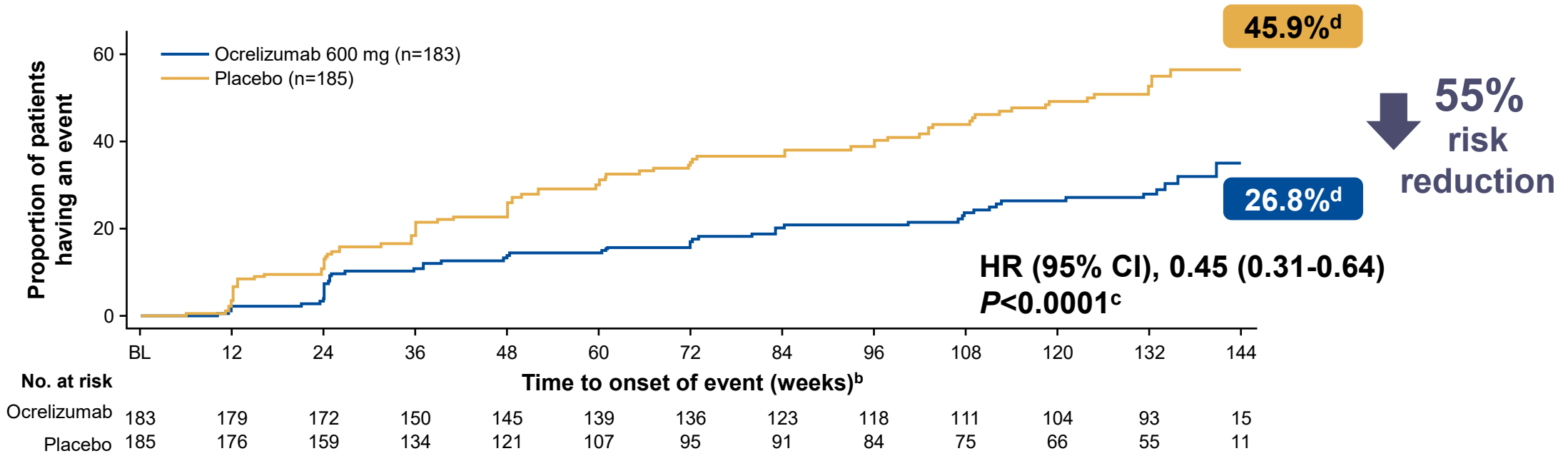


Components of cCDP	Ocrelizumab patients with events, n (%) (n=505)	Placebo patients with events, n (%) (n=508)	HR (95% CI)
Time to 24-week CDP in 9HPT	67 (13.3)	111 (21.9)	0.52 (0.38-0.71)
Time to 24-week CDP in EDSS	105 (20.8)	144 (28.4)	0.67 (0.52-0.86)

Clinical cutoff date: 15 January 2025. 9HPT, 9-Hole Peg Test; BL, baseline; cCDP, composite confirmed disability progression; CDP, confirmed disability progression; EDSS, Expanded Disability Status Scale; HR, hazard ratio. [a]Data from Weeks 156 and 168 are not shown here due to low n values. Event was defined as presence of 12-week cCDP. Baseline is the last assessment prior to or on the date of randomisation. Participants with missing verified strata were excluded from analysis. Participants without events prior to initiation of another MS DMT or commercial ocrelizumab were censored, unless they withdrew from study treatment due to lack of efficacy or had an initial disability progression prior to treatment switch, in which case an event was imputed. Participants without any prior progression events (including imputed events) during the double-blind treatment and follow-up 1 periods were censored at their last EDSS or 9-HPT assessment during these periods, whichever was earliest. [b]The percentage corresponds to the percentage of participants with an event during the double-blind treatment and follow-up 1 periods.

Primary Endpoint in the MRI-Active Population[a]

Ocrelizumab Showed a 55% Reduction on 12-Week Composite CDP on EDSS or 9HPT

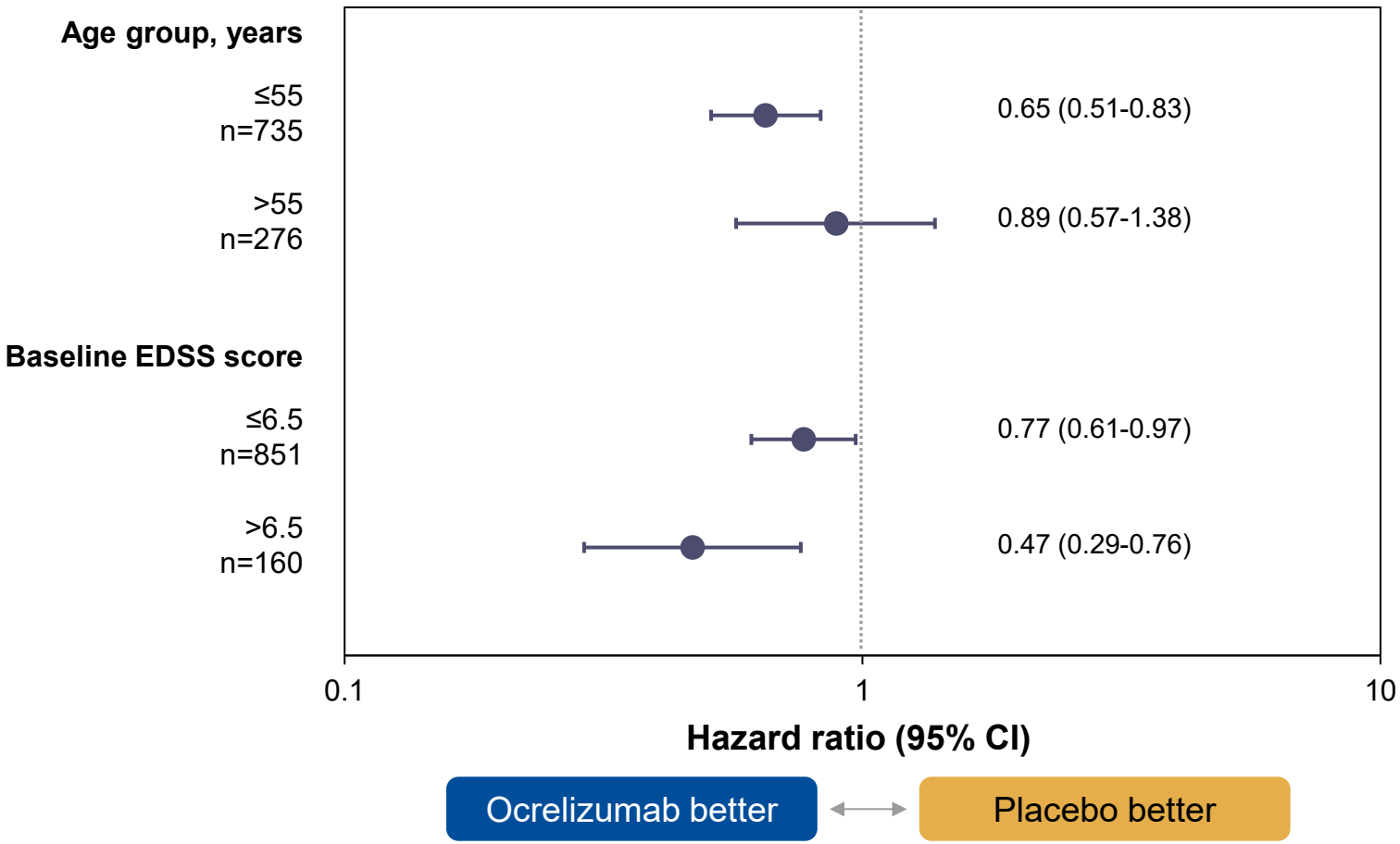


Components of cCDP	Ocrelizumab patients with events, n (%) (n=183)	Placebo patients with events, n (%) (n=185)	HR (95% CI)
Time to 12-week CDP in 9HPT	26 (14.2)	57 (30.8)	0.38 (0.23-0.61)
Time to 12-week CDP in EDSS	32 (17.5)	66 (35.7)	0.41 (0.27-0.62)

Clinical cutoff date: 15 January 2025. 9HPT, 9-Hole Peg Test; BL, baseline; cCDP, composite confirmed disability progression; CDP, confirmed disability progression; EDSS, Expanded Disability Status Scale; HR, hazard ratio; MRI, magnetic resonance imaging. [a]Defined as patients with T1 gadolinium-enhancing lesion(s) and/or new and/or enlarging T2 lesion(s) as detected by MRI scan during screening [b]Data from Weeks 156 and 168 are not shown here due to low n values. Event is defined as presence of 12-week cCDP. Baseline is the last assessment prior to or on the date of randomisation. Participants without events prior to initiation of another MS DMT or commercial ocrelizumab were censored, unless they withdrew from study treatment due to lack of efficacy or had an initial disability progression prior to treatment switch, in which case an event was imputed. Participants without any prior progression events (including imputed events) during the double-blind treatment and follow-up 1 periods were censored at their last EDSS or 9-HPT assessment during these periods, whichever was earliest. [c]*P* values are shown for primary/secondary endpoints only. [d]The percentage corresponds to the percentage of participants with an event during the double-blind treatment and follow-up 1 periods.

Efficacy in Predefined Subgroups

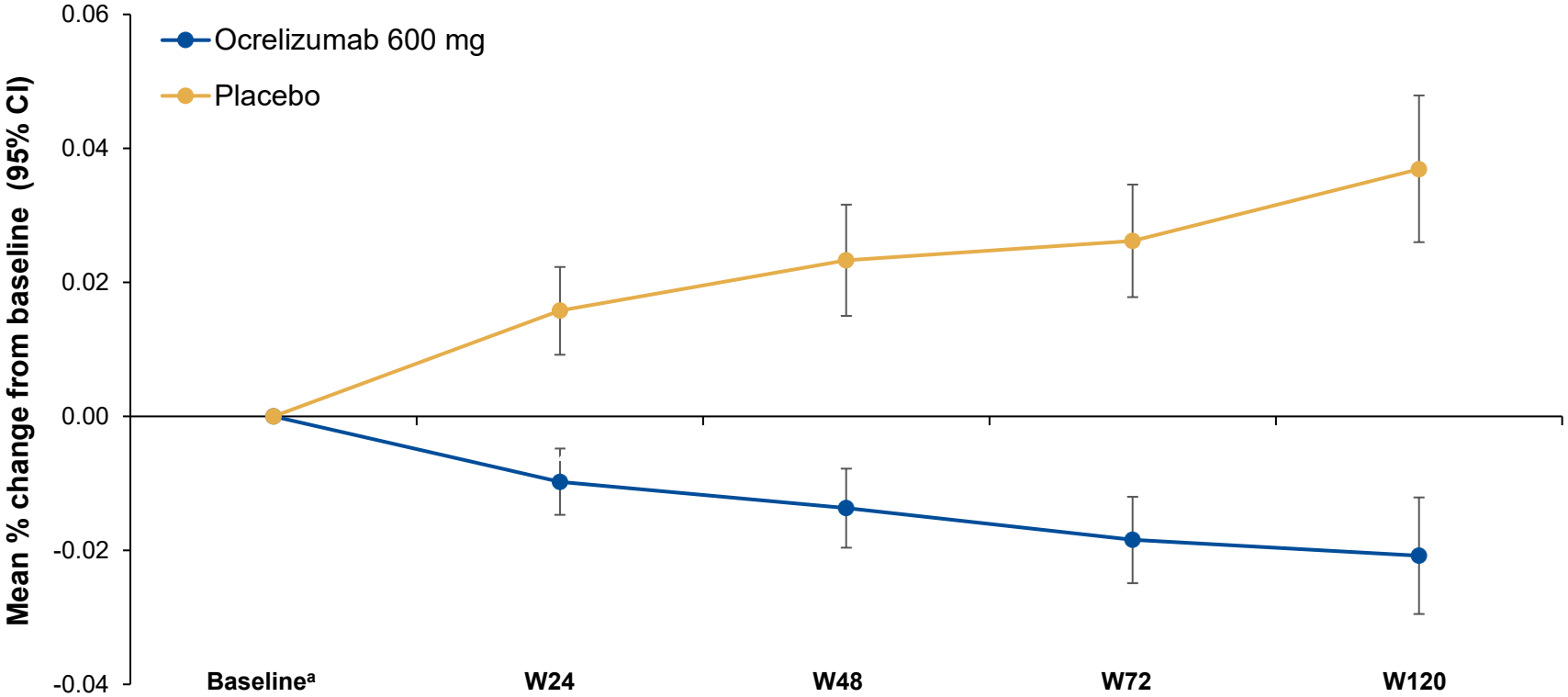
A Reduction in the Risk of Disability Progression Was Also Seen in Older and More Disabled Patients



Clinical cutoff date: 15 January 2025.
CDP, confirmed disability progression; EDSS, Expanded Disability Status Scale score.

Secondary Endpoint in All Patients

Radius of Total Volume of T2 Lesions Decreased With Ocrelizumab

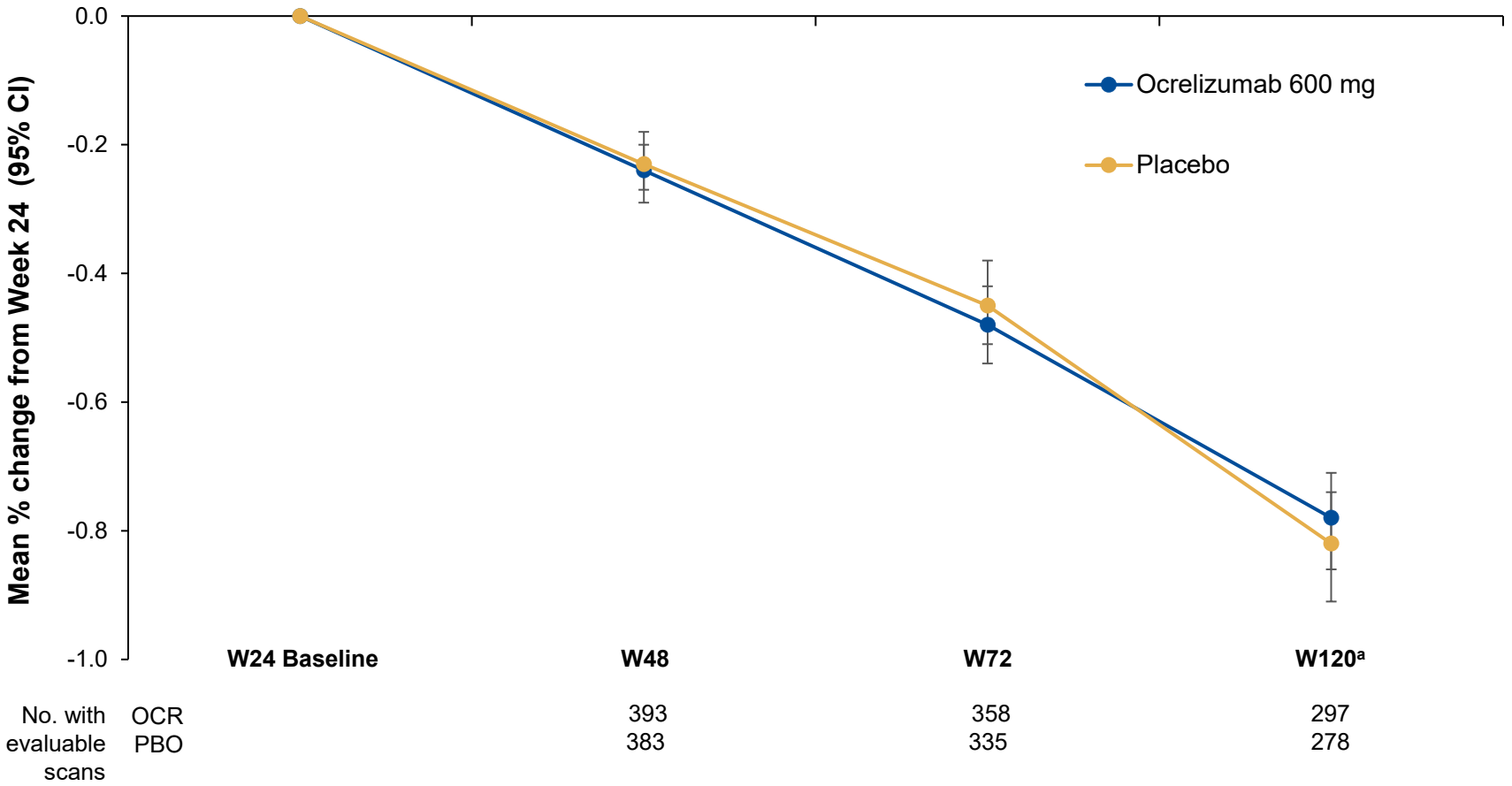


	Annual rate of change (95% CI), mm/y
Ocrelizumab (n=484)	−0.016 (−0.021 to −0.010)
Placebo (n=478)	0.021 (0.013-0.029)
Difference in annual rate of change (95% CI)	−0.037 (−0.046 to −0.028)
***P* value**	<0.0001

Clinical cutoff date: 15 January 2025.
OCR, ocrelizumab; PBO, placebo; W, week.
[a]Baseline is the last available assessment prior to or on the date of randomisation. All data post the intercurrent event treatment discontinuation were treated as missing following the hypothetical strategy; missing data were not imputed.
Due to limited availability, data are presented up to Week 120 only.

Secondary Endpoint in All Patients

No Difference in Percentage of Brain Volume Change Was Observed



	Annual rate of percent change from W24 in brain volume (95% CI)
Ocrelizumab (n=382)	−0.566 (−0.654 to −0.477)
Placebo (n=378)	−0.564 (−0.660 to −0.468)
Difference in annual rate of change (95% CI)	−0.002 (−0.091 to 0.087)
***P* value**	0.9711

Clinical cutoff date: 15 January 2025

OCR, ocrelizumab; PBO, placebo; W, week.

[a]All data post the intercurrent event treatment discontinuation were treated as missing following the hypothetical strategy; missing data were not imputed. Due to limited availability, data are presented up to Week 120 only.

Safety in All Patients

The Overall Safety Profiles Were Similar Between the Two Arms

Patients with ≥1 event, n (%)		Ocrelizumab (n=506)	Placebo (n=506)
All adverse events		379 (74.9)	360 (71.1)
Adverse events leading to study treatment discontinuation		15 (3.0)	12 (2.4)
Serious adverse events		65 (12.8)	67 (13.2)
Infusion-related reactions[a]		105 (20.8)	22 (4.3)
Infections	including COVID-19	245 (48.4)	226 (44.7)
	excluding COVID-19	190 (37.5)	187 (37.0)
Serious infections	including COVID-19	32 (6.3)	27 (5.3)
	excluding COVID-19	12 (2.4)	19 (3.8)
Malignancies		5 (1.0)	3 (0.6)
Deaths		11 (2.2)	10 (2.0)

Clinical cutoff date: 15 January 2025.

[a]Infusion-related reactions were more frequent in the ocrelizumab arm as expected due to the known safety profile of the treatment. Infusion-related reactions reported in the placebo arm were reactions to dummy infusions.

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More infusion-related reactions were observed in the ocrelizumab arm, as expected

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Serious infections	including COVID-19	**32 (6.3)**	**27 (5.3)**
	excluding COVID-19	**12 (2.4)**	**19 (3.8)**
Malignancies		5 (1.0)	3 (0.6)
Deaths		11 (2.2)	10 (2.0)

- Slightly more infections were observed in the ocrelizumab arm, but this difference was no longer evident when COVID-19 was excluded
- No opportunistic infections were observed

Clinical cutoff date: 15 January 2025.

[a]Infusion-related reactions were more frequent in the ocrelizumab arm as expected due to the known safety profile of the treatment. Infusion-related reactions reported in the placebo arm were reactions to dummy infusions.

Safety in All Patients

The Overall Safety Profiles Were Similar Between the Two Arms

Patients with ≥1 event, n (%)		Ocrelizumab (n=506)	Placebo (n=506)
All adverse events		379 (74.9)	360 (71.1)
Adverse events leading to study treatment discontinuation		15 (3.0)	12 (2.4)
Serious adverse events		65 (12.8)	67 (13.2)
Infusion-related reactions[a]		105 (20.8)	22 (4.3)
Infections	including COVID-19	245 (48.4)	226 (44.7)
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Deaths		11 (2.2)	10 (2.0)

- The proportion of patients with malignancies was similar in both arms
- Incidence rate in the ocrelizumab arm was within epidemiology range:
  - OCR: 0.43 (0.14-1.01) per 100 PY
  - Epi:[1] 0.67 (0.63-0.71) per 100 PY

Clinical cutoff date: 15 January 2025. Epi, epidemiology; OCR, ocrelizumab; PY, person-year.
[a]Infusion-related reactions were more frequent in the ocrelizumab arm as expected due to the known safety profile of the treatment. Infusion-related reactions reported in the placebo arm were reactions to dummy infusions.
1. Nielsen et al. 2006, Denmark MS Registry.

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No pattern of malignancies was observed[b]

Ocrelizumab (n=5):

- Breast cancer (1)
- Malignant melanoma (1)
- Pancreatic carcinoma (1)
- Metastatic pancreatic carcinoma (1)
- Prostate cancer (1)

Placebo (n=3):

- Acute myeloid leukaemia (1)
- Colorectal cancer (1)
- Endometrial adenocarcinoma (1)

Clinical cutoff date: 15 January 2025.

[a]Infusion-related reactions were more frequent in the ocrelizumab arm as expected due to the known safety profile of the treatment. Infusion-related reactions reported in the placebo arm were reactions to dummy infusions.

[b]The imbalance in malignancies observed in ORATORIO (2.3% [11/486] ocrelizumab vs 0.8% [2/239] placebo)[1] was not confirmed in ORATORIO-HAND (1.0% [5/506] ocrelizumab vs 0.6% [3/506] placebo).

1. Montalban X, et al. *N Engl J Med* 2017;376:209-220.

Conclusions

- In a large PPMS population that included older patients and those with more advanced disease, ocrelizumab was superior to placebo in delaying overall disability progression and worsening of upper limb function:
  - 30% risk reduction in 12-week composite CDP
  - 33% risk reduction in EDSS progression
  - 41% risk reduction in 9HPT progression
- The adverse event profile was balanced between the two arms and aligned with the known ocrelizumab safety profile
- ORATORIO-HAND is the first positive randomised controlled trial in MS using a composite endpoint

ORATORIO and ORATORIO-HAND are the only positive Phase III trials in PPMS.

ORATORIO-HAND confirmed the significant effect of ocrelizumab on disability progression in PPMS, also in older patients and those with more advanced disease.

9HPT, 9-Hole Peg Test; CDP, confirmed disability progression; EDSS, Expanded Disability Status Scale; PPMS, primary progressive multiple sclerosis.

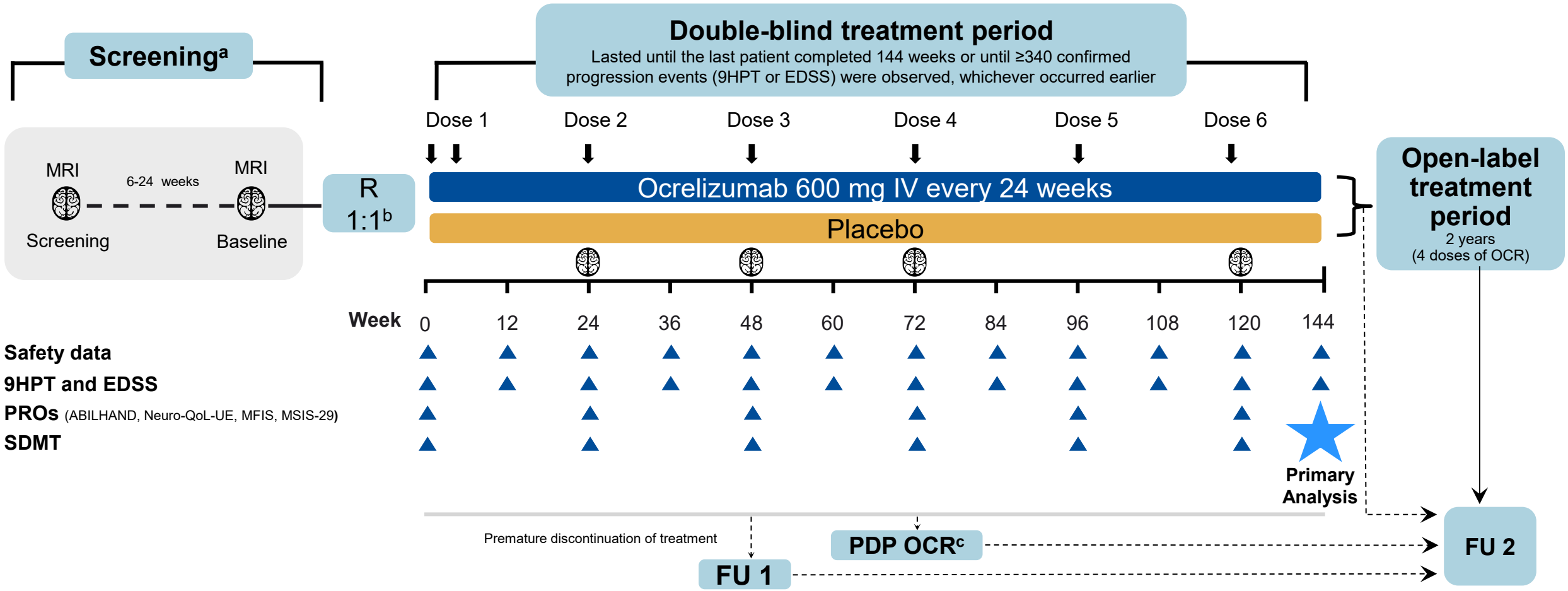
Acknowledgements

- We thank all the participants who volunteered for this trial and their families and site staff who provided support to the participants
- We are grateful to the study site investigators and staff who facilitated the trial's recruitment, enrollment and data collection
- We thank the collaborative team behind the study's conception, who guided the ethical and inclusive design of the ORATORIO-HAND trial framework

Supplement

Methods

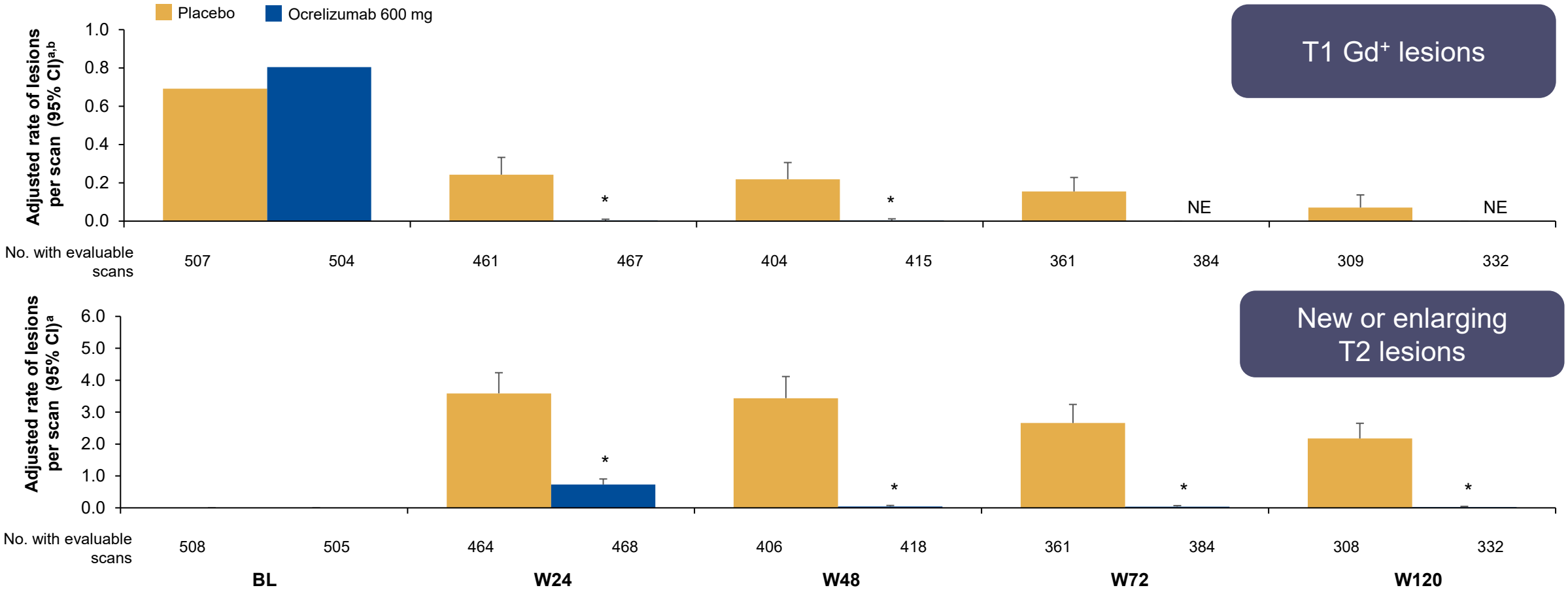
Study Design: Event Driven, Double-Blind, Placebo-Controlled Study



9HPT, 9-Hole Peg Test; EDSS, Expanded Disability Status Scale; FU, follow up; IV, intravenous; MFIS, Modified Fatigue Impact Scale; MRI, magnetic resonance imaging; MSIS-29, Multiple Sclerosis Impact Scale-29; Neuro-QoL-UE, Quality of Life in Neurological Disorders-Upper Extremity Function; OCR, ocrelizumab; PDP, post-double-progression; PRO, patient-reported outcome; R, randomised; SDMT, Symbol Digit Modalities Test. [a]The screening phase was designed to detect MRI activity: 2 MRI scans ≥6 weeks apart or 1 MRI scan that could be compared with a historical MRI scan. [b]Stratification factors were MRI activity, defined as any T1 gadolinium-enhancing lesion(s) or new/enlarging T2 lesion(s) during the screening period (yes vs no), age (≤55 vs >55 years), EDSS score (≤6.5 vs >6.5), and region (EU, UK and Canada vs other). [c]Patients who experienced a double-progression event during the double-blind treatment phase were given the option to switch to the PDP OCR phase after they completed at least 120 weeks of double-blind treatment and 120-week visit assessments.

Exploratory Endpoints in All Patients

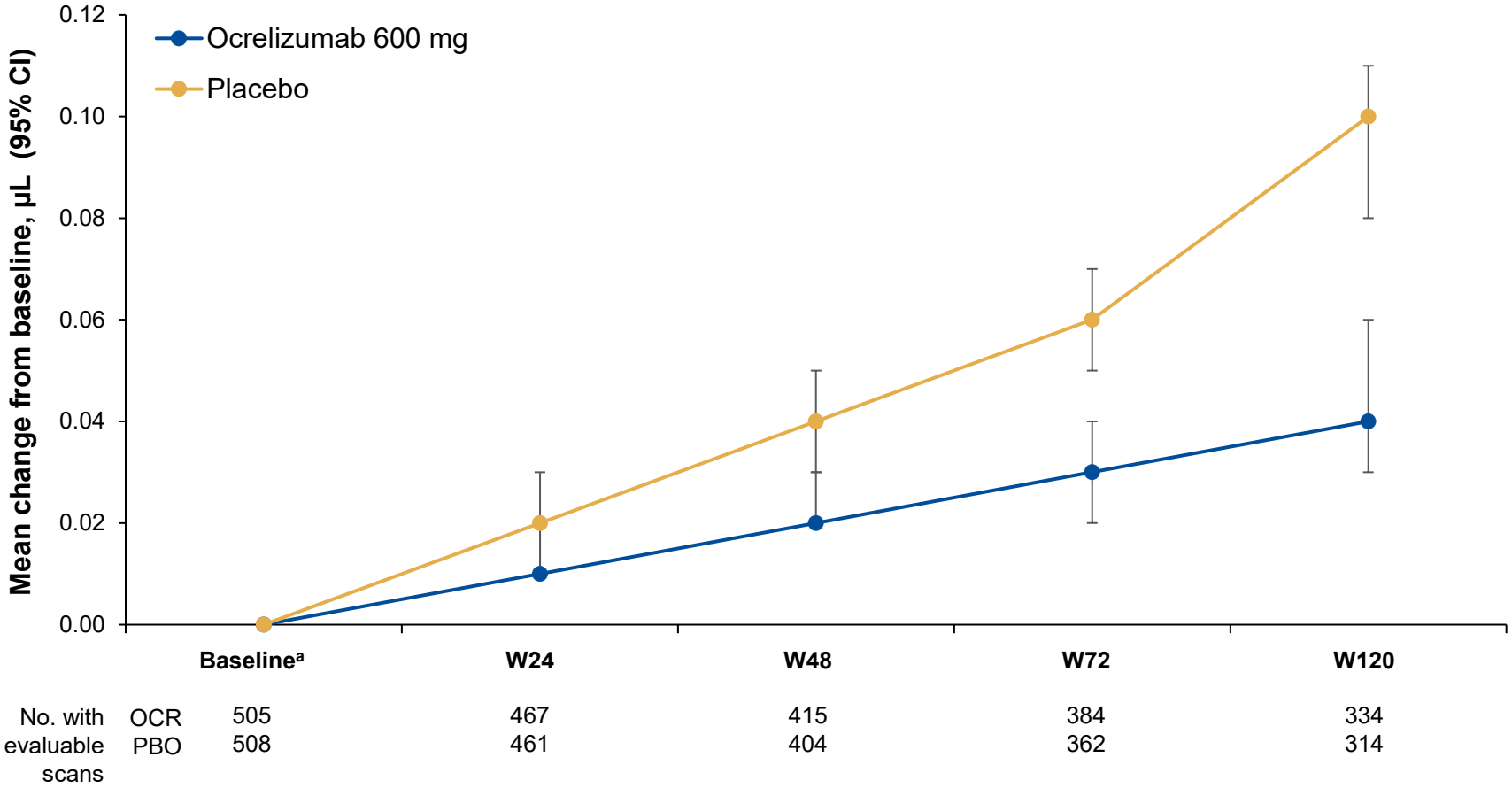
Near-Complete Suppression of Acute MRI Activity Was Observed



Clinical cutoff date: 15 January 2025.
BL, baseline; Gd+, gadolinium-enhancing; MRI, magnetic resonance imaging; NE, not evaluable (ie, no model output due to absence of new lesions); W, week.
*Adjusted rate is close to 0 but still estimable; $P < 0.0001$ (The statistical significance of the adjusted rate ratio is calculated using the Wald test).
[a]Rate of lesions per scan; estimates were derived from a negative binomial regression model: number of lesions = MRI activity (yes vs no) + age (≤55 vs >55 years) + Expanded Disability Status Scale score (≤6.5 vs >6.5) + Region (EU, UK and Canada vs other) + treatment (for new or enlarging T2 lesions: + offset (log [time from previous MRI scan in years]). [b]The unadjusted rate was used for the baseline rate of lesions per scan, computed as the total number of T1 Gd+ lesions divided by the total number of brain MRI scans. The baseline was defined as the most recent MRI prior to or on the date of randomisation. Due to limited availability, data are presented up to Week 120 only.

Exploratory Endpoint in All Patients

Ocrelizumab Significantly Reduced the Rate of Annual T1 Volume Expansion



	Annual rate of change (95% CI), µL/y
Ocrelizumab (n=505)	0.028 (0.019-0.037)
Placebo (n=508)	0.047 (0.036-0.057)
Difference in annual rate of change (95% CI)	0.019 (0.009-0.029)
***P* value**	0.0003

Clinical cutoff date: 15 January 2025

OCR, ocrelizumab; PBO, placebo; W, week.

[a]All data post the intercurrent event treatment discontinuation were treated as missing following the hypothetical strategy; missing data were not imputed. Due to limited availability, data are presented up to Week 120 only.

Safety in Predefined Subgroups

The Ocrelizumab Safety Profile Was Similar Across Subgroups

n (%)	Full analysis set		Age >55 years		EDSS >6.5	
	Ocrelizumab (n=506)	Placebo (n=506)	Ocrelizumab (n=139)	Placebo (n=137)	Ocrelizumab (n=77)	Placebo (n=84)
All AEs	379 (74.9)	360 (71.1)	115 (82.7)	99 (72.3)	54 (70.1)	56 (66.7)
AEs leading to study treatment discontinuation	15 (3.0)	12 (2.4)	7 (5.0)	5 (3.6)	6 (7.8)	2 (2.4)
SAEs	65 (12.8)	67 (13.2)	26 (18.7)	19 (13.9)	11 (14.3)	13 (15.5)
IRRs	105 (20.8)	22 (4.3)	21 (15.1)	6 (4.4)	13 (16.9)	3 (3.6)
Infections including COVID-19	245 (48.4)	226 (44.7)	76 (54.7)	68 (49.6)	39 (50.6)	38 (45.2)
Infections excluding COVID-19	190 (37.5)	187 (37.0)	60 (43.2)	53 (38.7)	34 (44.2)	33 (39.3)
SI including COVID-19	32 (6.3)	27 (5.3)	12 (8.6)	4 (2.9)	5 (6.5)	9 (10.7)
SI excluding COVID-19	12 (2.4)	19 (3.8)	4 (2.9)	3 (2.2)	3 (3.9)	6 (7.1)
Malignancies	5 (1.0)	3 (0.6)	3 (2.2)	2 (1.5)	1 (1.3)	1 (1.2)
Deaths	11 (2.2)	10 (2.0)	4 (2.9)	6 (4.4)	3 (3.9)	3 (3.6)

Clinical cutoff date: 15 January 2025.
AE, adverse event; EDSS, Expanded Disability Status Scale score; IRR, infusion-related reaction; SAE, serious adverse event; SI, serious infection.

Safety

Similar Pattern in the Causes of Deaths Was Observed in Both Arms

Cause of death, n	Ocrelizumab (n=506)	Placebo (n=506)
COVID-19 pneumonia	4	1
Pneumonia	0	2
Pulmonary oedema	1	0
Respiratory failure	0	1
Pneumothorax	0	1
Pulmonary embolism	0	1
Acute myocardial infarction	1	1
Choking	1	0
Suicide	1	0
Cystitis	1	0
Dehydration	1	0
Sudden cardiac death	1	0
Acute myeloid leukaemia	0	1
Central nervous system mass	0	1
Gastric ulcer haemorrhage	0	1
Total	11 (2.2%)	10 (2.0%)

Safety

There Were No Clusters in Malignancy Type

	Ocrelizumab (n=506) (PY=1161.3)				Placebo (n=506) (PY=1099.8)			
	Participants, n (%)	Events, n	Event rate per 100 PY	95% CI	Participants, n (%)	Events, n	Event rate per 100 PY	95% CI
All AEs	5 (1.0)	5	0.431	0.140-1.005	3 (0.6)	3	0.273	0.056-0.797
Neoplasms benign, malignant and unspecified (including cysts and polyps)[a]	5 (1.0)	5	0.431	0.140-1.005	3 (0.6)	3	0.273	0.056-0.797
Acute myeloid leukaemia	0	0	0.000	0.000-0.318	1 (0.2)	1	0.091	0.002-0.507
Breast cancer	1 (0.2)	1	0.086	0.002-0.480	0	0	0.000	0.000-0.335
Colorectal cancer	0	0	0.000	0.000-0.318	1 (0.2)	1	0.091	0.002-0.507
Endometrial adenocarcinoma	0	0	0.000	0.000-0.318	1 (0.2)	1	0.091	0.002-0.507
Malignant melanoma	1 (0.2)	1	0.086	0.002-0.480	0	0	0.000	0.000-0.335
Pancreatic carcinoma	1 (0.2)	1	0.086	0.002-0.480	0	0	0.000	0.000-0.335
Pancreatic carcinoma metastatic	1 (0.2)	1	0.086	0.002-0.480	0	0	0.000	0.000-0.335
Prostate cancer stage IV	1 (0.2)	1	0.086	0.002-0.480	0	0	0.000	0.000-0.335

The imbalance in malignancies observed in ORATORIO (2.3% [11/486] ocrelizumab vs 0.8% [2/239] placebo)[1] was not reproduced in ORATORIO-HAND (1.0% [5/506] ocrelizumab vs 0.6% [3/506] placebo)

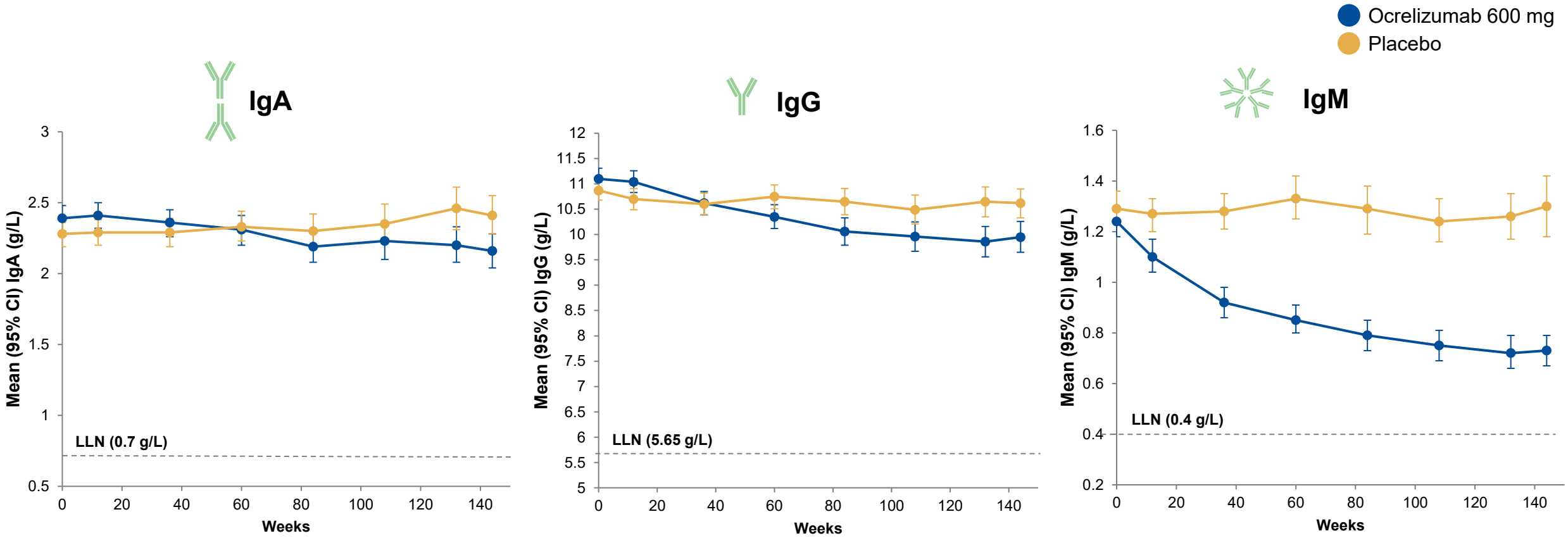
Clinical cutoff date: 15 January 2025. AE, adverse event; PY, person-year; SMQ, Standardised MedDRA Query; SOC, System Organ Class.

[a]While all preferred terms listed in this table are captured by the SMQ for malignant tumours, their primary classification within the MedDRA® hierarchy is under the SOC listed in the table heading. The SOC defines the official location of a term in the terminology, whereas the SMQ is a specialised tool for grouping and retrieving medically related terms for analysis.

1. Montalban X, et al. *N Engl J Med* 2017;376:209-220.

Safety

Mean Ig Levels Decreased Slightly From Baseline



Week	0	12	36	60	84	108	132	144
OCR, n	506	465	425	392	327	290	276	287
PBO, n	506	463	405	371	306	265	242	255

	0	12	36	60	84	108	132	144
	506	465	424	391	326	290	276	290
	506	463	406	373	306	265	242	254

	0	12	36	60	84	108	132	144
	506	465	425	392	327	290	277	287
	506	463	405	371	306	265	242	253

Ig, immunoglobulin; LLN, lower limit of normal; OCR, ocrelizumab; PBO, placebo.