Efficacy and safety of ocrelizumab in primary progressive multiple sclerosis, including older patients and those with more advanced disease (ORATORIO-HAND): a multicentre, double-blind, randomised, placebo-controlled, phase 3b study

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Summary

Background The ORATORIO trial showed that ocrelizumab reduced the risk of disability progression versus placebo in patients with primary progressive multiple sclerosis (PPMS). We aimed to elucidate the effect of ocrelizumab in older and more disabled patients with PPMS, particularly regarding hand function preservation.

Methods ORATORIO-HAND was a multicentre, double-blind, randomised, placebo-controlled, phase 3b study with 138 sites across 22 countries. Patients with PPMS aged 18–65 years and Expanded Disability Status Scale (EDSS) score of 3·0–8·0 were randomly assigned 1:1 to intravenous ocrelizumab 600 mg or placebo every 6 months for 144 weeks or until a prespecified number of progression events occurred. Masking was achieved by use of a placebo solution administered in the same manner as ocrelizumab. Double-blinding across all periods was maintained through separation of investigators responsible for efficacy and safety assessments. MRI scans were evaluated by a masked central reader, and laboratory parameters that could reveal treatment allocation were masked to site personnel until the primary analysis. Two coprimary estimands were defined, with the endpoint of time to onset of 12-week composite confirmed disability progression (12W-cCDP) in 9-Hole Peg Test or EDSS evaluated in all randomly assigned patients, and the same endpoint evaluated in a subset of patients with MRI activity at baseline. This study is registered with ClinicalTrials.gov, NCT04035005 and is ongoing and not recruiting.

Findings Between Aug 12, 2019, and Dec 10, 2024, of 1360 patients assessed for eligibility, 1013 were randomly assigned (ocrelizumab [n=505]; placebo [n=508]). The proportion of patients with 12W-cCDP was 165 (33%) of 505 with ocrelizumab and 205 (40%) of 508 with placebo (hazard ratio, 95% CI 0·70 0·57–0·86; relative risk reduction=30%; p=0·0007). In the MRI-active subgroup, a significant risk reduction was also observed in 12W-cCDP (risk reduction=55%; p<0·0001). The overall safety profile was similar in both groups. More infections (245 [48%] of 506 *vs* 226 [45%] of 506) were observed with ocrelizumab, but not after COVID-19 was excluded (38% *vs* 37%). Rates of serious adverse events and serious infections were similar between groups.

Interpretation Ocrelizumab was superior to placebo in delaying disability progression, with stronger effect on hand function, in a broad PPMS population including older patients and those with more advanced disease, while maintaining a manageable safety profile.

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Introduction

Primary progressive multiple sclerosis (PPMS) accounts for 10–15% of all multiple sclerosis cases and presents an important therapeutic challenge,[1] as most clinical trials have failed to identify effective treatments for patients with progressive forms of multiple sclerosis.[2] Ocrelizumab remains the only disease-modifying therapy (DMT) to show efficacy in a phase 3 trial in patients with PPMS.[3]

In the pivotal ORATORIO trial (NCT01194570), ocrelizumab showed a significant reduction in overall disability progression and worsening of the upper-limb function.[3,4] However, the effect of treatment in patients older than 55 years and those with more advanced disability (Expanded Disability Status Scale [EDSS] score >6·5) was not assessed, especially concerning the preservation of upper-limb function. For individuals with advanced multiple sclerosis, especially those using a

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See Online for appendix

Research in context

Evidence before this study

A systematic search of PubMed done on Sept 25, 2025, filtered by randomised clinical trials and using the terms "primary progressive multiple sclerosis OR PPMS" AND "disease-modifying therapy OR therapeutic" AND "phase 3", yielded 91 results. After further manual filtering, we identified four large randomised, placebo-controlled, phase 3 clinical trials: PROMiSe (glatiramer acetate), OLYMPUS (rituximab), INFORMS (fingolimod), and ORATORIO (ocrelizumab). Three studies used the Expanded Disability Status Scale score (EDSS) as the primary outcome, whereas INFORMS used a composite that included the EDSS, the 25-Foot Walk Test (25FWT), and the 9-Hole Peg Test (9HPT). Eligible patients had an age limit of 65 years, except in ORATORIO (55 years), and an EDSS score up to 6·5. ORATORIO was the only trial showing a treatment benefit on disability progression, making ocrelizumab the only disease-modifying therapy approved for the treatment of primary progressive multiple sclerosis (PPMS). However, its effect in patients older than 55 years and with more advanced PPMS, particularly on delaying worsening of hand function, is not fully understood.

Added value of this study

ORATORIO-HAND provides robust, placebo-controlled evidence for the efficacy of ocrelizumab in a broad population of patients with PPMS, notably including those with a high degree of disability (EDSS 6·–8·0) who are often excluded from pivotal trials. ORATORIO-HAND was designed with a composite primary endpoint that combines EDSS and 9HPT, to address the key limitation of the EDSS in capturing upper-limb dysfunction, which is a major contributor to disability in advanced disease. The positive outcome of this trial shows that ocrelizumab significantly delays disability progression, with a stronger effect observed across upper-limb measures. Crucially, the treatment benefit was most pronounced in patients with more advanced disease (EDSS score >6·5). These findings challenge the existing therapeutic ceiling in progressive multiple sclerosis, which suggests that the disease remains modifiable in later stages and that ocrelizumab can benefit a wider spectrum of patients than is currently recognised.

Implications of all the available evidence

The demonstration of ocrelizumab's efficacy in a second large randomised controlled trial solidifies the therapeutic rationale for treating PPMS, extending the window of opportunity to patients with advanced disease. These clinical findings are consistent with the hypothesised pathophysiological model of progressive multiple sclerosis as a length-dependent central axonopathy. This provides a compelling argument for shifting the focus of clinical assessment and treatment evaluation in advanced disease towards measures of upper-limb function. The validation of a composite endpoint incorporating upper-limb dexterity establishes a new standard for trial design in progressive multiple sclerosis. The adoption of similar endpoints in ongoing and future studies is essential for the robust evaluation of novel therapeutic agents. Collectively, this evidence counters the long-held notion of an intractable disease stage, offering a clear basis for intervention and highlighting the need to assess functional outcomes that reflect the underlying disease process while capturing aspects of the disease that are relevant to patients with multiple sclerosis.

wheelchair for ambulation, maintenance of manual dexterity is crucial to perform daily activities, preserve independence, and sustain quality of life.[5]

Standard clinical measures such as the EDSS are heavily weighted towards ambulatory function and inadequately capture the profound effect of upper-limb impairment.[6] To address this, other more sensitive and patient-centric endpoints have been developed. The 9-Hole Peg Test (9HPT), a component of composite assessments such as the Multiple Sclerosis Functional Composite,[7] is a widely accepted measure of manual dexterity that has been used in multiple trials.[8] A threshold of 20% change is often used to show clinically meaningful change[5] and is perceived as relevant by patients.[9] Interestingly, analyses of older trials suggest that DMTs might exert a greater therapeutic effect on upper-limb function than lower-limb function in advanced multiple sclerosis, which highlights the need for further investigation.[10]

ORATORIO-HAND was designed to evaluate the efficacy and safety of ocrelizumab in a broad and more representative PPMS population, including older patients and those who are more disabled and typically excluded from registration trials, by using both conventional assessments and clinically relevant measures targeting primarily upper-limb function.

Methods

Study design

ORATORIO-HAND was a multicentre, randomised, double-blind, placebo-controlled, event-driven, phase 3b trial, which enrolled patients with PPMS from 138 sites, across 22 countries (appendix 1 p 3). The study consisted of the following phases (appendix 1 p 33): screening, double-blind treatment (DBT), optional post-double-progression (PDP) period, follow-up 1, optional open-label extension, and follow-up 2. At screening, two mandatory MRI scans were done 6–24 weeks apart, or one MRI scan was done if a comparative historical scan had been acquired in the previous year. These scans were used to detect MRI activity (used as a randomisation factor), defined as any T1 gadolinium-enhancing [Gd+] lesion(s), any T2 lesion that was new and/or enlarging, or both. In the DBT phase, patients were treated every

24 weeks for up to 144 weeks or until at least 340 disability progression events on 9HPT or EDSS were reached (primary analysis), whichever occurred earlier. Patients who had a double-progression event (defined as a 20% increase in 9HPT time sustained for 24 weeks and EDSS-CDP [confirmed disability progression] sustained for 12 weeks) had the option to switch to treatment with ocrelizumab after completing 120 weeks in the DBT. All patients who discontinued the DBT phase prematurely (including patients who received other DMTs for multiple sclerosis, commercial ocrelizumab, or no treatment) entered the follow-up 1 phase, which ran in parallel with the DBT phase, with the same efficacy and safety assessments. Details of the optional open-label extension phase after completing 144 weeks of DBT and the follow-up 2 phase are provided in appendix 1 (p 33).

The trial was done in accordance with the guidelines for Good Clinical Practice of the International Conference of Harmonisation, the principles of the Declaration of Helsinki, and additional local regulations. The protocol, informed consent form, any information given to the patient, and relevant supporting information were approved by the institutional review board and ethics committee (appendix 1 p 45). The protocol and statistical analysis plan are available in appendix 2, and important changes that occurred after the start of the trial are listed in appendix 1 (p 21). Protocol deviations were similar between treatment groups. In the ocrelizumab group, 272 major protocol deviations were reported in 147 participants (29%). In the placebo group, 238 major protocol deviations were reported in 135 participants (27%). No major protocol deviations posed an increased safety risk to any participant continuing study treatment or were considered to have affected the integrity of the study findings. This study is registered with ClinicalTrials.gov, NCT04035005.

Participants

Key eligibility criteria included age 18–65 years, a diagnosis of PPMS as specified in the 2017 McDonald criteria (briefly, a minimum of 1 year of disability progression independent of clinical relapses diagnosed either retrospectively or prospectively, which must include a minimum two of three possible supporting features: the presence of T2-hyperintense lesions in one or more brain regions, two or more T2-hyperintense lesions in the spinal cord, and the presence of cerebrospinal fluid-specific oligoclonal bands),[11] documented history or presence at screening of elevated IgG index or one or more IgG oligoclonal bands, an EDSS score of at least 3·0–8·0, the ability to complete the 9HPT in more than 25 s (mean of the two hands) and within 240 s with each hand at both screening and baseline, and the following disease duration from the onset of multiple sclerosis symptoms: less than 20 years for an EDSS score of 7·0–8·0, less than 15 years for an EDSS score of 5·5–6·5, and less than 10 years for an EDSS score of 5·0 or less. Key exclusion criteria included any previous treatment with B-cell-targeted therapies. All inclusion and exclusion criteria are listed in appendix 1 (p 12). All participants provided written informed consent before any study-related activities. Sex, race, and ethnicity data were self-reported, as permitted by local regulations.

Randomisation and masking

Patients were randomly assigned (1:1) to receive ocrelizumab or placebo by use of Simplify Study (version 3.19). Randomisation was stratified by MRI activity at baseline (yes *vs* no), age (≤55 years *vs* >55 years), EDSS score (≤6·5 *vs* >6·5), and region (EU, the UK, and Canada *vs* other). Stratification by MRI activity was implemented to ensure balance within the MRI-active subgroup (prespecified primary estimand). Age and EDSS stratifications were selected to achieve balanced distributions across subgroups. Regional stratification accounted for differences in patient access to commercial ocrelizumab.

Masking was achieved by use of a placebo solution with the same composition and configuration, administered in the same manner as ocrelizumab. Rigorous double-blinding across all periods (DBT, PDP, and follow-up 1) was maintained through a dual-assessor model that separated investigators responsible for efficacy and safety assessments. All MRI scans were evaluated by a masked central reader, and specific laboratory parameters that could reveal treatment allocation (eg, $CD19^+$ cell counts and immunoglobulin concentrations) were masked to site personnel until the primary analysis. See appendix 1 for additional details of randomisation and masking (p 18).

See Online for appendix 2

Procedures

The first dose of ocrelizumab (on the DBT, PDP, and open-label extension periods) or placebo (DBT phase only) was administered as two 300-mg intravenous infusions 14 days apart, and subsequent doses were administered as a single 600-mg intravenous infusion every 24 weeks. 9HPT and EDSS were assessed in all patients by the examining investigator at screening, baseline, and every 12 weeks. Patients completed questionnaires every 24 weeks, including the Quality of Life in Neurological Disorders-Upper Extremity Function scale (Neuro-QoL-UE), assessing upper-limb function associated activities of daily living.[12] Post-baseline mandatory MRI scans were done at weeks 24, 48, and 72, and every 48 weeks thereafter. Safety data were collected throughout all periods of the study.

Outcomes

The primary objective was to compare the efficacy of ocrelizumab on confirmed disability progression with that of placebo in all randomly assigned patients (the intention-to-treat population) and in the MRI-active subgroup (coprimary estimands). The primary efficacy

endpoint was a two-component composite confirmed disability progression (cCDP), defined as the time to the first occurrence of at least one of the following progression events, sustained for at least 12 weeks: CDP in 9HPT, defined as at least a 20% worsening from baseline in time to complete 9HPT; CDP in EDSS, defined as an increase of at least 1·0 point from baseline in patients with a baseline EDSS score of no more than 5·5 or an increase of at least 0·5 points in patients with a baseline EDSS score of more than 5·5. Assessments occurring within 30 days after a protocol-defined relapse were not used for confirmation of disability progression. For information on intercurrent events and imputation strategy see the appendix 1 (p 11).

In hierarchical order, the secondary efficacy endpoints were time to 12-week CDP in 9HPT, time to 12-week CDP in EDSS, time to 24-week CDP in 9HPT, time to 24-week CDP in EDSS, annual rate of change from baseline in total volume of T2 lesions, and annual rate of percentage change in total brain volume from week 24. The primary and secondary endpoints were also evaluated in the following patient subgroups in the intention-to-treat population, unless otherwise stated, as exploratory analyses: age older than 55 years versus up to 55 years, EDSS score up to 6·5 versus more than 6·5, MRI-inactive versus MRI-active, male and female patients (intention-to-treat population, MRI-active subgroup, and MRI-inactive subgroup), region (EU, the UK, and Canada), ORATORIO-like patients (yes or no), and duration since multiple sclerosis symptom onset in years (≤10, >10 to ≤15, or >15). In a post-hoc analysis, the primary endpoint and respective subcomponents were also evaluated in MRI-inactive versus MRI-active subgroups, in which MRI activity was defined by the presence of T1 Gd+ lesions at baseline. An additional post-hoc analysis was evaluation of the primary endpoint and respective subcomponents with a 48-week confirmation window; disability events confirmed after 48 weeks are more likely to be irreversible.[13] Exploratory endpoints were time to 24-week composite CDP, time to wheelchair use (defined as confirmed EDSS score ≥7·0 in patients with baseline EDSS scores ≤6·5), annual rate of change from baseline in T1-hypointense lesion volume, and mean change from baseline to week 120 in the Neuro-QoL-UE score.

Safety endpoints in the study included adverse events, serious adverse events, adverse events leading to study treatment withdrawal, vital signs, and laboratory test results. An adverse event was defined as any untoward medical occurrence in a study participant, regardless of causal attribution. All safety endpoints were evaluated in a descriptive manner. All endpoints are listed in appendix 1 (p 16).

The study protocol was revised to refine the patient population, optimise trial operations, and align with evolving regulatory standards (appendix 1 p 21). Of note, the study was amended to transition from an event-driven to a fixed-duration design (144 weeks), and subsequently to an event-driven design with maximum follow-up (144 weeks). The primary endpoint was also changed from time to 9HPT worsening to a composite measure of disability progression as described above.

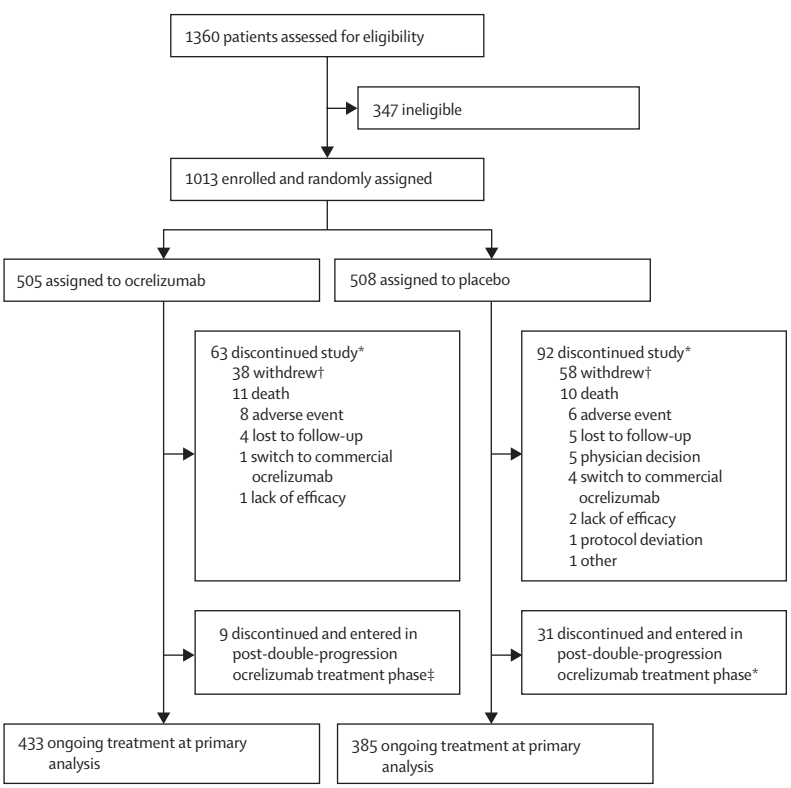

Figure 1: **Trial profile**
*Discontinued study during double-blind treatment or follow-up 1. †Categories for withdrawal by patient were retrieved from a manual review of individual patient narratives. Ocrelizumab: personal reasons (no further clarification received; n=20); perceived lack of efficacy (n=5); difficulties in following the schedule or visiting the site (n=3); Ukraine war (n=4); relocation (n=3). Placebo: personal reasons (no further clarification received; n=25); perceived lack of efficacy (n=13); difficulties in following the schedule or visiting the site (n=8); Ukraine war (n=4); perceived safety concern (n=2); other treatment or commercial ocrelizumab (n=3). ‡Patients who experienced a double-progression event (defined as a 20% increase in 9-Hole Peg Test time sustained for 24 weeks and an Expanded Disability Status Scale-confirmed-disability progression sustained for 12 weeks) were given the option to switch to treatment with ocrelizumab, but only once they had completed 120 weeks in the double-blind treatment. To maintain the masking in the treatment arm, the first dose of post-double-progression ocrelizumab treatment was administered as two infusions of 300 mg given 14 days apart for all patients. Patients who discontinued from the post-double progression ocrelizumab phase could continue to be followed up in the follow-up 2 phase.

Statistical analysis

The sample size of the study was established on the basis of a two-group test of equal exponential survival. With a sample size of 1000 patients, with at least 350 patients in the MRI-active population, a double-blind treatment phase of 144 weeks, an annual dropout rate of 10%, and a randomisation ratio of 1:1, it was predicted that approximately 340 events would be observed in all randomly assigned patients (placebo progression rate 40%) to achieve 80% power to detect a hazard ratio (HR) of 0·70 at a type I error rate of 0·0146 and

approximately 75·5% power to detect an HR of 0·75 at a type I error rate of 0·05. Similarly, it was expected that approximately 122 events would be observed in the MRI-active subgroup (placebo progression rate 44%), to achieve approximately 78% power to detect an HR of 0·60 at a type I error rate of 0·04.

Main efficacy analyses were done in the intention-to-treat population and the predefined MRI-active subgroup. The safety population included all patients who received at least one dose of the study drug. The primary endpoint was analysed in both primary efficacy populations. The HR was estimated by use of a Cox proportional hazards model, and the p value was calculated from a log-rank test, both stratified by randomisation factors. To control the overall type I error rate at 0·05, the alpha was split between the two populations by use of the Spiessens–Debois method.[14] The testing strategy used a fallback and loopback procedure, allowing for one population to be tested at the full 0·05 alpha level if the other first showed significance with its allocated alpha. Secondary endpoints were tested hierarchically in the all-randomly assigned patient population to control for multiplicity. Analyses of secondary endpoints in the MRI-active subgroup were considered exploratory. All primary and secondary efficacy endpoints were adjusted for the following stratification factors: MRI activity at baseline (yes *vs* no), age (≤55 years *vs* >55 years), EDSS score (≤6·5 *vs* >6·5), and region (EU, the UK, and Canada *vs* other).

For MRI endpoints, a random coefficient regression model was used to quantify the mean difference in annual rate of change or percentage change. To handle the skewness of the lesional volume distribution, a cubic root transformation was applied (transformed units from cm^3per year to cm per year).

For the Neuro-QoL-UE, mean change from baseline to week 120 was estimated by use of a mixed-effect model for repeated measures. The significance of the estimated difference in adjusted means was calculated by use of the Wald test.

An independent data-monitoring committee monitored and evaluated patient safety throughout the study until the primary analysis. Safety outcomes were assessed descriptively. Safety was evaluated in all patients who received at least one dose of study drug up until they received ocrelizumab in the PDP period, in the open-label extension, or commercially (after study treatment withdrawal), or until they received any other DMT after study treatment withdrawal.

Statistical analyses were done with SAS (version 9.4) and R (version 4.3.3).

Role of the funding source

The funder of the study designed the trials and participated in data collection, data analysis, data interpretation, and writing of the report.

Results

Recruitment was done between Aug 12, 2019, and Dec 10, 2024; the clinical cutoff date for the primary analysis was Jan 15, 2025. In total, 1360 patients were screened for eligibility, and 1013 patients were eligible and randomly assigned to either ocrelizumab (n=505) or placebo (n=508). More patients in the placebo group (n=31, 6%) than in the ocrelizumab group (n=9, 2%) entered the PDP period, and additionally, more patients discontinued from the DBT and follow-up 1 phases in the placebo group (n=92, 18% *vs* n=63, 13%). Details and reasons for discontinuation are presented in figure 1. Baseline demographics and disease characteristics were well balanced across treatment groups. Most patients were White (>90% in both groups), followed by American Indian or Alaskan Native (4% ocrelizumab, 3% placebo), with less than 1% in both groups for Asian, Black or African American, and Native Hawaiian or other Pacific Islander. Less than 10% of patients were Hispanic

	Ocrelizumab (n=505)	Placebo (n=508)
Age		
Years, mean (SD)	48 (11)	47 (11)
Years,* median range	48 (18–66)	47 (22–66)
≤55 years	366 (72%)	371 (73%)
>55 years	139 (28%)	137 (27%)
Female	290 (57%)	278 (55%)
Race		
American Indian or Alaska Native	18 (4%)	14 (3%)
Asian	0	2 (<1%)
Black or African American	2 (<1%)	1 (<1%)
Native Hawaiian or other Pacific Islander	2 (<1%)	0
White	464 (92%)	480 (94%)
Multiple or unknown	19 (4%)	11 (2%)
Ethnicity		
Hispanic or Latinx	31 (6%)	22 (4%)
Not Hispanic or Latinx	457 (90)	476 (94%)
Not stated or unknown	17 (3%)	10 (2%)
Expanded Disability Status Scale score	6·0 (3·0–8·0)	6·0 (2·5–8·0)
>6·5	77 (15%)	84 (17%)
9-Hole Peg Test, s	34·2 (25·1–216·9)	33·8 (24·5–221·8)
Patients with MRI activity	183 (36%)	185 (36)
T1 Gd+ lesions	121 (24%)	113 (22%)
New or enlarging T2 lesions†	181 (36%)	185 (36)
Duration since symptom onset, years‡	9·4 (0·7–27·6)	9·0 (0·7–37·4)
Duration since diagnosis, years	3·6 (0·1–26·4)	3·7 (0·1–24·4)
Previous disease-modifying treatment	42 (8%)	31 (6%)
Total volume of lesions on T2-weighted images, cm^3	16·6 (0·3–102·7)	17·5 (0·0–118·9)
Normalised brain volume, cm^3	1478·6 (1101·9–1787·3)	1485·0 (1175·8–1806·0)

Data are mean (SD), median range, or n (%). Gd+=gadolinium-enhancing. *All participants were younger than 66 years at the time of signing informed consent; however, one participant in each group of the intention-to-treat population was 66 years at the time of random assignment. †New or enlarging T2 lesions detected between two scans acquired during screening or baseline. ‡n=12 patients with disease duration above 20 years at random assignment (eight in the ocrelizumab group and four in the placebo group) were enrolled in the study.

Table 1: **Baseline demographics and disease characteristics in all patients**

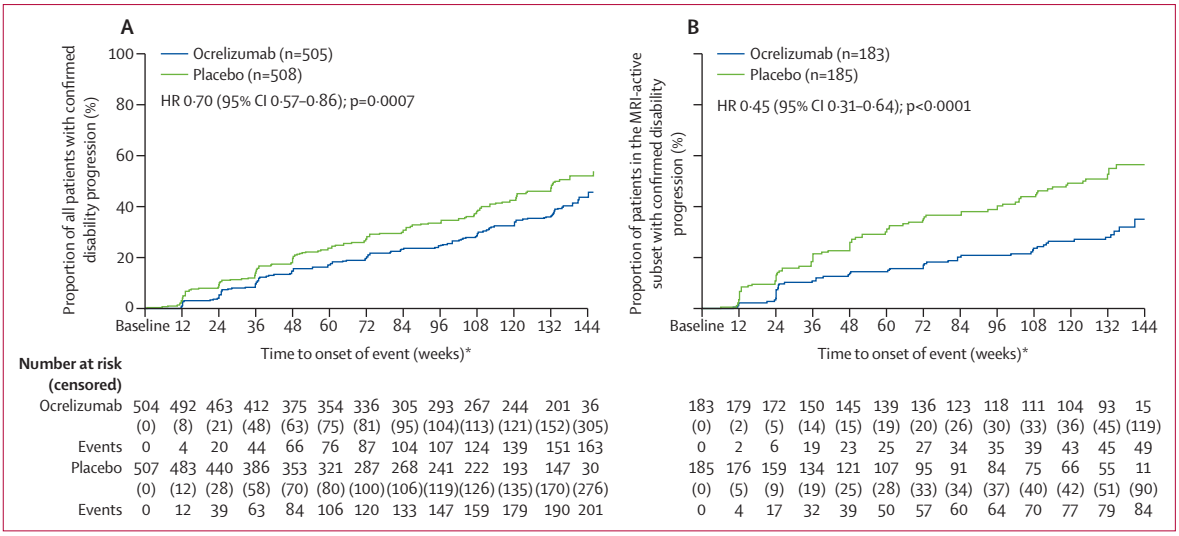

Figure 2: **Time to onset of 12-week composite confirmed disability progression in all patients (A) and the MRI-active subset (B)†**
EDSS=Expanded Disability Status Scale. HR=hazard ratio. Clinical cutoff date Jan 15, 2025. *Data from weeks 156 and 168 are not shown here owing to low n values. †Defined as patients with T1 Gd-enhancing lesion(s) at baseline or new or enlarging T2 lesion(s) as detected in two separate scans during screening or at baseline. Data from weeks 156 and 168 are not shown here owing to low n values. For the full analysis set, HRs were estimated by Cox regression. HRs and log-rank test p value were stratified by MRI activity (yes *vs* no), age (≤55 years *vs* >55 years), EDSS score (≤6·5 *vs* >6·5), region (EU, the UK, and Canada *vs* other). MRI-active subset: HRs were estimated by Cox regression. HR and log-rank test p value were stratified by age (≤55 years *vs* >55 years), EDSS score (≤6·5 *vs* >6·5), region (EU, the UK, and Canada *vs* other).

or Latinx (6% ocrelizumab, 4% placebo). Notably, approximately 27% of patients were aged at least 55 years, and approximately 15% had an EDSS score of more than 6·5 (table 1). The median trial duration was 2·8 years in both groups.

The percentage of all randomly assigned patients with 12-week cCDP (coprimary endpoint) was 33% with ocrelizumab versus 40% with placebo, resulting in a significant 30% risk reduction in disability progression compared with placebo (HR 0·70; 95% CI, 0·57–0·86; p=0·0007), and an absolute risk reduction of 7% (number needed to treat=13; figure 2A, table 2, 3). Ocrelizumab also showed a significant reduction in the risk of disability progression in each individual component (secondary endpoints): 41% risk reduction (p=0·0002) in 12-week CDP in 9HPT, corresponding to progression rates of 17% with ocrelizumab and 25% with placebo (figure 3A, table 2); and 33% risk reduction (p=0·0013) in 12-week CDP in EDSS, corresponding to progression rates of 23% with ocrelizumab and 31% with placebo (figure 3B, table 2).

When the 24-week confirmation window was used, a greater treatment effect was observed in the 24-week cCDP (35% risk reduction, p=0·0001; exploratory endpoint) and the 24-week CDP in 9HPT (48% risk reduction, p<0·0001; secondary endpoint), but a similar effect in the 24-week CDP by EDSS (33% risk reduction, p=0·0018; secondary endpoint). A similar trend of an even greater treatment effect and lower progression rates was observed when the 48-week confirmation window was used (table 2, table 3).

The percentage of patients who were MRI-active with 12-week cCDP (coprimary endpoint) was 27% with ocrelizumab versus 46% with placebo, resulting in a significant 55% risk reduction in disability progression compared with placebo (HR 0·45; 95% CI, 0·31–0·64; p<0·0001; figure 2B, table 2). A significant 60% risk reduction in 24-week cCDP was observed in the MRI-active subgroup (table 3), whereas non-significant 11% risk reductions in 12-week cCDP and 15% risk reductions in 24-week cCDP, were observed in the MRI-inactive subgroup (table 3).

The prespecified analysis defined MRI activity by the presence of T1 Gd+ lesions and/or new or enlarging T2 lesions. In a post-hoc analysis, where MRI activity was defined only by the presence of T1 Gd+ lesions, significant risk reductions in 12-week and 24-week cCDP were observed for both subgroups: 45% and 51% risk reduction for patients who were MRI-active, and 24% and 28% risk reductions for patients who were MRI-inactive, respectively. Among patients who were MRI-inactive, the greatest reduction (40%) was observed in the 24-week CDP in 9HPT (table 3).

Ocrelizumab showed a significant risk reduction in disability progression across all EDSS ranges, notably showing greater reduction in patients with an EDSS score of more than 6·5: 49% risk reduction in 12-week cCDP, 60% risk reduction in 12-week CDP-EDSS, and 41% risk reduction in 12-week CDP-9HPT. Results with a 24-week cCDP were consistent. For subgroup details on demographics and disease characteristics, see appendix 1 (p 23).

In patients who were ambulatory at baseline (EDSS score ≤6·5, ocrelizumab n=423 and placebo n=426), ocrelizumab showed a significant 52% risk reduction in

requiring the use of a wheelchair (12-week confirmed). The risk reduction was even more pronounced when the 24-week and 48-week confirmation windows were used (59% and 60%, respectively), and among patients with MRI activity at baseline (risk reduction of 86% to 90%). Results were also significant among patients without T1 Gd+ lesions when a 24-week confirmation window was used (appendix 1 p 34).

In the prespecified age subgroup analysis, ocrelizumab showed significant risk reduction versus placebo in 12-week cCDP in patients aged 55 years (HR 0·65, 95% CI 0·51–0·83), and significant effects were also observed across all other disability endpoints (appendix 1 p 34).

Ocrelizumab showed a significant risk reduction across all disability endpoints in female but not male patients. Female patients with MRI activity, age younger than 55 years, and an EDSS score of more than 6·5 showed the strongest treatment effect. Among male patients, there was greater treatment benefit in those with MRI activity and age younger than 55 years, with significant results on CDP in 9HPT (appendix 1 p 35).

The total volume of T2-hyperintense lesions from baseline to week 120 decreased with ocrelizumab (mean percentage change, –2% [95% CI –2·9 to –1·1]) and increased with placebo (mean percentage change, 6% [95% CI 3·7–7·6]), resulting in a significant difference in the annual rate of change (difference, –0·037; p<0·0001; table 2 and figure 3C). A greater increase in total T1 hypointense lesion volume was observed with placebo (mean percentage change, 24% [95% CI 19·7–28·0]) than with ocrelizumab (mean percentage change, 11% [95% CI 8·8–14·1]), resulting in a significant difference in the annual rate of change (difference, –0·019; p=0·0003; appendix 1 p 42). There was no difference in the annual rate of percentage change from week 24 in total brain volume between the two groups (–0·566% per year with ocrelizumab and –0·564% per year with placebo; difference, –0·002; p=0·97; table 2 and figure 3D), nor was there a difference when assessed from baseline (data not shown).

In all randomly assigned patients, worsening in the Neuro-QoL-UE score was significantly greater in the placebo group than the ocrelizumab group (mean change from baseline, –5·24 *vs* –2·14 points, respectively; p=0·03). In the MRI-active subgroup, improvement in the score was observed in the ocrelizumab group (+0·77 points) versus greater worsening in the placebo group (–6·13 points, p=0·0046; appendix 1 p 43).

The percentage of patients who had at least one adverse event was 75% with ocrelizumab and 71% with placebo, with the difference primarily driven by infusion-related reactions (IRRs). Serious adverse events were reported in 13% of patients who received ocrelizumab and 13% of patients who received placebo. Adverse events led 3% of patients in the ocrelizumab group and 2% of patients in the placebo group to discontinue treatment (table 4). 11 adverse events with fatal outcomes (2%) were observed in the ocrelizumab group, and ten (2%) in the placebo group (table 4). Causes of death were overall similar between the two groups, with no specific pattern, except for there being more cases of COVID-19 pneumonia being observed in patients receiving ocrelizumab (appendix 1 p 29).

	Ocrelizumab (n=505)	Placebo (n=508)	p value
Coprimary endpoint: time to onset of 12-week cCDP			
All patients			
Number of patients evaluated	504	507	..
Patients with event	165 (33%)	205 (40%)	..
HR	0·70 (0·57 to 0·86)	..	0·0007
MRI-active patients			
Number of patients evaluated	183	185	..
Patients with event	49/183 (27%)	85/185 (46%)	..
HR	0·45 (0·31 to 0·64)	..	<0·0001
Key secondary and exploratory endpoints in intention-to-treat population			
Time to 12-week CDP in 9HPT			
Number of patients evaluated	504	507	..
Patients with event	84/504 (17%)	126/507 (25%)	..
HR	0·59 (0·44 to 0·78)	..	0·0002
Time to 12-week CDP in EDSS			
Number of patients evaluated	504	507	..
Patients with event	116 (23%)	156 (31%)	..
HR	0·67 (0·53 to 0·86)	..	0·0013
Time to 24-week CDP in 9HPT			
Number of patients evaluated	504	507	..
Patients with event	67/504 (13%)	111 (22%)	..
HR	0·52 (0·38 to 0·71)	..	<0·0001
Time to 24-week CDP in EDSS			
Number of patients evaluated	504	507	..
Patients with event	105 (21%)	144 (28%)	..
HR	0·67 (0·52 to 0·86)	..	0·0018
Time to 24-week cCDP*			
Number of patients evaluated	504	507	..
Patients with event	140 (28%)	189 (37%)	..
HR	0·65 (0·52–0·81)	..	0·0001
Change from baseline in total volume of T2 lesions (annual rate, cm per year†)			
Number of patients evaluated	484	478	..
Annual rate of change	–0·016 (–0·021 to –0·010)	0·021 (0·013 to 0·029)	..
Difference in annual rate of change	–0·037 (–0·046 to –0·028)	..	<0·0001
Percent change in total brain volume from week 24 (annual rate, %)‡			
Number of patients evaluated	382	378	..
Rate of change	–0·566 (–0·654 to –0·477)	–0·564 (–0·660 to –0·468)	..
Difference in rate of change	–0·002 (–0·091 to 0·087)	..	0·97

Data are n (%) and HR (95% CI). 9HPT=9-Hole Peg Test. CDP=confirmed disability progression. cCDP=composite confirmed disability progression. EDSS=Expanded Disability Status Scale. HR=hazard ratio. *Time to 24-week cCDP is an exploratory endpoint but is included here for data completeness. †Lesional volumes were converted from cm^3 per year to cm per year through a cubic root transformation. ‡Analysis included patients with a week 24 MRI assessment and at least one additional MRI assessment post-week 24.

Table 2: **Summary of coprimary and secondary endpoints**

	All patients n=1011		Definition 1 (presence or absence of T1 Gd+ lesions or new or enlarging T2 lesions)*				Definition 2 (presence or absence of T1 Gd+ lesions)*			
			MRI-active, n=368		MRI-inactive, n=643		MRI-active, n=234		MRI-inactive, n=777	
	Ocrelizumab versus placebo with event, %; NNT	HR (95% CI)	Ocrelizumab versus placebo with event, %; NNT	HR (95% CI)	Ocrelizumab versus placebo with event, %; NNT	HR (95% CI)	Ocrelizumab versus placebo with event, %; NNT	HR (95% CI)	Ocrelizumab versus placebo with event, %; NNT	HR (95% CI)
Composite confirmed disability progression										
12-week	33% *vs* 40%; 13	0·70 (0·57–0·86)	27% *vs* 46%; 5	0·45 (0·31–0·64)	36% *vs* 37%; 88	0·89 (0·69–1·16)	29% *vs* 42%; 8	0·55 (0·35–0·86)	34% *vs* 40%; 16	0·76 (0·60–0·97)
24-week	28% *vs* 37%; 11	0·65 (0·52–0·81)	23% *vs* 44%; 5	0·40 (0·28–0·59)	30% *vs* 33%; 33	0·85 (0·65–1·13)	26% *vs*41%; 7	0·49 (0·30–0·78)	29% *vs* 36%; 13	0·72 (0·56–0·93)
48-week	24% *vs* 33%; 11	0·64 (0·50–0·81)	20% *vs* 39%; 5	0·40 (0·27–0·60)	26% *vs* 29%; 33	0·83 (0·62–1·12)	22% *vs* 36%; 7	0·50 (0·31–0·82)	24% *vs* 32%; 14	0·70 (0·53–0·92)
Expanded Disability Status Scale										
12-week	23% *vs* 31%; 13	0·67 (0·53–0·86)	18% *vs* 36%; 5	0·41 (0·27–0·62)	26% *vs* 28%; 56	0·89 (0·66–1·20)	21% *vs*34%; 8	0·52 (0·31–0·87)	24% *vs* 30%; 16	0·75 (0·57–0·99)
24-week	21% *vs* 28%; 13	0·67 (0·52–0·86)	18% *vs* 34%; 6	0·43 (0·28–0·65)	23% *vs* 25%; 41	0·88 (0·64–1·21)	21% *vs* 33%; 8	0·54 (0·32–0·91)	21% *vs* 27%; 16	0·75 (0·56–1·00)
48-week	18% *vs* 24%; 16	0·68 (0·52–0·89)	16% *vs* 30%; 7	0·45 (0·29–0·70)	19% versus 21%; 55	0·88 (0·62–1·24)	18% *vs* 27%; 11	0·58 (0·31–1·00)	18% *vs* 23%; 19	0·74 (0·54–1·01)
9-Hole Peg Test										
12-week	17 *vs* 25; 12	0·59 (0·44–0·78)	14 *vs* 31; 6	0·38 (0·23–0·61)	18 *vs* 21; 30	0·77 (0·54–1·10)	15 *vs* 30; 7	0·37 (0·20–0·67)	17 *vs* 23; 16	0·68 (0·49–0·94)
24-week	13 *vs* 22; 12	0·52 (0·38–0·71)	11*vs* 28; 6	0·32 (0·19–0·56)	15 *vs* 19; 25	0·69 (0·47–1·02)	12 *vs* 26; 7	0·32 (0·16–0·63)	14 *vs* 21; 14	0·60 (0·42–0·85)
48-week	10 *vs* 19; 12	0·50 (0·35–0·70)	7 *vs* 22; 7	0·25 (0·13–0·49)	12 *vs* 17; 23	0·68 (0·45–1·03)	7 *vs* 20; 8	0·29 (0·13–0·66)	11 *vs* 18; 15	0·58 (0·39–0·85)

Gd+=gadolinium-enhancing. HR=hazard ratio. NNT=number needed to treat (absolute risk reduction, calculated using proportions with disability events rounded to one decimal place). *In the ORATORIO-HAND protocol, MRI activity was defined as presence of T1 Gd+ lesions at baseline and/or new or enlarging T2 lesions detected in two separate scans during screening and/or baseline (definition 1); in the ORATORIO study, MRI activity was defined as presence of T1 Gd+ lesions at baseline (definition 2).

Table 3: **Subgroup analyses of composite confirmed disability progression and component endpoints based on baseline MRI activity defined using two different definitions**

IRRs were more commonly observed in the ocrelizumab group (21%) than the placebo group (4%). In the ocrelizumab group, most patients (94%) had mild or moderate IRRs, with only one patient having a serious IRR (after first infusion; patient was recovering at the time of study withdrawal). All other IRRs resolved (table 4).

Infections were the most common adverse event in the study and were observed in 245 (48%) of 506 patients receiving ocrelizumab and 2269 (45%) of 506 patients receiving placebo. When COVID-19 was excluded, 38% of patients with ocrelizumab and 37% with placebo had an infection. Respiratory infections were the most common type of infections (ocrelizumab 39% *vs* 33% placebo), followed by urinary tract infections (ocrelizumab 12% *vs* 15% placebo; table 4). Most infections were mild or moderate in both groups (ocrelizumab 436 [91%] of 480; placebo 407 [93%] of 439). Serious infections were reported in 32 (6%) of 506 patients treated with ocrelizumab (2% excluding COVID-19) and 27 (5%) of 506 (4% excluding COVID-19) patients treated with placebo, with respiratory and urinary tract infections being the most common. No serious opportunistic infections were observed. Most serious infections resolved in both groups (ocrelizumab 82%; placebo 81%), and treatment was discontinued owing to infections in only 1% of patients in both groups.

Malignancies were reported in 1% of patients treated with ocrelizumab (n=5) and 1% of patients treated with placebo (n=3); no pattern of type of malignancy was observed (table 4).

At week 132, the percentages of patients in the ocrelizumab versus placebo groups with Ig values below the lower limit of normal were 27% versus 4% for IgM, less than 1% versus 0% for IgG, and 1% versus <1% for IgA. For additional information on trajectories of immunoglobulins see appendix 1 (p 44).

No cases of serious liver injury or Hy's law were observed.

The adverse event profile of ocrelizumab and placebo in prespecified subgroup analysis (age, sex, EDSS, and MRI activity) was generally consistent with that observed in the overall safety population, with some notable differences in the age and EDSS subgroups (appendix 1 p 27).

In the subgroup of patients older than 55 years, a higher proportion of patients in the ocrelizumab group had infections (55%; 58·1 per 100 patient-years) and serious infections (9%; 5·3 per 100 patient-years) than did those in the placebo group (infections 50%; 41·7 per

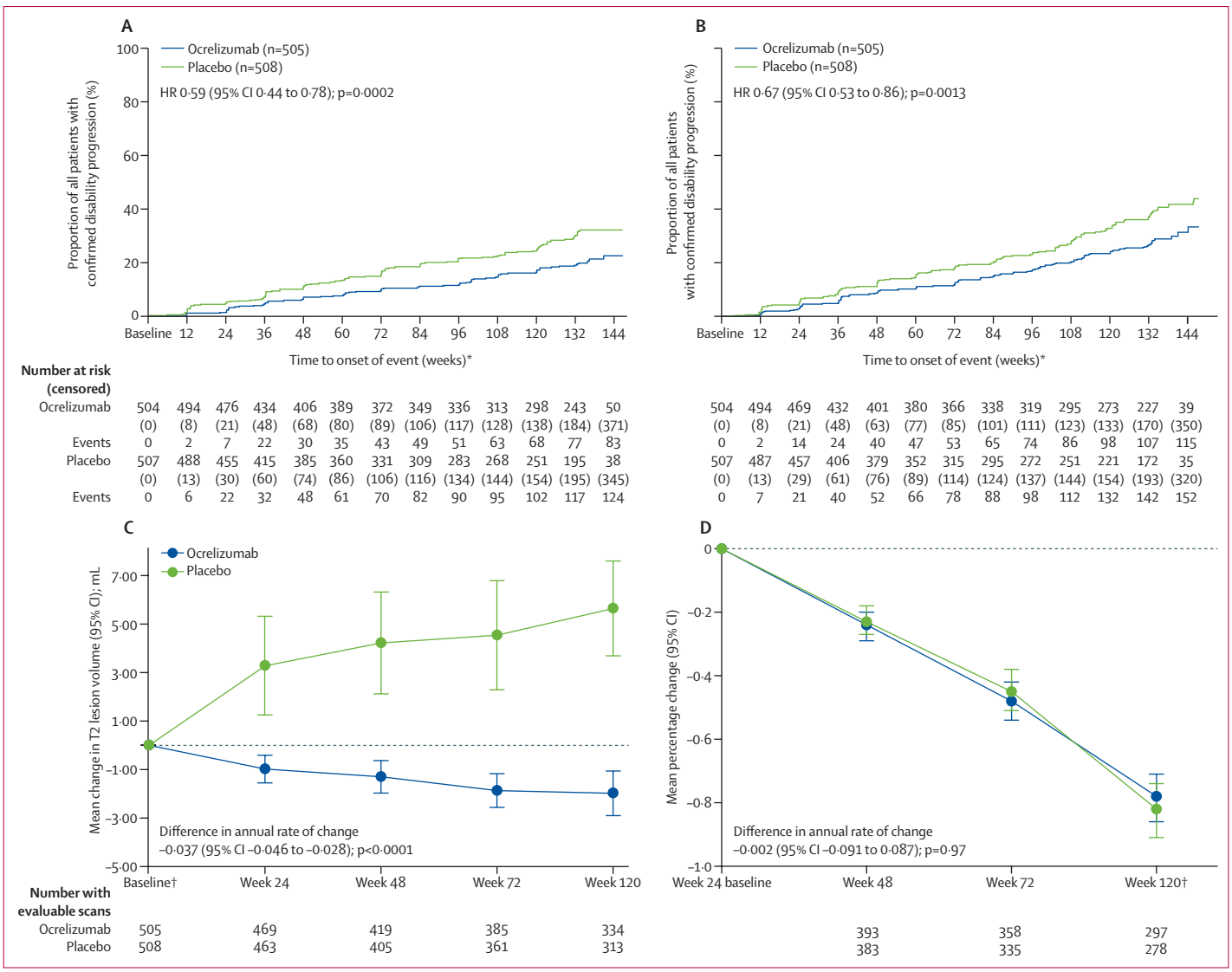

Figure 3: **Key secondary endpoints**

(A) Time to onset of 12-week 9-Hole Peg Test-confirmed disability progression. (B) Time to onset of 12-week EDSS-CDP in all patients. (C) Mean change from baseline to week 120 in total volume of T2 lesions. (D) Percentage change from week 24 to week 120 in total brain volume. EDSS=Expanded Disability Status Scale. EDSS-CDP= Expanded Disability Status Scale-confirmed disability progression. HR=hazard ratio. *Data from weeks 156 and 168 are not shown here owing to low n values. †Owing to poor availability, data are presented up to week 120 only. For parts A and B all patients' HRs were estimated by Cox regression; HRs and log-rank test p value were stratified by MRI activity (yes *vs* no), age (≤55 years *vs* >55 years), EDSS score (≤6·5 *vs* >6·5), region (EU, the UK, and Canada *vs* other). For part C estimates of annual rates of change are taken from a random coefficient regression model; the significance of the estimated mean difference is calculated using the Wald test. For part D estimates of annual rates of change are taken from a random coefficient regression model; the statistical significance of the estimated mean difference is calculated using the Wald test.

100 patient-years; serious infections 3%; 1·4 per 100 patient-years). When COVID-19 events were removed, the proportion of patients with infections remained higher with ocrelizumab (43%, 44·7 per 100 patient-years) than with placebo (39%, 32·6 per 100 patient-years), owing to higher frequency of urinary tract infections (18·7 *vs* 12·6 per 100 patient-years) and upper respiratory tract infections (12·2 *vs* 9·8 per 100 patient-years). For serious infections, the difference disappeared when excluding COVID-19, with 3% (rate 2·0 per 100 patient-years) in the ocrelizumab group and 2% (rate 1·1 per 100 patient-years) in the placebo group (table 4).

In the subgroup of patients with an EDSS score of more than 6·5, infections were reported in 50% of ocrelizumab patients (rate 60·0 per 100 patient-years) and 45% of placebo patients (rate 49·1 per 100 patient-years). After excluding COVID-19, infections were reported in 43% of the ocrelizumab group and 40% of the placebo group; rates of infections remained higher in the ocrelizumab versus placebo group (50·5 *vs* 43·7 per 100 patient-years), owing to higher rates of urinary tract infections. No notable differences were seen in rates of serious infections. Relevant patient characteristics of the two groups in this subgroup can be found in appendix 1 (p 23).

	n (%)		Rate per 100 patient-years (95%CI)*	
	Ocrelizumab (n=506)†	Placebo (n=506)	Ocrelizumab (n=506)†	Placebo (n=506)
All adverse events	379 (75%)	360 (71%)	143·5 (136·7–150·6)	127·8 (121·2–134·7)
Adverse events leading to study treatment discontinuation	15 (3%)	12 (2%)	1·3 (0·7–2·1)	1·2 (0·6–2·0)
Serious adverse events	65 (13%)	67 (13%)	8·5 (6·9–10·4)	8·2 (6·6–10·1)
Infusion-related reactions	105 (21%)	22 (4%)	13·9 (11·9–16·3)	3·4 (2·4–4·6)
Infections	245 (48%)	226 (45%)	41·3 (37·7–45·2)	39·9 (36·3–43·8)
Lower respiratory (including COVID-19)	141 (28%)	111 (22%)	14·6 (12·5–17·0)	11·4 (9·5–13·5)
COVID-19	97 (19%)	70 (14%)	9·1 (7·5–11·0)	6·6 (5·2–8·3)
Upper respiratory	82 (16%)	77 (15%)	9·3 (7·6–11·2)	9·7 (8·0–11·8)
Urinary tract	63 (12%)	76 (15%)	12·0 (10·1–14·1)	11·9 (10·0–14·1)
Serious infections				
Including COVID-19	32 (6%)	27 (5%)	3·4 (2·4–4·6)	2·8 (1·9–4·0)
Excluding COVID-19	12 (2%)	19 (4%)	1·5 (0·9–2·3)	2·0 (1·3–3·0)
Malignancies‡	5 (1%)	3 (<1%)	0·4 (0·1–1·0)	0·3 (0·1–0·8)
Deaths§	11 (2%)	10 (2%)	0·9 (0·5–1·7)	0·9 (0·4–1·7)

Data are n (%) unless stated otherwise. *Rates per 100 patient-years account for time on treatment, as the trial had variable duration and discontinuation rates were different between the two groups. †One patient randomly assigned to the placebo group mistakenly received ocrelizumab at the week 2 visit in the double-blind period; this patient was included in the ocrelizumab group for safety analyses. ‡Malignancies are identified using adverse events falling into the Standardised Medical Dictionary for Regulatory Activities queries "Malignant tumours (SMQ)". Ocrelizumab group—breast cancer (n=1), malignant melanoma (n=1), pancreatic carcinoma (n=1), metastatic pancreatic carcinoma (n=1), and stage IV prostate cancer (n=1); placebo group—acute myeloid leukaemia (n=1), colorectal cancer (n=1), and endometrial adenocarcinoma (n=1). §For reported deaths during the study, please see appendix (p 26).

Table 4: **Adverse events in the safety population during the double-blind treatment and follow-up 1 phase**

No notable differences were observed between female and male patients, or patients with or without MRI activity at baseline. For detailed information see appendix 1 (p 29).

Discussion

ORATORIO-HAND is the largest double-blind, controlled treatment trial to date done in a broad population of patients with PPMS, which included older and more disabled patients. Ocrelizumab was superior to placebo in delaying overall disability progression and worsening of upper-limb function, with a 30% risk reduction in 12-week confirmed progression in either the EDSS or 9HPT, and consistent benefit across the individual components (risk reduction of 41% in 9HPT progression and 33% in EDSS progression).

ORATORIO-HAND was designed to prospectively address the key eligibility gaps of the ORATORIO trial, which excluded patients older than 55 years or with an EDSS score of more than 6·5.[3] The study included approximately 27% of patients aged 55 years and older, and 16% with an EDSS score of more than 6·5. Compared with the ORATORIO population, this population had a 44% longer median disease duration and greater hand function impairment, taking a mean of 7 s longer to do the 9HPT. The treatment effect on EDSS progression observed in ORATORIO-HAND (33% risk reduction) was numerically greater than that reported in ORATORIO (24%), whereas the effect on 9HPT progression was similar (41% *vs* 44%).[4] In the subgroup of predominantly wheelchair-dependent individuals (EDSS >6·5), ocrelizumab showed an even stronger effect, reducing the risk of 12-week cCDP by 49% and the risk of 12-week 9HPT progression by 41%. Although multiple observational studies have shown clinical benefits with ocrelizumab for patients with PPMS and an EDSS score of more than 6·5,[15,16] this study provides the first randomised, controlled evidence of a DMT in patients with advanced PPMS, with benefits extending to delaying and even preventing worsening of hand function, which is crucial for maintaining independence and quality of life and might be of relevance to clinical decision making, subject to patient and clinician goals.[5] This effect on upper-limb function was also perceived by patients, as shown by the significantly lower decline in the Neuro-QoL-UE score compared with placebo, with improvement observed even in MRI-active patients treated with ocrelizumab. Among patients who were still ambulatory at baseline (EDSS ≤6·5), ocrelizumab led to a significant reduction in the risk of requiring a wheelchair (52% risk reduction), a key disability milestone in multiple sclerosis. These results are consistent with a previous analysis in ORATORIO.[17]

Although the therapeutic benefit of ocrelizumab was more evident in patients up to 55 years compared with those older than 55 years, the results suggest that the benefit extends to many patients up to age 65 years. Although a significant treatment benefit was not observed in patients older than 55 years, those with an EDSS score of more than 6·5 showed a highly robust treatment effect (49% risk reduction). In this subgroup, approximately 25% were aged 55 years or older. These results challenge notions of a rigid therapeutic ceiling based on age or disease stage. The debate on the concept of therapeutic futility associated with age is ongoing;[15,18] however, the findings here, as well as accruing evidence on ocrelizumab from large real-world cohorts,[15,19] suggest that age cutoffs for use of ocrelizumab in PPMS might lack biological justification.[19]

Ocrelizumab showed a more pronounced benefit in patients with MRI activity at baseline (defined by T1 Gd+ or new or enlarging T2 lesions), with a 55% risk reduction in 12-week cCDP. These results are consistent with previous results from ORATORIO[3] and OLYMPUS (rituximab),[20] and partly reflect the observation that untreated patients with PPMS with acute activity have a higher risk of disability accrual.[21–23] Although the prespecified analysis showed no significant effect in the MRI-inactive subgroup, a post-hoc analysis using ORATORIO's definition of MRI activity (presence of T1 Gd+ lesions only) showed a significant treatment benefit in both MRI-active and MRI-inactive subgroups. In this analysis, patients without MRI activity treated with

ocrelizumab had a 28% risk reduction in 24-week composite progression and a 40% risk reduction in 24-week 9HPT progression. This suggests that ocrelizumab modifies the disease process even in the absence of acute focal inflammation—particularly in pathways, such as the upper-limb motor pathways, which have greater functional reserve and are more likely to be resistant to progression.[10] Ocrelizumab significantly reduced the accumulation of T2 and T1 hypointense lesion volume compared with placebo. The reduction in the evolution of chronic T1 hypointense lesions, or so-called black holes, is particularly relevant, as these lesions reflect severe tissue damage, including axonal loss and matrix destruction, and are associated with long-term disability accrual.[24,25] In contrast to ORATORIO,[3] in this trial a significant effect on brain volume loss was not observed. Post-hoc analyses (not shown) stratifying by different ages (≤45 years *vs* >45 years and ≤55 years *vs* >55 years) and disease duration (≤10 year *vs* >10 year) cutoffs showed no treatment difference in any subgroup, suggesting that the older population and age-related atrophy do not fully account for this discrepancy. Although an association has previously been shown between whole brain atrophy and greater physical disability progression, evidence remains heterogeneous.[26] Therefore, the reason for the dissociation between the robust clinical benefit and the lack of effect on brain volume remains unclear. It is possible that a treatment effect on spinal cord atrophy, a strong independent marker of disability[27,28] might show consistency with clinical outcomes, and future analyses will need to explore this hypothesis.

The adverse event profile in ORATORIO-HAND was overall balanced between ocrelizumab and placebo, and consistent with the known safety profile for ocrelizumab.[3,29,30] As expected,[31] infusion-related reactions were a common adverse event in the ocrelizumab group, but mostly mild or moderate and showing resolution.

The higher proportion of patients with infections in the ocrelizumab group (245 [48%] of 506 *vs* 226 [45%] of 506) was driven by cases of COVID-19; when COVID-19 was excluded, infection rates were nearly identical (38% *vs* 37%), and the rate of serious infections was numerically lower with ocrelizumab than placebo (rate 1·5 *vs* 2·0 per 100 patient-years). After excluding COVID-19 events, the proportion of patients with infections remained higher with ocrelizumab in the older than 55 years subgroup (43% *vs* 39%). Similarly, infection rates were higher in the subset with EDSS scores of more than 6·5 who received ocrelizumab. These results were mostly driven by upper respiratory infections (eg, nasopharyngitis) in the subgroup older than 55 years and by urinary tract infections in the group with EDSS scores of more than 6·5. Notably, the risk for serious infections (excluding COVID-19) was not increased in these two subgroups. It should be noted that patients in the ocrelizumab group with an EDSS score of more than 6·5 were more likely to be female (66% *vs* 51%); in previous analyses of the OPERA and ORATORIO studies, female patients were shown to have a higher risk of non-serious urinary tract infections than male patients.[30]

Finally, the incidence rate of malignancies in the ocrelizumab group (0·4 per 100 patient-years) was not significantly different from that in the placebo group and fell within the expected epidemiological range (0·7 per 100 patient-years),[32] with no clusters of specific types of malignancies (eg, breast cancer).

For more on **incidence rates** see https://www.dmsr.dk/

This study has multiple strengths. It is the second and largest study to date, with a robust, double-blind, placebo-controlled design, to show the impact of ocrelizumab in patients with PPMS—including an older and more disabled population—and using a novel and clinically meaningful composite endpoint. Whereas approximately 25% of patients in real-world cohorts have EDSS scores of more than 6·5,[15,33] our enrolled cohort had approximately 15% with EDSS scores of more than 6·5. More disabled populations are difficult to recruit and retain in clinical trials owing to barriers associated with increased disability, including transportation, accessibility, fatigue or cognitive burden, and need for caregiver support.[34,35] Recruitment also occurred during the COVID-19 pandemic, when disabled populations were self-isolating for their safety. The consistency of the treatment effect across multiple endpoints and clinically relevant subgroups strengthens the validity of the findings. Several limitations should be considered. Although ocrelizumab achieved a 30% relative risk reduction in the primary endpoint, the 7% absolute risk reduction means nearly one-third of treated patients still had 12-week confirmed disability progression. However, when applying a 48-week confirmation window, which more accurately captures permanent, irreversible disability progression, less than 25% of patients receiving ocrelizumab had disability progression in either EDSS or 9HPT. Worsening in hand function or requirement of a wheelchair, both key milestones relating to a change in patient independence, was seen in just 10% and 4% of patients in the ocrelizumab group. Ultimately, although ocrelizumab meaningfully delays major disability milestones, these results underscore the ongoing challenge of fully halting progressive multiple sclerosis and the necessity for continued therapeutic innovation. Additionally, although multiple relevant subgroup analyses were prespecified, the sample sizes were relatively small for some subgroups; therefore, caution should be used when interpreting the findings which, although grounded on findings from ORATORIO,[3] were exploratory in nature. The study was not powered to detect significant treatment effects in certain subgroups (eg, age <55 years). Post-hoc analyses using T1 Gd+ lesions only to define MRI activity were done as part of a hypothesis-generating approach. The majority of enrolled participants were White and not Hispanic or Latinx, and no specific measurements were taken during enrolment to increase diversity in terms of race and ethnicity. Considering the low numbers of participants from different groups, no further analyses were done. The study has a relatively short duration

(approximately 3 years). Although long-term data from ORATORIO spanning over a decade[36] support the long-term efficacy and safety of ocrelizumab in patients with PPMS, long-term efficacy and safety data in older patients and those with more advanced disease are lacking. Efficacy and safety will continue to be assessed throughout the open-label extension phase.

In conclusion, ORATORIO-HAND confirms and expands on the findings of ORATORIO, showing that ocrelizumab significantly delays major disability milestones, including loss of hand function, in a broad population of patients with PPMS. The safety profile was consistent with the well established profile of ocrelizumab. These findings are of great importance for the multiple sclerosis community, as they extend the window of opportunity for treatment in patients of older age and with advanced disease, and potentially across the entire spectrum of overlapping multiple sclerosis phenotypes.

Contributors

All authors (GG, LA, RB, GRC, MC, JD, JH, JK, XM, KWS, CT, JSW, AB, UB, LC, CG, MM, H-MS, PS, QW, KY, and JO) contributed to, reviewed, and approved the final draft of the paper. All authors verified the underlying data, had full access to all the data in the study, and had final responsibility for the decision to submit for publication. GG, LA, RB, GRC, MC, CG, JH, JK, H-MS, UB, QW, and JSW contributed to conceptualisation and design, methodology development, data analysis, and manuscript review and editing. GG, RB, KY, UB, MC, and JD contributed to data collection, data interpretation, and review. LC contributed to conceptualisation, formal analysis, methodology, validation, visualisation, and manuscript review and editing. The authors attest to adherence to the trial protocol, along with the accuracy and completeness of the data reporting.

Declaration of interests

GG has received compensation for serving as a consultant, speaker, or research support from Astoria Biologica, Biogen, BMS, F Hoffman-La Roche, Genentech, Kiniksa, Merck KGaA/EMD Serono, Moderna, Sandoz, Sanofi, Viracta, and Zenas BioPharma; has stocks in Astoria Biologica; and has received payment for expert testimony from Novartis. LA has received honoraria from Sanofi-Genzyme and Merck Serono, consulting fees from Novartis, and institutional research grant support from Sanofi-Genzyme and Merck Serono; and has received compensation for participation in a data safety monitoring board or advisory board for Novartis and Sanofi-Genzyme. RB has received research support from Biogen, Eli Lilly, F Hoffman-La Roche, Genentech, and Novartis; personal compensation for consulting from Alexion, Amgen, Cadenza, Sanofi, and TG Therapeutics; and manuscript support from F Hoffman-La Roche. GRC has received compensation for participation in data and safety monitoring boards for Applied Therapeutics, AI Therapeutics, AMO Pharma, Argenx, AstraZeneca, Avexis Pharmaceuticals, Bristol Meyers Squibb, CSL Behring, Cynata Therapeutics, DiaMedica Therapeutics, Horizon Pharmaceuticals, Immunic, Inhibrix, Karuna Therapeutics, Kezar Life Sciences, Medtronic, Merck, Meiji Seika Pharma, Mitsubishi Tanabe Pharma Holdings, Prothena Biosciences, Novartis, Pipeline Therapeutics (Contineum), Regeneron, Sanofi-Aventis, Teva Pharmaceuticals, United BioSource, and University of Texas Southwestern, and in consulting for Alexion, Antisense Therapeutics–Percheron, Avotres, Biogen, Clene Nanomedicine, Clinical Trial Solutions, Endra Life Sciences, Cognito Therapeutics, F Hoffman-La Roche, Genentech, Genzyme, Hoya Corporation, Immunic, Immunosis Pty, Klein-Buendel Incorporated, Kyverna Therapeutics, Linical, Merck–Serono, Noema, Neurogenesis, Perception Neurosciences, Protalix Biotherapeutics, Regeneron, Revelstone Consulting, SAB Biotherapeutics, Sapience Therapeutics, Scott & Scott, and Tenmile; has received institutional grants from University of Alabama at Birmingham, AL, USA; and holds non-financial leadership or fiduciary roles in the Birmingham Jewish Federation, Birmingham Jewish Foundation, and Graffman Endowment Committee. JD reports personal honoraria for speaking, serving on advisory boards, or attending meetings from Amicus, AstraZeneca, Bayer Schering Pharma, Er-Kim, F Hoffman-La Roche, Hemofarm, Janssen–Johnson and Johnson, Medis, Merck, Novartis, PharmaSwiss, and TEVA; and grant or contract support from the Ministry of Science, Technological Development and Innovation of the Republic of Serbia. JH or his affiliated institutions have received either consulting fees, honoraria, support to attend meetings, compensation for participation on a data safety monitoring or advisory board, or research support from CHARIOT MS, F Hoffmann-La Roche, Sanofi, and Novartis; his institution received licences for rating scales. XM's institution has received compensation for lecture honoraria and travel expenses, participation in scientific meetings, or clinical advisory board participation in recent years from F Hoffmann-La Roche, Merck, Novartis, and Sanofi-Genzyme. KWS received honoraria for speaking and consulting for AstraZeneca, Biogen, Bristol Myers Squibb, F Hoffman-La Roche, Merck, Novartis, and TG Therapeutics and travel compensation for EAN 2024 from TEVA. CT has a research grant (PI24/01277 and FORT23/00034) from the Spanish Ministry of Science and Innovation and has received compensation for consulting, speaking engagements, and attending meetings for Bristol Myers Squibb, F Hoffman-La Roche, Immunic Therapeutics, Merck, Novartis, and Sanofi. JSW has received personal compensation for consulting and serving on scientific advisory boards with Cleveland Clinic Foundation, EMD Serono, Novartis, F Hoffmann-La Roche–Genentech, Sandoz and Zenas BioPharma; and manuscript support from F Hoffmann-La Roche; royalties are received for out-licensed anti-viral monoclonal antibodies through UTHealth as a proportion of what UTHealth receives from Millipore. AB, UB, LC, CG, MM, H-MS, PS, QW, and KY are employees and some are also shareholders of F Hoffmann-La Roche. JO has received compensation for consulting from Amgen, Biogen Idec, Cabaletta, EMD Serono, F Hoffmann-La Roche, Novartis, Sanofi-Genzyme, and Sudo Biosciences and research funding from Biogen Idec, Brain Canada, F Hoffmann-La Roche, MS Canada, National MS Society, and the Waugh Family Chair in MS Research. MC and JK declare no competing interests.

Data sharing

Qualified researchers can request access to individual patient level data through the clinical study data request platform. Further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, are also available. Anonymised records for individual patients across more than one data source external to Roche cannot, and should not, be linked owing to a potential increase in risk of patient reidentification.

For more on the **clinical study data request platform** see https://vivli.org/; further details on Roche's criteria for eligible studies are available at https://vivli.org/members/ourmembers/

For more on **how to request access to related clinical study documents** see https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm

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