Long-term follow-up from the ORATORIO trial of ocrelizumab for primary progressive multiple sclerosis: a post-hoc analysis from the ongoing open-label extension of the randomised, placebo-controlled, phase 3 trial

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Summary

Background The safety and efficacy of ocrelizumab in primary progressive multiple sclerosis were shown in the phase 3 ORATORIO trial. In this study, we assessed the effects of maintaining or switching to ocrelizumab therapy on measures of disease progression and safety in the open-label extension phase of ORATORIO.

Methods ORATORIO was an international, multicentre, double-blind, randomised, placebo-controlled, phase 3 trial done at 182 study locations including academic centres, hospitals, and community speciality centres within 29 countries across the Americas, Australia, Europe, Israel, New Zealand, and Russia. Patients with primary progressive multiple sclerosis aged 18–55 years who had an Expanded Disability Status Scale (EDSS) score of 3·0–6·5 were eligible for enrolment. Those who had previous treatment with B-cell-targeted therapies or other immunosuppressive medications were excluded. Eligible participants were randomly assigned (2:1) to receive either intravenous infusion of 600 mg of ocrelizumab (two 300 mg infusions 14 days apart) or placebo every 24 weeks for at least 120 weeks until a prespecified number (n=253) of disability events occurred. After the double-blind phase, patients entered an extended controlled period of variable duration, during which they and investigators became aware of treatment allocation. Following this period, patients could enter an optional open-label extension, during which they continued ocrelizumab or switched from placebo to ocrelizumab. Time to onset of disability progression was confirmed at 24 weeks with four measures (ie, increase in EDSS score, ≥20% increase in time to complete the 9-Hole Peg Test [9HPT], ≥20% increase in time to perform the Timed 25-Foot Walk [T25FW], and composite progression defined as the first confirmed occurrence of any of these three individual measures), as was time to requiring a wheelchair (EDSS ≥7). Conventional MRI measures were also analysed. The intention-to-treat population was used for the safety and efficacy analyses; all analyses, and their timings, were done post hoc. ORATORIO is registered with ClinicalTrials.gov, NCT01194570, and is ongoing.

Findings From March 3, 2011, to Dec 27, 2012, 488 patients were randomly assigned to the ocrelizumab group and 244 to the placebo group. The extended controlled period started on July 24, 2015, and ended on April 27, 2016, when the last patient entered the open-label extension. Overall, 544 (74%) of 732 participants completed the double-blind period to week 144; 527 (97%) of 544 entered the open-label extension phase, of whom 451 (86%) are ongoing in the open-label extension. After at least 6·5 study years (48 weeks per study year) of follow-up, the proportion of patients with progression on disability measures was lower in those who initiated ocrelizumab early than in those initially receiving placebo for most of the measures of 24-week confirmed disability progression: EDSS, 51·7% *vs* 64·8% (difference 13·1% [95% CI 4·9–21·3]; p=0·0018); 9HPT, 30·6% *vs* 43·1% (12·5% [4·1–20·9]); p=0·0035); T25FW, 63·2% *vs* 70·7% (7·5% [–0·3 to 15·2]; p=0·058); composite progression, 73·2% *vs* 83·3% (10·1% [3·6–16·6]; p=0·0023); and confirmed time to requiring a wheelchair, 11·5% *vs* 18·9% (7·4% [0·8–13·9]; p=0·0274). At study end, the percentage change from baseline was lower in those who initiated ocrelizumab early than in those initially receiving placebo for T2 lesion volume (0·45% *vs* 13·00%, p<0·0001) and T1 hypointense lesion volume (36·68% *vs* 60·93%, p<0·0001). Over the entire period, in the ORATORIO all ocrelizumab exposure population, the rate of adverse events was 238·09 (95% CI 232·71–243·57) per 100 patient-years and serious adverse events was 12·63 (95% CI 11·41–13·94) per 100 patient-years; the most common serious adverse events were infections at 4·13 (95% CI 3·45–4·91) per 100 patient-years. No new safety signals emerged compared with the double-blind phase of ORATORIO.

Interpretation Compared with patients switching from placebo, earlier and continuous ocrelizumab treatment provided sustained benefits on measures of disease progression over the 6·5 study years of follow-up. Although this study shows the benefit of earlier intervention with ocrelizumab in primary progressive disease, progression remains an important unmet need in multiple sclerosis. Further research should focus on how the potential benefits described in this study might be improved upon, particularly over longer time periods.

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Introduction

The double-blind period of the ORATORIO study established ocrelizumab as the first treatment to show a benefit on disability progression and MRI measures in patients with primary progressive multiple sclerosis.[1] Prevention of long-term disability progression is an important outcome for patients with multiple sclerosis,[2] as higher levels of disability, including requiring a wheelchair, are associated with physical, emotional, and financial challenges, contributing to an overall reduced quality of life.[3–5] Open-label extension studies provide long-term information about safety and efficacy of disease-modifying therapies and inform the patient–clinician dialogue in treatment choices. Few data are available from open-label

Research in context

Evidence before this study

The value of open-label extension studies in establishing the long-term safety and efficacy of disease-modifying therapies is established in relapsing multiple sclerosis. Few data are available for progressive forms of the disease because randomised controlled trials of most disease-modifying therapies have been unsuccessful. We did a PubMed search using the dates Jan 1, 1970, to Feb 1, 2020. We restricted the search to the titles and abstracts of papers and to papers of human clinical trials published in English only. We searched for studies using the following terms: "(primary progressive multiple sclerosis OR PPMS)" AND "(disease-modifying therapy)" AND "(open-label extension)". We did not find any comparable studies of primary progressive multiple sclerosis. The positive results of siponimod in secondary progressive multiple sclerosis on disability progression (EXPAND study) have yet to be extended to its open-label phase. Moreover, the open-label extension phase of the ASCEND study of natalizumab in patients with secondary progressive multiple sclerosis confirmed the lack of efficacy seen in the double-blind period on disability progression as measured with a multicomponent primary outcome. Using a novel primary composite endpoint, the INFORMS study also did not show any benefit of fingolimod in primary progressive multiple sclerosis; consequently, no open-label extension was done. The unique effect of ocrelizumab in ORATORIO, which is, to the best of our knowledge, the first phase 3 study to show benefit of a disease-modifying therapy on disability progression in primary progressive multiple sclerosis, led to the inclusion of most patients who completed the double-blind period in the open-label extension, which remains ongoing.

Added value of this study

The ORATORIO open-label extension provides evidence of a consistent, long-term benefit of ocrelizumab on disease progression in primary progressive multiple sclerosis, and highlights the benefit of earlier initiation of ocrelizumab in this population. The chronic, gradually progressive nature of multiple sclerosis makes long-term outcomes particularly important. The rigorous collection and documentation that occur in an extended clinical trial setting can provide accurate characterisation of the clinically relevant effects that can be achieved with early and persistent ocrelizumab therapy in primary progressive multiple sclerosis. Importantly, the risks of deterioration in patients with primary progressive multiple sclerosis as assessed with individual and composite measures of progression were lower in those who initiated ocrelizumab at the start of the double-blind period, compared with those who switched from placebo at the start of the open-label extension; differences in disability progression were evident over the duration of all phases of the study, indicating that patients who switch do not catch up. The time to lose the ability to ambulate and require a wheelchair was longer in the group who started ocrelizumab earlier. The relatively high MRI lesion accrual in patients with primary progressive multiple sclerosis treated with placebo in ORATORIO, which was readily controlled in those treated with or switched to ocrelizumab therapy, suggests a common underlying pathology in relapsing multiple sclerosis and primary progressive multiple sclerosis, in which pathological features do not demarcate specific disease phases but are part of a continuum. The reassuring safety profile of ocrelizumab over 6·5 study years in patients with primary progressive multiple sclerosis mirrors similar long-term data in relapsing multiple sclerosis.

Implications of all the available evidence

These analyses show, through 6·5 study years of follow-up in the ORATORIO trial, a sustained benefit of early and continuous ocrelizumab treatment on disease progression in primary progressive multiple sclerosis, as assessed by several outcome measures. Except for ocrelizumab, randomised controlled trials of disease-modifying therapies in primary progressive multiple sclerosis have not shown beneficial effects, contrary to relapsing multiple sclerosis. The similarities in the effect of ocrelizumab on measures of disease progression, and measures of clinical and MRI activity, seen in ORATORIO and the OPERA studies, coupled with a wealth of additional data for underlying pathology, challenge the current paradigm separating relapsing from progressive courses of the disease. The efficacy of some sphingosine-1-receptor modulators in both relapsing multiple sclerosis and secondary progressive multiple sclerosis supports such a simplification. Future data, especially long term, for populations with multiple sclerosis will help to address whether relapsing and secondary progressive multiple sclerosis represent parts of a single disease continuum, with the associated implications for regulatory policy and clinical decisions.

extension studies in progressive forms of multiple sclerosis, particularly primary progressive disease, because most disease-modifying therapies have been unsuccessful in randomised clinical trials.[6–19]

In ORATORIO, following completion of the double-blind period and unblinding of study centres, patients could enter an open-label extension phase, via an extended control period. Herein we report interim safety and efficacy data over 3·5 study years (in which a study year is defined as 48 weeks) of open-label extension follow-up (ie, at least 6·5 study years of follow-up since the start of the trial), which is currently ongoing. We focus on clinically meaningful measures of disability—including ambulation, upper-limb function, and time to requiring a wheelchair—as well as MRI measures, which are often overlooked in primary progressive multiple sclerosis.

Methods

Study design and participants

ORATORIO (NCT01412333) was an international, multicentre, double-blind, randomised, placebo-controlled, phase 3 trial investigating the safety and efficacy of ocrelizumab in people with primary progressive multiple sclerosis (appendix p 1). ORATORIO was done at 182 study locations including academic centres, hospitals, and community speciality centres within 29 countries across the Americas, Australia, Europe, Israel, New Zealand, and Russia.

Participants were enrolled if they met the key eligibility criteria, which included an age of 18–55 years, a diagnosis of primary progressive multiple sclerosis as determined by the McDonald criteria (2005 revision),[20] and an Expanded Disability Status Scale (EDSS) score of 3·0–6·5 inclusive at screening. Participants were excluded if they met the key exclusion criteria, which included a history of relapsing-remitting, secondary progressive, or progressive relapsing disease, as well as previous treatment with B-cell-targeted therapies and other immunosuppressive medications. All patients completing the double-blind period were eligible to enter the open-label extension.

The trial protocol for ORATORIO was approved by the relevant institutional review boards or ethics committees, and is available online. We obtained written informed consent from all patients (at the screening visit, within 4 weeks before randomisation),[1] and all patients provided written re-consent before entry into the open-label extension.

Procedures

The randomised part of the study, including randomisation and masking, has been fully described elsewhere.[1] Briefly, randomisation was done through voice entry of the patient's date of birth into an interactive response technology (using IXRS, Almac Group) whereupon the treatment groups were assigned, with stratification by age and geographical region.

Briefly, ORATORIO consists of three treatment periods: the core double-blind period, the extended controlled period, and the open-label extension phase (appendix p 1). At the start of the double-blind period, 732 patients were randomly assigned (2:1) to receive either 600 mg of ocrelizumab (administered as two 300 mg intravenous infusions 14 days apart; n=488) or placebo (n=244) every 24 weeks for at least 120 weeks, until a prespecified number of 253 patients had a 12-week-confirmed disability progression on the EDSS (ie, the primary outcome; an event-driven clinical trial design). The open-label extension was dependent on a positive result of the prespecified primary outcome and implemented based on a positive benefit–risk assessment, as prespecified in the study protocol. Blinded treatment continued until the benefit-risk assessment, at which point patients were unmasked and gradually moved into the open-label extension phase. Patients were considered to be in the extended-controlled treatment period between the primary cutoff date (the date on which the prespecified number of progression events was reached) up to the first dose of ocrelizumab in the open-label extension. Clinical visits for ocrelizumab administration and clinical assessments took place every 24 weeks during the open-label extension phase; MRI assessments were done every 48 weeks. Patients who discontinued prematurely, including for safety reasons, or who did not wish to enter the open-label extension phase, were included in the safety follow-up.

See Online for appendix

Patients who were initially randomly assigned to receive ocrelizumab continued to receive it in the open-label extension (ie, the continuous ocrelizumab group), whereas those who were randomly assigned to the placebo group were switched to ocrelizumab treatment at the start of the open-label extension phase (ie, the placebo to ocrelizumab group; appendix p 2); in essence, a delayed start cohort. Patients in the open-label extension were given the first 600 mg dose of ocrelizumab as two 300 mg infusions 14 days apart; subsequent doses were administered as a single 600 mg infusion every 24 weeks. The cutoff date for clinical data included in these analyses was Jan 7, 2019; by this date, all ongoing patients were followed for at least 6·5 study years, 3·5 study years of which were in the open-label extension phase.

Outcomes

All the analyses, and their timings, in the open-label extension were post hoc and were over at least 6·5 study years. For all the analyses, the same endpoint definitions as for the primary, secondary, and exploratory endpoints used in the double-blind phase of ORATORIO were used,[1] with the addition of the time to requiring a wheelchair (EDSS ≥7), a key clinical disability milestone for patients with multiple sclerosis. Analyses from the double-blind baseline used the intention-to-treat population; analyses from the baseline of the open-label extension assigned the open-label extension participants according to their originally randomised treatment group. At the start of the open-label extension, a new baseline was derived and

For the **ORATORIO protocol** see https://www.nejm.org/doi/suppl/10.1056/NEJMoa1606468/suppl_file/nejmoa1606468_protocol.pdf

measures at or closest to this baseline were used as the reference for subsequent assessments.

During the open-label extension, all progression measures were confirmed for at least 24 weeks (ie, time to onset of 24-week confirmed disability progression). 24-week confirmed disability progression on the EDSS was defined as an increase in EDSS score from the double-blind baseline of at least 1·0 point (or 0·5 points for a baseline score above 5·5), and 24-week confirmed disability progression on the 9-Hole Peg Test (9HPT) and on the Timed 25-Foot Walk (T25FW) were defined as an increase from the double-blind baseline of at least 20% in the time taken to complete these measures observed for a period of at least 24 weeks. Composite 24-week confirmed disability progression was defined as the first occurrence of any of the disability measures (ie, 24-week confirmed disability progression on the EDSS, 9HPT, or T25FW). Time to requiring a wheelchair was defined as the time to onset of 24-week confirmed progression to an EDSS score of 7·0 or more, at which individuals are classified as being unable to walk 5 m even with aid and are essentially restricted to a wheelchair.[21]

To further explore whether the treatment effect of ocrelizumab was maintained over time, a counterfactual analysis of each disability measure was done. This analysis estimates the treatment effect of ocrelizumab on disability progression assuming that patients who were on placebo in the double-blind period would have stayed on placebo (counter to the fact). The hazard ratio (HR) for the Kaplan-Meier survival curves for the actual (placebo to ocrelizumab *vs* continuous ocrelizumab) and modelled (continuous placebo *vs* continuous ocrelizumab) analyses provide an indication of the magnitude of effect of ocrelizumab in both scenarios; a lower HR (larger effect) might be anticipated had patients on placebo not switched to ocrelizumab.

MRI assessments were done at baseline, week 24, week 48, and week 120 in the double-blind period, and at open-label extension day 1 and each study year thereafter (ie, open-label extension weeks 48, 96, and 144). Patients entered the open-label extension between 144 and 294 weeks after randomisation; consequently, the timing of MRI assessments in the open-label extension differed between patients relative to randomisation. To adjust for the different measurement schedules, annualised changes were calculated using the change and time relative to the previous MRI assessment. Additionally, open-label extension MRI scans were categorised relative to the time of randomisation using 48-week intervals—eg, any MRI done in the open-label extension between weeks 240 and 288 after randomisation was categorised as week 264. Brain MRI lesion activity was assessed as the number of new or enlarging T2 lesions and T1 gadolinium-enhancing lesions, and the percentage change from baseline and annualised change from the previous scheduled visit in total T2 lesion volume and total T1 hypointense lesion volume. Brain volume change was assessed using the percentage change from baseline in whole brain volume using SIENA/X[22] and the percentage change in cortical grey matter volume was assessed using paired Jacobian integration.[23] Annualised change in whole brain volume and grey matter volume on MRI scans was measured with respect to the previous relevant scheduled visit.

All patients who received any study treatment were included in the safety population. All data collected during all phases of the study and the safety follow-up were included in the safety analyses. Safety outcomes are reported for up to the end of the extended controlled period using the ORATORIO intention-to-treat population. Safety outcomes are reported for up to the clinical cutoff date using the ORATORIO all exposure population (patients who received any dose of ocrelizumab during all phases of the entire study, including patients originally randomly assigned to the placebo group, after the switch to open-label ocrelizumab treatment). Outcomes assessed included adverse events, serious adverse events, discontinuations for adverse events, serious infections, neoplasms, and deaths.

Statistical analysis

Time to 24-week confirmed disability progression outcomes was assessed by the Kaplan-Meier and Cox survival analyses in the intention-to-treat population, over at least 6·5 study years; HRs were estimated by Cox regression stratified by geographical region (USA *vs* the rest of the world) and age (≤45 years *vs* >45 years), and comparison of the survival distributions used the log-rank test. p values for difference in event rates were calculated using a *t* test on the survival curves' estimates at the indicated timepoints and the associated SD derived by the Greenwood formula.[24] For comparisons, a $p<0·05$ was considered statistically significant. HRs are presented for the entire study to show the advantage of initiating ocrelizumab earlier versus those who switched from placebo, as well as for the open-label extension only, to explore the effect of delayed initiation of ocrelizumab treatment. Details of the counterfactual[25] and associated sensitivity analyses[26,27] are provided in the appendix (p 15).

All MRI measure analyses were adjusted for age (≤45 years *vs* >45 years) and geographical region (USA *vs* the rest of the world). The number of new T1 gadolinium-enhancing lesions and the number of new or enlarging T2 lesions were analysed using a negative binomial model. The percentage change from double-blind baseline and annualised change in total T1 and T2 lesion volumes were analysed by the mixed-effect model of repeated measures, also adjusted for baseline total T1 and T2 lesion volume (appendix p 15). The percentage change from double-blind baseline in whole brain volume and grey matter volume was analysed using the mixed-effect model of repeated measures, also adjusted for double-blind baseline whole brain volume or grey matter volume (appendix p 15).

All annualised rate calculations assumed a study year of 48 weeks. The analyses based on the data up to Jan 7, 2019, are part of the yearly analyses done to describe the long-term benefit to risk of patients treated with ocrelizumab. The last patient was randomly assigned to ocrelizumab on Dec 27, 2012; therefore, by Jan 7, 2019, all patients could have been in the study for at least 312 weeks (ie, 6·5 study years). A 48-week study year was adopted as this was consistent with the 12-week scheduled visits for the study assessments. MRI measures used the baseline of the open-label extension as the reference point for the subsequent 48-weekly assessments (open-label extension weeks 48, 96, and 144). Safety outcomes are reported as event rates per 100 patient-years of exposure, with 95% CIs based on the Poisson distribution.

We did all the statistical analyses using the program SAS (version 9.4). The ORATORIO trial is registered with ClinicalTrials.gov, NCT01194570, and the open-label extension is ongoing.

Role of the funding source

The funder of the study had responsibility for the study design in conjunction with the approval of the steering committee. The funder also had a role in data collection, data analysis, data interpretation, and writing of the report. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

From March 3, 2011, to Dec 27, 2012, 488 patients were randomly assigned to the ocrelizumab group and 244 to the placebo group (figure 1). The extended controlled period spanned the interval from the end of the double-blind period on July 24, 2015, to the first open-label extension dose of ocrelizumab for each individual. The extended controlled period was completed when the last patient who finished the double-blind period entered the open-label extension, on April 27, 2016. The extended controlled period provided approximately three additional months of blinded controlled data and 6 months of unblinded controlled follow-up; patients gradually entered the open-label extension during this period, between Nov 5, 2015, and April 27, 2016. Between Nov 15, 2016, and Oct 30, 2017, ten individuals re-enrolled into the open-label extension after early discontinuation of randomised treatment. The open-label extension is ongoing, and is currently planned to continue until December, 2022, to provide for the organised collection of data over approximately 10 years.

Patient demographics and disease characteristics at study baseline were reported,[1] and are summarised in table 1. Disposition through the open-label extension by original randomised treatment group (ie, the placebo group or ocrelizumab group) is shown in figure 1. Overall, of the 732 patients randomly assigned in the intention-to-treat population, 544 (74%) completed the double-blind period to week 144, of whom 517 (95%) of 544 subsequently entered the open-label extension. Additionally, ten further patients re-enrolled into the open-label extension after early discontinuation of randomised treatment, bringing total open-label extension enrolment in the study to 527 (72%) of 732 originally randomised patients. At the time of data cutoff, most open-label extension patients (388 [74%] of 527) had reached at least open-label extension week 144; 76 (14%) of 527 had discontinued,

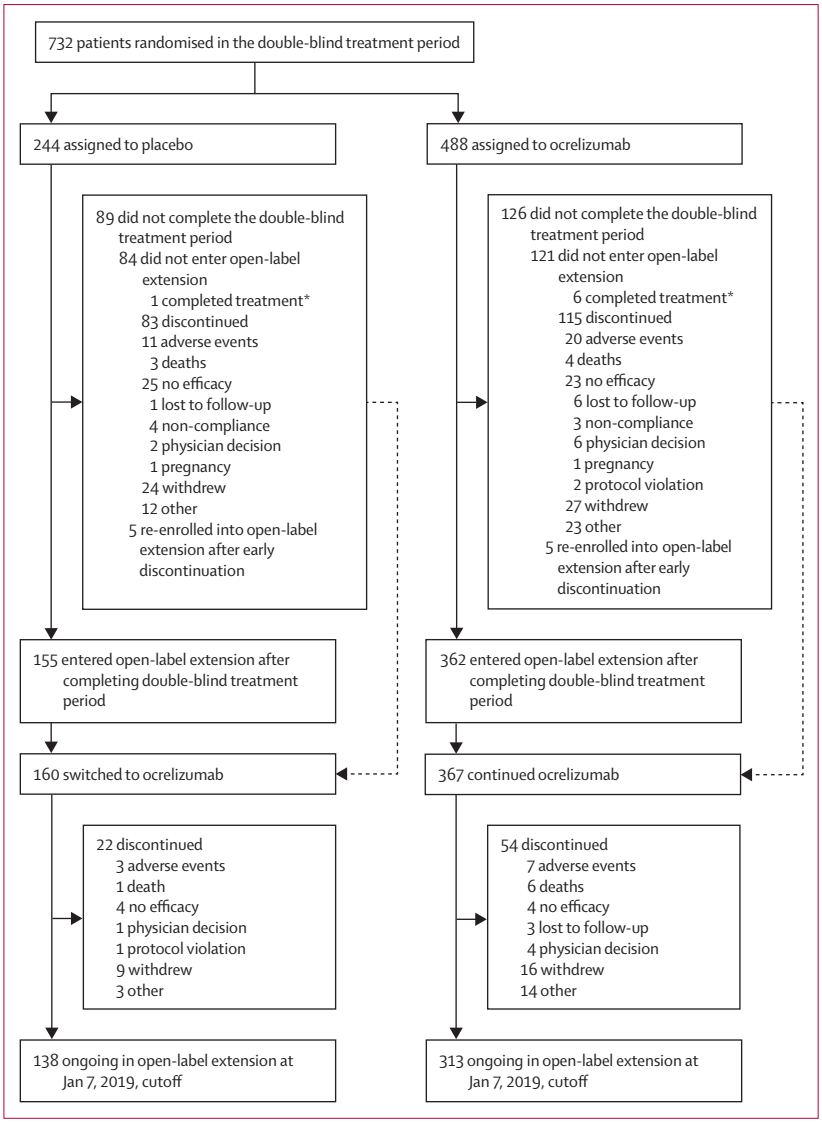

Figure 1: **Patient disposition**
Because of the event-driven nature of the double-blind period, not all patients entered the open-label extension at the same time relative to randomisation (appendix p 2). Some of the patients who were randomised early remained in the double-blind period up to week 240, before entering the open-label extension. Patients then remained on treatment and entered into the open-label extension (n=155 in the placebo group; n=362 in the ocrelizumab group) after completing the double-blind period, or withdrew after further treatment in the double-blind period and did not enter into the open-label extension (n=3 in the placebo group; n=14 in the ocrelizumab group). Completing the double-blind period meant that they had not withdrawn from treatment at the time of the primary cutoff (July 24, 2015). *Patient had not withdrawn from treatment when given the opportunity to move into the open-label extension, and decided to not enter the open-label extension.

	Double-blind period baseline		Double-blind period baseline, open-label extension population		Open-label extension baseline	
	Placebo (n=244)	Ocrelizumab (n=488)	Placebo (n=160)	Ocrelizumab (n=367)	Placebo followed by ocrelizumab (n=160)	Continued on ocrelizumab (n=367)
Age (years)	44·4 (8·3)	44·7 (7·9)	45·6 (7·7)	44·8 (7·8)	49·2 (7·7)	48·5 (7·8)
Sex						
Female	124 (51%)	237 (49%)	82 (51%)	174 (47%)	82 (51%)	174 (47%)
Male	120 (49%)	251 (51%)	78 (49%)	193 (53%)	78 (49%)	193 (53%)
Expanded Disability Status Scale score	4·7 (1·2)	4·7 (1·2)	4·7 (1·2)	4·6 (1·2)	5·2 (1·5)	4·9 (1·5)
Patients with T1 gadolinium-enhancing lesions*	60 (25%)	133 (28%)	33 (21%)	102 (28%)	25 (16%)	1 (0·3%)
Number of T1 gadolinium-enhancing lesions*	0·6 (1·6)	1·2 (5·1)	0·5 (1·2)	1·3 (5·7)	0·3 (1·0)	0·0 (0·2)
Number of T2 lesions†	48·2 (39·3)	48·7 (38·2)	46·3 (36·4)	48·0 (39·2)	49·5 (32·6)	50·0 (36·3)
T2 lesion volume (cm^3)*	10·9 (13·0)	12·7 (15·1)	10·3 (11·9)	12·7 (14·4)	11·2 (12·8)	12·2 (13·6)
T1 hypointense lesion volume (cm^3)*	4·2 (6·1)	5·2 (7·9)	4·0 (6·0)	5·1 (7·1)	5·4 (7·8)	5·9 (8·3)
Normalised brain volume (cm^3)	1469·9 (88·7)	1462·9 (83·9)	1465·5 (84·3)	1459·9 (83·4)	NC	NC

Data are mean (SD) or n (%). Demographics and disease characteristics are based on all patients entering the open-label extension. NC=not collected. *Open-label extension baseline score is the latest score from the week 120 assessment and open-label extension first dose. †Open-label extension baseline score is the assessment at the first dose of ocrelizumab in the open-label extension phase.

Table 1: **Baseline demographics and disease characteristics for the ORATORIO populations at the start of the double-blind period and open-label extension**

most commonly at the patient's request (25 [33%] of 76), and 451 (86%) of 527 were ongoing.

Over the duration of the open-label extension phase, timepoint analysis showed that the proportion of patients with 24-week confirmed disability progression on individual and composite measures of disability from the double-blind baseline remained lower in patients receiving continuous ocrelizumab compared with those switching from placebo to ocrelizumab at the end of the double-blind period (figure 2). By week 168, the proportion with 24-week confirmed disability progression on EDSS was significantly lower in the patients receiving continuous ocrelizumab than in those switching to ocrelizumab (33·3% *vs* 44·7%; difference 11·4% [95% CI 3·4–19·4]; p=0·005). This difference between the treatment groups was maintained at 6·5 study years of follow-up (51·7% *vs* 64·8%; difference 13·1% [95% CI 4·9–21·3]; p=0·0018). Similar event rate results were observed at week 312 for patients receiving continuous ocrelizumab compared with those switching to ocrelizumab for the time to requiring a wheelchair analysis (11·5% *vs* 18·9%; difference 7·4% [95% CI 0·8–13·9]; p=0·0274), 24-week confirmed disability progression on 9HPT (30·6% *vs* 43·1%; difference 12·5% [4·1–20·9]; p=0·0035) and T25FW (63·2% *vs* 70·7%; difference 7·5% [–0·3 to 15·2]; p=0·058), and the composite measure (73·2% *vs* 83·3%; difference 10·1% [3·6–16·6]; p=0·0023; figure 2). Forest plots of the difference in event rate for all disability outcomes at study weeks 120–312 are in the appendix (pp 3, 4).

The HR for patients receiving continuous ocrelizumab compared with those switching to ocrelizumab for time to first 24-week confirmed disability progression as measured by EDSS over all phases of the study was 0·72 (95% CI 0·58–0·89; p=0·0021). The overall HRs for the other 24-week confirmed disability progression measures were 0·65 (95% CI 0·50–0·86; p=0·002) for 9HPT, 0·77 (0·64–0·94; p=0·0101) for T25FW, 0·73 (0·61–0·88; p=0·0006) for the composite measure, and 0·58 (0·38–0·89; p=0·0112) for the time-to-requiring a wheelchair (EDSS ≥7·0). Using the baseline of the start of the open-label extension, there were no significant differences between patients receiving continuous ocrelizumab compared with those switching to ocrelizumab for all progression measures, except for the confirmed disability progression T25FW (HR 0·71 [95% CI 0·52–0·97]; p=0·0283; figure 2). For all disability measures, the HRs estimated by the counterfactual method were lower compared with the original method (appendix pp 5–7). The sensitivity analyses were consistent with the results of the main counterfactual analysis (appendix p 13).

Patients receiving continuous ocrelizumab maintained the near-complete suppression of both T1 gadolinium-enhancing and new or enlarging T2 lesion numbers seen at the end of the double-blind period through to open-label extension week 144 (appendix p 8). Patients switching to ocrelizumab had almost complete and sustained suppression of new MRI lesion disease activity throughout the open-label extension (appendix p 8). In the open-label extension phase, there was no difference in T1 gadolinium-enhancing and new or enlarging T2 lesion counts in patients receiving continuous ocrelizumab compared with those switching from placebo, except for new or enlarging T2 lesions at two timepoints where lesion numbers were already very low (appendix p 8).

Patients receiving continuous ocrelizumab maintained the near-complete suppression of MRI T2 lesion activity seen in the double-blind period through to open-label extension week 144 (appendix pp 9, 10). Patients switching

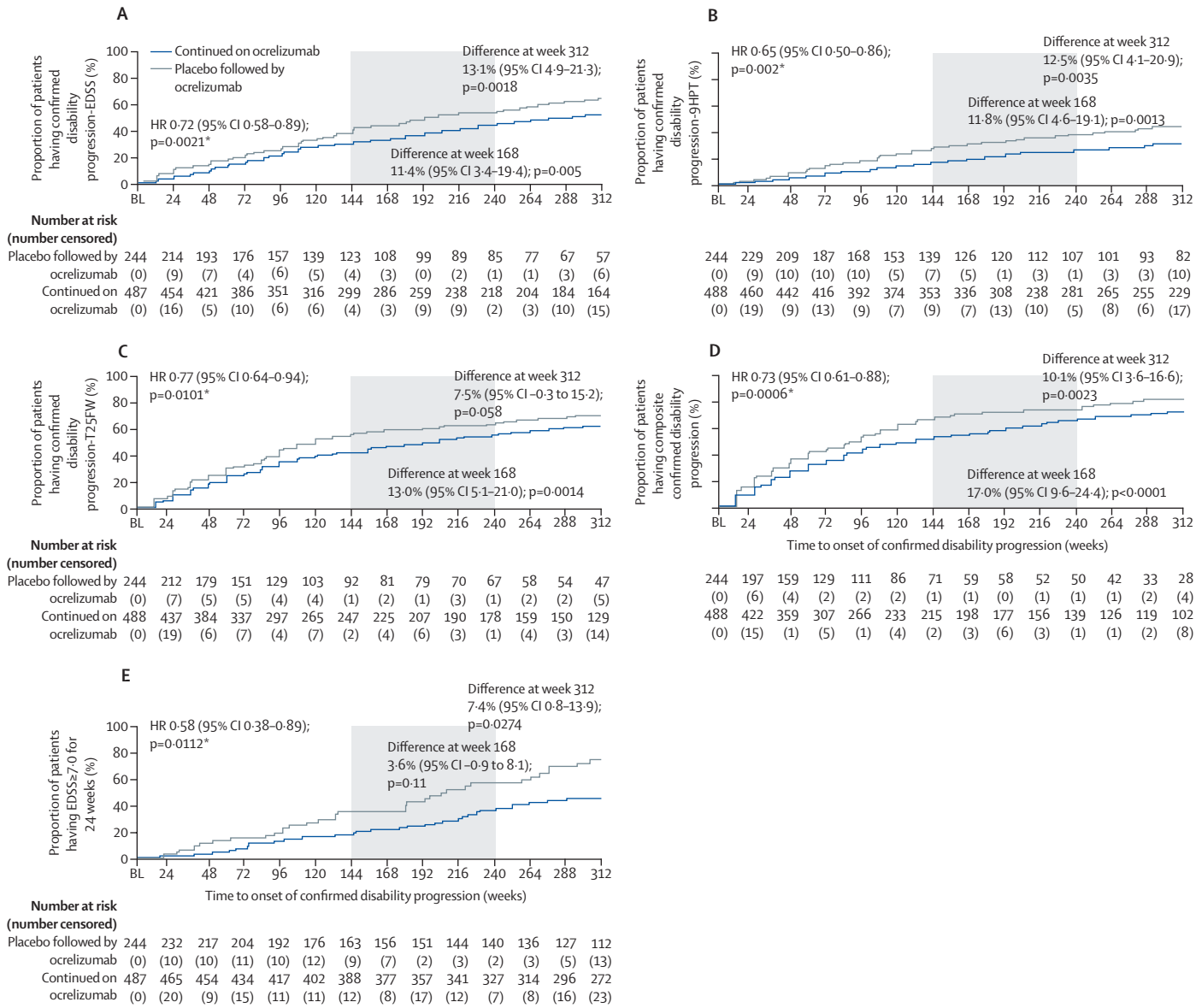

Figure 2: **Time to onset of 24-week confirmed disability progression outcomes and time to requiring a wheelchair across the entire study period**
(A) 24-week confirmed disability progression as assessed with the EDSS. (B) 24-week confirmed disability progression as assessed with the 9HPT. (C) 24-week confirmed disability progression as assessed with the T25FW. (D) Composite 24-week confirmed disability progression. (E) Time to requiring a wheelchair (ie, EDSS ≥7·0). Patients with missing EDSS scores at baseline were excluded (one patient receiving ocrelizumab had a missing EDSS score at baseline and was excluded from the 24-week confirmed disability progression and time-to-wheelchair analyses). Patients with initial disability progression who discontinued from treatment without subsequent EDSS scores had their results imputed. The difference at week 168 (the time when most patients had switched to ocrelizumab) and week 312 (ie, 6·5 study years) represents the difference in event rate (percentage and 95% CI) between the placebo group that switched to ocrelizumab and participants who continued on ocrelizumab. The event-driven study design required patients to move into an extended controlled period after completing the prespecified 120 weeks of the double-blind period; in the extended controlled period, blinded treatment continued before the assessment of the primary endpoint and unblinding. The extended controlled period spanned the interval from the end of the double-blind period to the first open-label extension dose of ocrelizumab for each individual. The extended controlled period was completed when the last patient who finished the double-blind period entered the open-label extension. The shaded area represents this gradual switching of patients from placebo to ocrelizumab and entry to the open-label extension. Using the baseline of the start of the open-label extension, the HRs during the open-label extension phase for time to 24-week confirmed disability progression were: 0·98 (95% CI 0·71–1·35; p=0·90) for EDSS; 0·70 (0·45–1·08; p=0·11) for 9HPT; 0·71 (0·52–0·97; p=0·0283) for T25FW; 0·85 (0·66–1·10; p=0·21) for the combined measure; and 0·66 (0·32–1·36; p=0·26) for EDSS ≥7·0. BL=Baseline. 9HPT=9-Hole Peg Test. EDSS=Expanded Disability Status Scale. HR=hazard ratio. T25FW=Timed 25-Foot Walk. *For the double-blind period, extended controlled period, and open-label extension phase.

to ocrelizumab had almost complete and sustained suppression of MRI T2 lesion activity from study year 2·5 to study year 6·5 (appendix pp 9, 10). At open-label extension week 144, patients continuously treated with ocrelizumab had significantly lower rates of T2 lesion volume change versus the double-blind baseline, compared with those switching to ocrelizumab (adjusted rate 13·002% *vs* 0·447%; p<0·0001; appendix pp 9, 10).

	ORATORIO double-blind period and extended controlled period		ORATORIO double-blind period, extended controlled period, and open-label extension phase (all exposure population)*
	Placebo (n=239)	Ocrelizumab (n=486)	Ocrelizumab (n=644)
Any adverse event	258·88 (247·33–270·82)	252·09 (244·39–259·98)	238·09 (232·71–243·57)
Adverse events leading to study treatment discontinuation	1·10 (0·47–2·16)	1·25 (0·76–1·92)	0·99 (0·67–1·41)
Serious adverse events	12·07 (9·68–14·87)	10·15 (8·65–11·83)	12·63 (11·41–13·94)
Fatalities	0·41 (0·08–1·20)	0·25 (0·07–0·64)	0·42 (0·22–0·71)
Infections and infestations	72·5 (66·5–79·0)	70·8 (66·8–75·0)	73·16 (70·19–76·22)
Urinary tract infection	17·8 (14·9–21·2)	15·1 (13·2–17·1)	18·23 (16·77–19·80)
Nasopharyngitis	17·7 (14·8–21·0)	12·8 (11·1–14·6)	12·88 (11·65–14·21)
Upper respiratory tract infection	2·9 (1·8–4·4)	5·2 (4·2–6·5)	5·16 (4·39–6·02)
Influenza	3·4 (2·2–5·1)	4·6 (3·6–5·7)	3·85 (3·19–4·60)
Bronchitis	2·9 (1·8–4·4)	2·6 (1·9–3·5)	2·79 (2·23–3·44)
Injury, poisoning, and procedural complications	36·3 (32·1–41·0)	43·5 (40·3–46·8)	35·19 (33·13–37·33)
Infusion-related reaction	20·3 (17·2–23·8)	31·0 (28·3–33·9)	22·24 (20·62–23·96)
Musculoskeletal and connective tissue disorders	31·7 (27·7–36·0)	22·8 (20·5–25·3)	21·60 (20·0–23·29)
Back pain	7·4 (5·6–9·7)	4·8 (3·8–6·0)	4·42 (3·72–5·22)
Arthralgia	4·3 (2·9–6·0)	3·0 (2·2–4·0)	2·63 (2·09–3·26)
Pain in extremity	4·7 (3·2–6·5)	2·4 (1·7–3·2)	2·02 (1·55–2·58)
General disorders and administration site conditions	15·6 (12·9–18·8)	12·7 (11·0–14·6)	11·5 (10·3–12·8)
Fatigue	4·4 (3·0–6·2)	1·9 (1·3–2·7)	1·5 (1·1–2·0)
Nervous system disorders	22·4 (19·1–26·1)	22·6 (20·3–25·1)	19·48 (17·97–21·10)
Headache	6·7 (5·0–8·9)	6·3 (5·1–7·6)	5·0 (4·25–5·85)
Psychiatric disorders	11·8 (9·4–14·6)	7·7 (6·4–9·2)	6·02 (5·19–6·95)
Depression	5·1 (3·6–7·0)	2·4 (1·7–3·3)	1·99 (1·52–2·55)
Serious infections	3·02 (1·89–4·57)	2·74 (1·99–3·68)	4·13 (3·45–4·91)
Malignancies†	0·27 (0·03–0·99)	0·93 (0·52–1·54)	0·91 (0·61–1·32)

Data are per 100 patient-years of exposure (95% CI). For the double-blind period and extended controlled period the data cutoff was Jan 20, 2016; for the all exposure population the data cutoff was Jan 7, 2019. Adverse events were encoded using the Medical Dictionary for Regulatory Activities (version 18.1) for the double-blind period and extended controlled period, and using MedDRA (version 21.1) for the all exposure population. System organ classes listed are those with at least one event categorised using the MedDRA preferred term occurring at a rate of 2·0 events per 100 patient-years or more. Serious infections listed are those occurring at a rate of 0·5 events per 100 patient-years or more. Patient-years are based on a 52-week year. *Patients who received any dose of ocrelizumab during all phases of the study, including patients originally randomly assigned to the placebo group, after the switch to open-label ocrelizumab treatment. †In the double-blind period and extended controlled period, multiple occurrences of the same adverse event are counted multiple times, whereas in the open-label extension, malignancies are based on multiple occurrences of the same adverse event counted once because of changes in the prespecified method of reporting adverse events in the double-blind period and open-label extension phase, to align with the approach used for the collection of long-term data.

Table 2: **Adverse events, serious adverse events, and adverse events leading to discontinuation for patients receiving ocrelizumab or placebo during all phases of ORATORIO**

At open-label extension week 144, mean percentage change in T1 lesion volume from baseline was 60·925% in patients switching to ocrelizumab versus 36·676% in those receiving continuous ocrelizumab (p=0·0008; appendix pp 9, 10). Patients receiving continuous ocrelizumab maintained low levels of MRI T1 hypointense lesion volume change seen in the double-blind period through to study year 6·5, assessed as the rate of annualised percentage change from the previous visit, and a reduction was seen in patients switching to ocrelizumab after the start of the open-label extension (appendix pp 9, 10). Throughout the open-label extension phase, no difference in annualised MRI T1 lesion volume was observed in patients receiving continuous ocrelizumab compared with those switching to ocrelizumab (appendix pp 9, 10).

At open-label extension week 144, patients treated continuously with ocrelizumab compared with those switching to ocrelizumab had numerically, but not significantly, lower rates of brain atrophy measured by a change from the double-blind baseline in whole brain volume (adjusted rate –3·077% *vs* –3·366%; p=0·13) and cortical grey matter volume (adjusted rate –2·525% *vs* –2·642%; p=0·38; appendix pp 11, 12). When expressed as annualised percentage change in volume, the adjusted rates were generally stable during the open-label extension phase for patients switching to ocrelizumab and those continuing ocrelizumab (appendix pp 11, 12).

Table 2 summarises the incidence and exposure-adjusted rates of adverse events among all patients receiving ocrelizumab in ORATORIO up to the end of the extended controlled period or up to the clinical cutoff date. As of Jan 7, 2019, 644 patients with primary progressive multiple sclerosis had received ocrelizumab during the double-blind period or extended controlled period and associated open-label extension phase. The rate of adverse events over the entire period in the ocrelizumab all exposure population was 238·09 (95% CI 232·71–243·57) per 100 patient-years,

lower than the rate observed up to the end of the extended controlled period for either ocrelizumab or placebo in patients with primary progressive multiple sclerosis (258·88 events per 100 patient-years [95% CI 247·33–270·82] in the placebo group and 252·09 [244·39–259·98] in the ocrelizumab group). The most frequent adverse events were infusion-related reactions. The most common class of event was infections and infestations, primarily non-serious urinary tract infections and nasopharyngitis. Overall, the rate of serious adverse events was 12·63 (95% CI 11·41–13·94) per 100 patient-years in the ORATORIO all exposure population, consistent with the rates observed up to the end of the extended controlled period (12·07 events per 100 patient-years [95% CI 9·68–14·87] in the placebo group and 10·15 [8·65–11·83] in the ocrelizumab group). The rate of infections per 100 patient-years was 73·16 (95% CI 70·19–76·22) in the ORATORIO all exposure population, consistent with the rate observed up to the end of the extended controlled period for both groups (72·5 [66·5–79·0] for the placebo group and 70·8 [66·8–75·0] for the ocrelizumab group).

The most common serious adverse events were classified as serious infections. These occurred at a rate of 4·13 per 100 patient-years (95% CI 3·45–4·91) over the entire period (all events corresponding to the Medical Dictionary for Regulatory Activities preferred terms occurred at individual rates <1 per 100 patient-years), and this overall rate was similar to that observed up to the end of the extended controlled period (3·02 events per 100 patient-years [95% CI 1·89–4·57] in the placebo group and 2·74 [1·99–3·68] in the ocrelizumab group), with overlapping 95% CIs. Both in the ORATORIO all exposure population and in both groups of the double-blind period, the most common serious infections were urinary tract infections, pneumonia, and cellulitis. One potential serious opportunistic infection was reported in the open-label extension period: serious candida sepsis that resolved in a patient who had stopped ocrelizumab treatment 11 months previously and was receiving cancer chemotherapy. As of Jan 7, 2019, no cases of progressive multifocal leukoencephalopathy were identified in the overall ORATORIO study population.

As of Jan 7, 2019, the rate of all malignancies per 100 patient-years in the ORATORIO all exposure population was 0·91 (95% CI 0·61–1·32) and up to the end of the extended controlled period the rate was 0·27 (0·03–0·99) for the placebo group and 0·93 (0·52–1·54) for the ocrelizumab group. A list of malignancies occurring in the all exposure population throughout the entire study as of January, 2019, is provided in the appendix (pp 16, 17).

The rate per 100 patient-years of adverse events leading to treatment withdrawals in the ORATORIO all exposure population (study year 6·5 was 0·99 [95% CI 0·67–1·41]) remained low and did not increase over time (the rate observed up to the end of the extended controlled period was 1·10 [0·47–2·16] in the placebo group and 1·25 [0·76–1·92] in the ocrelizumab group).

Over 6·5 study years, a reduction in serum immunoglobulin concentrations was observed in the ORATORIO population. At baseline, the number of patients with immunoglobulin concentrations below the lower limit of normal (LLN) was three (0·5%) of 642 for IgG, one (0·2%) of 641 for IgA, and three (0·5%) of 642 for IgM. Over 6·5 study years, for the majority of patients, immunoglobulin concentrations remained above the LLN (appendix p 14); the numbers of ocrelizumab-treated patients with a decrease below the LLN at study year 6·5 (ie, week 312) were 14 (5%) of 262 for IgG, 13 (5%) of 234 for IgA, and 64 (29%) of 218 for IgM.

Discussion

ORATORIO was the first treatment trial to show a clinical benefit on disability progression in patients with primary progressive multiple sclerosis treated with ocrelizumab.[1] So far, the ORATORIO open-label extension shows a consistent and sustained treatment-associated benefit in multiple measures of confirmed disability progression over a period of 6·5 study years. The benefit associated with ocrelizumab use in the open-label extension was consistent with that seen in the double-blind period and was maintained over time, supporting earlier treatment initiation with ocrelizumab and persistent benefit with maintained therapy. Disability accrual occurred at similarly low rates in the two groups during the open-label extension phase, with the exception of T25FW, in which the rates observed 2·5 study years after entry into the open-label extension in patients switching to ocrelizumab were higher than in patients treated continuously with ocrelizumab; however, they were similar to the rates in patients treated with ocrelizumab from randomisation during the double-blind period. EDSS, T25FW, and 9HPT (all confirmed at 24 weeks, which was more likely to reflect permanent accrual of disability than earlier confirmation[28]) were lower in patients originally treated with ocrelizumab than in those who were not over 6·5 study years, although the statistical difference was lost at the final time point for the T25FW. After 6·5 study years, a substantial difference in the relative risk of losing the ability to ambulate independently (time to requiring a wheelchair) was evident in the two treatment groups. This difference suggests that ocrelizumab might affect the gradual disability accrual that occurs over extended time periods and often leads to substantial impairment and loss of independence. The continued benefit of earlier treatment on disability measures was supported by the counterfactual analyses, suggesting that the treatment benefit of ocrelizumab would have been maintained throughout the open-label extension had patients stayed on placebo. The safety profile observed in the open-label extension was generally consistent with that observed during the controlled period. Consistent with results of previously reported trials, the incidence rates of malignancies in patients treated with ocrelizumab remained within the range of placebo data from clinical trials of

multiple sclerosis and epidemiological data for this patient population.[29,30]

At 6·5 study years, patients with continuous ocrelizumab treatment from randomisation had a non-significantly lower brain atrophy rate, as measured by change from baseline in whole brain volume, than did those with a delayed ocrelizumab treatment start. Cortical grey matter volume showed a nominal directional difference in patients with primary progressive multiple sclerosis receiving ocrelizumab early compared with those whose initiation of active therapy was delayed. The reduced frequency of MRI scans in the open-label extension, coupled with the relatively small change in brain volume assessed over an extended period, might present difficulties for interpretation of the data, although the annualised rates of whole brain volume and cortical grey matter change showed consistently lower rates among patients on continuous ocrelizumab than in those who switched to ocrelizumab. The utility of brain volume change as a way of monitoring primary progressive multiple sclerosis, particularly progression, is uncertain. Other novel MRI measures, such as slowly evolving lesions, might better correlate with disease progression than atrophy and be more sensitive to the effects of disease-modifying therapies.[31] Additionally to this trend in brain atrophy observed through the double-blind period and the open-label extension, earlier treatment resulted in a rapid and sustained benefit on other MRI measures compared with delayed ocrelizumab initiation at open-label extension entry.

The effect of ocrelizumab on new T1 and T2 lesion numbers is of interest, as these MRI measures correlate with acute inflammatory pathology and its consequences, and accumulating T1 hypointense and T2 lesion volumes are associated with disability progression in patients with multiple sclerosis.[31–33] A rapid and ongoing increase in the percentage change in T2 lesion volume was observed in the placebo-treated patients until active treatment with ocrelizumab was initiated following week 120 of the double-blind period. This difference stabilised following the switch from placebo to ocrelizumab during the open-label extension and remained similar in both the switch and continuous patient groups throughout the open-label extension. T1 hypointense lesion changes behaved differently. The benefit of ocrelizumab on maintaining low levels of volume change seen in the double-blind period was evident in patients on switching to ocrelizumab in the open-label extension. However, a gradual increase in both groups during the open-label extension was seen. These data are consistent with previous results from observational studies, where a greater proportional increase in T1 hypointense lesion compared with T2 hyperintense lesion number or load was shown in patients with primary progressive multiple sclerosis.[32] Similarly, fingolimod had a greater effect on T2 hyperintense lesions than T1 hypointense lesions in a randomised controlled treatment trial.[34] Interestingly, the almost complete suppression of MRI activity with ocrelizumab, in the ORATORIO double-blind phase and open-label extension reflected in the number of gadolinium-enhancing T1 and new and enlarging T2 lesions in patients receiving continuous ocrelizumab and those switching to ocrelizumab, was similar to that observed in the open-label extension of the OPERA studies.[35] The surprisingly high MRI T2 lesion accrual in patients with primary progressive multiple sclerosis treated with placebo in ORATORIO might suggest a common underlying pathology in relapsing multiple sclerosis and primary progressive multiple sclerosis.

In the ORATORIO study, the durable efficacy of ocrelizumab across disability and MRI endpoints over 6·5 study years was associated with a consistent safety profile. This finding was accompanied by a low rate of attrition, with most discontinuations occurring in the double-blind period (183 [25%] of 732 in the intention-to-treat population). Of the patients originally randomised, 527 (72%) of 732 entered the open-label extension (representing 96% of 549 patients completing the double-blind period), with 505 (96%) of 527 completing at least 48 weeks of treatment and 451 (86%) ongoing in the open-label extension. Infusion-related reactions and minor infections were the most common adverse events observed both in the double-blind period plus extended controlled period and over the entire 6·5 study year period. Rates of serious adverse events and discontinuations related to adverse events were low. The reduction in serum immunoglobulin concentrations, in particular IgM, can be explained by the mechanism of action of ocrelizumab.[1] However, immunoglobulin concentrations remained within normal ranges for most patients. In a pooled population of the patients who received ocrelizumab in the OPERA and ORATORIO trials, serious infections following episodes of a drop in immunoglobulin concentrations below the LLN were rare, consisting mainly of urinary tract infections, cellulitis, and pneumonia; most resolved with standard treatment, and most patients remained on ocrelizumab.[36] No cases of progressive multifocal leukoencephalopathy were observed in this study, consistent with other phase 2 and 3 clinical trials of ocrelizumab. To date, no cases have been observed in the ongoing open-label extensions of these studies or in the other ongoing clinical trials in patients with multiple sclerosis. Outside of clinical trials, each of the nine reported cases of progressive multifocal leukoencephalopathy in ocrelizumab-treated patients with relapsing multiple sclerosis or primary progressive multiple sclerosis has been associated with clinically significant contributing risk factors (eight occurred in patients switching from other highly effective disease-modifying therapies [so-called carry-over progressive multifocal leukoencephalopathy], and one occurred in a 78-year-old patient with pre-existing grade 1 lymphopenia). No other cases of progressive multifocal leukoencephalopathy with ocrelizumab had been reported up to April 30, 2020, when an estimated 158 000 patients with relapsing multiple sclerosis or primary progressive

multiple sclerosis had received ocrelizumab treatment for approximately 190 000 patient-years).

As with all open-label extension data, the absence of a control group is a study limitation. Similarly, the majority of study attrition occurred during the double-blind period, and the subsequent high open-label extension enrolment of 95% among those who completed the double-blind period—and low re-enrolment of those who did not—results in a survivor bias common to open-label extension assessments that might confound the generalisability of the results. Open-label treatment might also lead to bias, particularly regarding the interpretation and reporting of adverse events. Although these limitations should be acknowledged, multiple sclerosis is a chronic, gradually progressive illness that evolves over years, and long-term outcomes are arguably more relevant to people with multiple sclerosis than the short-term clinical trials. Although real-world observational data can help to describe such long-term treatment effects, the rigorous collection and documentation that occur in a clinical trial setting provide a more accurate characterisation of the clinically relevant effects and delay to meaningful milestones (eg, delay in time to requiring a wheelchair) that can be achieved with early and persistent ocrelizumab therapy in primary progressive multiple sclerosis. It is important to note that, although there was a continued benefit for patients who initiated ocrelizumab 3–5 study years earlier, subgroup analyses were not done on patients who were earlier on in their multiple sclerosis disease course.

In conclusion, the data through 6·5 study years of follow-up in the ORATORIO study show a consistent and sustained benefit of early and continuous ocrelizumab treatment on disease progression in primary progressive multiple sclerosis, as assessed by several outcome measures. Additionally, the safety profile of ocrelizumab over 6·5 study years in this patient group was reassuring and consistent with similar long-term data in relapsing multiple sclerosis.

Contributors

JSW wrote the original draft. JSW, DLA, H-PH, XM, AS, SH, LK, and SLH participated in the original study design, statistical analysis plan, data analysis, and data interpretation, and revised the manuscript. IB participated in data analysis and data interpretation, and revised the manuscript. BB, RTN, MM, JO, and HK participated in data interpretation and revised the manuscript. All authors read and approved the final manuscript.

Declaration of interests

JSW has received personal fees for consulting, serving on a scientific advisory board, speaking, or other activities with AbbVie, Actelion, Alkermes, Brainstorm Cell Therapeutics, Celgene, EMD Serono, GeNeuro, GW Pharma, MedDay Pharmaceuticals, NervGen Pharma, Novartis, Otsuka, PTC Therapeutics, Roche/Genentech, and Sanofi Genzyme; and royalties for out licensed monoclonal antibodies through UTHealth from Millipore Corporation. DLA has received personal fees for consulting from Acorda, Albert Charitable Trust, Biogen, Celgene, F Hoffmann-La Roche, GeNeuro, Frequency Therapeutics, MedDay Pharmaceuticals, Merck Serono, Novartis, Sanofi-Aventis, and Wave Life Sciences; grants from Biogen, Immunotec, and Novartis; and an equity interest in NeuroRx Research. BB has received research support, personal fees for consulting, serving on a scientific advisory board, or other activities from Bayer, Celgene, Merck, Genzyme, Biogen, Novartis, Roche, Actelion, and MedDay Pharmaceuticals. H-PH has received honoraria for consulting, serving on steering committees, and speaking at scientific symposia with approval from the Rector of Heinrich Heine University Düsseldorf from Bayer Healthcare, Biogen, Celgene Receptos, F Hoffmann-La Roche, GeNeuro SA, MedImmune, Merck, Novartis, Octapharma, Teva, TG Therapeutics, and VielaBio. XM has received speaker honoraria and travel expense reimbursement for participation in scientific meetings, has been a steering committee member of clinical trials, and has served on advisory boards of clinical trials for Actelion, Biogen, Celgene, Excemed, Merck Serono, Novartis, F Hoffmann-La Roche, Sanofi Genzyme, and Teva Pharmaceutical; and has received non-financial support from the National Multiple Sclerosis Society and the Multiple Sclerosis International Foundation. RTN has consulted for Alkermes, Bayer AG, Biogen, Celgene, EMD Serono, Genentech, Genzyme, Lundbeck, NervGen, Novartis, TG Therapeutics, Third Rock Ventures, and Viela Bio. MM, HK, AS, IB, and SH are employees and shareholders of F Hoffmann-La Roche. JO is an employee and shareholder of F Hoffmann-La Roche; and has previously received personal fees for consulting or a grant from Biogen, Celgene, and Teva. LK has received research support in the last 3 years to their institution (University Hospital Basel) via steering committee, advisory board, and consultancy fees from Actelion, Allergan, Almirall, Bayer Healthcare, Baxalta, Biogen, Celgene Receptos, CSL Behring, Desitin, Eisai, Excemed, Genzyme, Japan Tobacco, Merck, Novartis, Pfizer, Roche, Sanofi, Santhera, and Teva; licence fees for Neurostatus-UHB products; and grants from Bayer, Biogen, Novartis, the Swiss MS Society, the Swiss National Research Foundation, Innosuisse, and the European Union and Roche Research Foundation to the Research of the MS Center in Basel. SLH serves on the board of trustees for Neurona and on scientific advisory boards for Annexon, Molecular Stethoscope, Bionure and Alector; and has received travel reimbursement and writing assistance from F Hoffmann-La Roche and Novartis AG for CD20-related meetings and presentations.

Data sharing

Qualified researchers can request access to individual patient level data through the clinical study data request platform. Further details about Roche's criteria for eligible studies are available online. Further details on Roche's global policy on the sharing of clinical information and how to request access to related clinical study documents are found online.

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For **Roche's global policy on the sharing of clinical information and how to request access** 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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