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Five-years of ocrelizumab in relapsing multiple sclerosis: OPERA studies open-label extension

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Abstract

Objective

To assess over 3 years of follow-up, the effects of maintaining or switching to ocrelizumab (OCR) therapy on clinical and MRI outcomes and safety measures in the open-label extension (OLE) phase of the pooled OPERA studies in relapsing multiple sclerosis.

Methods

After 2 years of double-blind, controlled treatment, patients continued OCR (600 mg infusions every 24 weeks) or switched from interferon (IFN) β -1a (44 μ g 3 times weekly) to OCR when entering the OLE phase (3 years). Adjusted annualized relapse rate, time to onset of 24-week confirmed disability progression/improvement (CDP/CDI), brain MRI activity (gadolinium-enhanced and new/enlarging T2 lesions), and percentage brain volume change were analyzed.

Results

Of patients entering the OLE phase, 88.6% completed Year 5. The cumulative proportion with 24-week CDP was lower in patients who initiated OCR earlier, vs patients initially receiving IFN β -1a (16.1% vs 21.3% at Year 5; $p=0.014$). Patients continuing OCR maintained, and those switching from IFN β -1a to OCR attained near complete and sustained suppression of new brain MRI lesion activity from Year 3 to 5. Over the OLE phase, patients continuing OCR exhibited less whole brain volume loss from double-blind study baseline vs those switching from IFN β -1a (–1.87% vs –2.15% at Year 5; $p<0.01$). Adverse events were consistent with past reports and no new safety signals emerged with prolonged treatment.

Conclusion

Compared with patients switching from IFN β -1a, earlier and continuous OCR treatment up to 5 years provided sustained benefit on clinical and MRI measures of disease progression.

Clinical Trial Identifier Numbers

NCT01247324/NCT01412333

Classification of evidence

This study provides Class III evidence that earlier and continuous treatment with ocrelizumab provided sustained benefit on clinical and MRI outcomes of disease activity and progression compared with patients switching from IFN β -1a. The study is rated Class III because of the initial treatment randomization disclosure that occurred after inclusion in OLE.

Introduction

Ocrelizumab (OCR) is a humanized monoclonal antibody that selectively targets CD20+ B cells, while preserving the capacity for B-cell reconstitution and pre-existing humoral immunity.^{1,2} In Phase III randomized, double-blind, double-dummy trials with identical designs (OPERA I [NCT01247324] and OPERA II [NCT01412333]) in relapsing multiple sclerosis (RMS), OCR demonstrated superior efficacy for preventing relapses and disability worsening, and a higher rate of disability improvement, compared with subcutaneous interferon (IFN) β -1a given 3 times weekly.³ Significant benefits of OCR on MRI outcomes, including the reduction of the number of gadolinium-enhancing T1 lesions, new or newly enlarged hyperintense T2 lesions, new hypointense T1 lesions, and brain volume loss (baseline to Week 96) were also reported.³ Here, we report the interim efficacy and safety results of OCR over the 3-year follow-up in the open-label extension (OLE) phase of Phase III trials in patients with RMS (5 years of total follow-up).

Methods

Trial design and patients

As previously detailed,³ OPERA I (NCT01247324) and OPERA II (NCT01412333) were Phase III, multicenter, randomized, double-blind, double-dummy, IFN β -1a controlled trials with identical designs, of OCR in patients with RMS (data available from Dryad, figure e-1, <https://doi.org/10.5061/dryad.stqjq2bzw>). Key eligibility criteria included an age of 18 to 55 years, diagnosis of multiple sclerosis (MS; 2010 revised McDonald criteria)⁴ and screening Expanded Disability Status Scale (EDSS) score of 0 to 5.5. Consistency of baseline characteristics and treatment effects across both OPERA studies met pre-determined criteria for pooled efficacy analysis, including annualized relapse rate (ARR) and confirmed disability progression (CDP).³ Following completion of the double-blind controlled treatment phase (DBP) of both trials, patients meeting specific criteria (data available from Dryad, supplemental data, <https://doi.org/10.5061/dryad.stqjq2bzw>) were eligible to enter an OLE phase to evaluate the long-term safety, tolerability, and efficacy of OCR in RMS; patients who declined or who were not eligible (since there was an OLE screening phase) to participate in the OLE phase entered safety follow-up. Patients entering the OLE phase first entered the OLE screening phase, which lasted up to 4 weeks. At the start of the OLE phase, patients who received OCR in the DBP continued OCR and patients from the IFN β -1a group were switched to OCR, given every 24 weeks; in order to maintain blinding and in accordance with the start of the DBP, all patients received the first dose of OCR as 2 separate 300 mg infusions, 2 weeks apart. Patient treatment allocation was unblinded after the last data point from

the last patient from the DBP was received. The 96-week core studies were conducted between 2011 and 2015. The first patient completing the DBP entered the OLE phase in August 2013; the last ongoing patient entered the OLE phase in February 2015. The clinical cut-off date for inclusion of data in this analysis was February 5, 2018. The OLE phase is planned until December 2020, with the collection of data for up to 8 years.

Standard Protocol Approvals, Registrations, and Patient Consents

The relevant institutional review boards/ethics committees approved the trial protocols (NCT01247324 and NCT01412333). All patients provided written informed consent.

Classification of evidence

This study provides Class III evidence that earlier and continuous treatment with ocrelizumab provided sustained benefit on clinical and MRI outcomes of disease activity and progression compared with patients switching from IFN β -1a. The study is rated Class III because of the initial treatment randomization disclosure that occurred after inclusion in OLE.

Efficacy assessments

The following endpoints, which were also measured during the 96-week DBP, are reported for the OLE phase, using the pooled OPERA trial population:

Annualized relapse rate: the ARR was calculated as the total number of protocol-defined relapses (occurrence of new or worsening neurologic symptoms [consistent with an increase of at least half a step on the EDSS score, or 2 points on one of the appropriate Functional Systems Score (FSS), or 1 point on 2 or more of the

appropriate FSS] that were attributable to MS) for all patients in the treatment group divided by the total patient-years (PY) of exposure to that treatment.

24-week confirmed disability progression/improvement: CDP was defined as an increase in the EDSS score from the baseline of the DBP or of the OLE phase of at least 1.0 point (increase of ≥ 0.5 points if baseline EDSS score > 5.5); confirmed disability improvement (CDI) was defined as a reduction in EDSS score ≥ 1.0 point compared with baseline of the DBP or of the OLE phase (reduction of ≥ 0.5 point if baseline EDSS score > 5.5). For analyses based on the OLE phase only, a re-baseline of EDSS was performed for all patients, including those who had an event of CDP/CDI during the DBP. All analyses from the DBP baseline were based on the intention-to-treat (ITT) population, except for CDI which was performed in the prespecified sub-group of the ITT population with EDSS ≥ 2.0 . All analyses from OLE baseline were based on the OLE population with treatment group assignment based on the originally randomized treatment, except for CDI which was performed in the prespecified sub-group of the OLE population with EDSS ≥ 2.0 . For both CDP and CDI, re-baselining at the start of OLE provides a representation of efficacy during the OLE period unconfounded by any disease activity during the DBP, hence values for the proportion of patients with events during DBP and re-baselined OLE may not correspond with those of the combined DBP and OLE period.

Mean change from baseline in EDSS score: mean change from baseline in EDSS score was assessed at scheduled visits during the DBP and the OLE phase.

Acute brain MRI lesion activity: the total number of new or newly enlarged T2 lesions and total number of T1 gadolinium-enhancing lesions on brain MRI was assessed every 48 weeks in the OLE phase.

Brain volume change: percentage change in whole brain volume (WBV) assessed using SIENA/X.⁵ Percent change in cortical gray matter volume (GMV) and white matter volume (WMV) assessed using paired Jacobian integration.⁶ All analyses from the DBP baseline were based on the ITT population. All analyses from OLE baseline were based on the OLE population with treatment group assignment based on the originally randomized treatment.

No evidence of disease activity (NEDA): NEDA status was defined as the combined absence of: protocol-defined relapses; 24-week CDP; new or enlarging T2 lesions; and T1 gadolinium-enhancing lesions.

Safety

All patients who received any study treatment were included in the safety population. All data collected during the DBP and OLE and the safety follow-up were included in the safety analyses. Safety outcomes are reported for the OLE phase using the pooled OPERA I and OPERA II ITT population.

Statistical analyses

ARR was analyzed with the use of a GEE Poisson regression model in the ITT population. CDP/CDI at 24 weeks were assessed using Kaplan–Meier and Cox survival analysis in the ITT population and for CDI, in patients with a baseline EDSS score of ≥ 2.0 ; hazard ratios were estimated by stratified Cox regression. Mean change from baseline in EDSS score was analyzed using the mixed-effect model of repeated measures (MMRM). The number of new T1 Gd-enhancing lesions and the number of new or enlarging T2 lesions were analyzed using a negative binomial model; in previously reported analysis³ of lesion outcomes during the DBP, results were adjusted for baseline T2 lesion volume, baseline EDSS score (≤ 2.5 vs > 2.5),

and geographic region (United States vs rest of the world). However, as patients had no new T1 Gd-enhancing lesions/new or enlarging T2 lesions at several timepoints it was impossible to fit a statistical model, and unadjusted rates were adopted for the OLE instead. The change in WBV, GMV, and WMV was analyzed using the MMRM, adjusted for baseline WBV or GMV or WMV and baseline EDSS score (<4.0 vs ≥4.0), study, and geographic region (United States vs rest of the world). NEDA was analyzed using the Cochran–Mantel–Haenszel test stratified by study, geographic region (United States vs rest of the world), and baseline EDSS score (<4.0 vs ≥4.0) in a modified ITT population, which included all patients in the ITT population, but patients who discontinued treatment early for reasons other than lack of efficacy or death and had NEDA before early discontinuation were excluded. Safety outcomes are reported as incidence rates (events per 100 patient years exposure) with Poisson distribution-based confidence intervals.

Data Availability

Qualified researchers may request access to individual patient level data through the clinical study data request platform (www.clinicalstudydatarequest.com). Further details on Roche's criteria for eligible studies are available here:

<https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Roche.aspx>.

For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here:

https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm.

Results

Patient disposition, demographics, and disease characteristics

Patient disposition and reasons for discontinuation are shown in figure 1 by treatment group. More than 94% of patients in both groups who completed the DBP entered the OLE phase. Of 827 patients treated with OCR during the DBP, 702 (84.9%) entered the OLE phase and 623 (75.3%) remained at Year 5. Of the 829 patients treated with IFN β -1a in the DBP, 623 (75.2%) entered the OLE phase and 551 (66.5%) remained at Year 5. Overall, 1,174 of 1,325 patients (89%) who entered the OLE phase of the OPERA studies completed Year 5, representing 71% of the originally enrolled population (N=1,656). Patient demographics and disease characteristics for the pooled studies at baseline of the DBP and at the start of the OLE phase were well balanced between treatment arms and between the ITT population and those patients with a baseline EDSS score of ≥ 2.0 (table 1). The number of OCR doses received (mean $\pm$ SD; median [range]) in the OLE phase population was 7.3 ± 2.0 ; 8.0 (1–10) for continuous OCR patients and 7.4 ± 1.9 ; 8.0 (1–10) in patients switching from IFN β -1a to OCR.

Clinical efficacy assessments

Patients receiving continuous OCR maintained a low ARR through Year 1 to Year 5 (0.14, 0.13, 0.10, 0.08, and 0.07; figure 2). Switching from IFN β -1a to OCR at the start of the OLE phase was associated with a significant reduction in ARR (0.20 in Year 2 to 0.10 in Year 3; adjusted rate ratio [95% CI]: 2.069 [1.547, 2.766], $p < 0.001$; 52% relative reduction) which was maintained through Years 4 and 5 (0.08 and 0.07; figure 2). In the OLE phase, there was no difference in ARR at Years 3, 4, and

5 in patients receiving continuous OCR compared with those switching from IFN β -1a ($p>0.5$, all comparisons; figure 2).

Over the duration of the DBP and OLE periods, timepoint analysis demonstrated that the proportion of patients with 24-week CDP from baseline remained significantly lower in patients receiving continuous OCR compared with those switching from IFN β -1a to OCR at the end of the DBP (Year 2: 7.7% vs 12.0%; $p=0.005$), at the end of Year 3 (10.1% vs 15.6%; $p=0.002$), at the end of Year 4 (13.9% vs 18.1%; $p=0.03$), and at the end of Year 5 (16.1% vs 21.3%; $p=0.014$; figure 3A). The hazard ratio for patients receiving continuous OCR compared with those switching from IFN β -1a to OCR for time to first 24-week CDP during the DBP was 0.60 (95% CI 0.43–0.84; $p=0.003$); after re-baselining at the end of the DBP (i.e. start of the OLE), the hazard ratio during the OLE phase was 1.06 (95% CI 0.8–1.41; $p=0.7$) (data available from Dryad, figure e-2A, <https://doi.org/10.5061/dryad.stjq2bzw>).

The proportion of patients with 24-week CDI over the duration of the DBP and OLE periods (figure 3B) in patients with a baseline EDSS score of ≥ 2.0 was numerically higher in patients receiving continuous OCR compared with those switching from IFN β -1a to OCR at the end of the DBP (Year 2: 16.8% vs 13.3%; $p=0.099$), at the end of Year 3 (20.6% vs 16.6%; $p=0.089$), at the end of Year 4 (23.7% vs 18.9%; $p=0.057$), and at the end of Year 5 (25.8% vs 20.6%; $p=0.046$). The hazard ratio for improvement (time to first 24-week CDI) from BL to the end of the DBP in patients receiving continuous OCR compared with those switching from IFN β -1a to OCR was 1.31 (95% CI 0.96–1.78; $p=0.06$; figure 3B); after re-baselining at the end of the DBP (i.e. start of the OLE), the hazard ratio during the OLE phase was 0.89 (95% CI

0.61–1.31; $p=0.6$) (data available from Dryad, figure e-2B, <https://doi.org/10.5061/dryad.stqjq2bzw>).

Patients continuing OCR had a lower mean change from baseline in EDSS score compared with patients switching from IFN β -1a to OCR, at the end of the DBP (Year 2: -0.146 vs 0.032 ; $p<0.001$), during Year 3 (-0.118 vs 0.010 ; $p=0.008$), during Year 4 (-0.057 vs 0.041 ; $p=0.06$), and during Year 5 (-0.043 vs 0.058 ; $p=0.07$) (data available from Dryad, figure e-3, <https://doi.org/10.5061/dryad.stqjq2bzw>).

MRI efficacy assessments

Patients receiving continuous OCR maintained the near complete suppression of MRI disease activity seen in the DBP through to Year 5 (figure 4A and 4B): the unadjusted rate of total T1 Gd-enhancing lesions was 0.017 at the end of the DBP (for Year 2 only), 0.005 at Year 3, 0.017 at Year 4, and 0.006 at Year 5; and for new or newly enlarged T2 lesions the unadjusted rate was 0.063 over Year 2, 0.091 over Year 3, 0.080 over Year 4, and 0.031 over Year 5. Patients switching from IFN β -1a to OCR had almost complete and sustained suppression of MRI lesion disease activity from Year 3 to Year 5 (figure 4A and 4B): the unadjusted rate of total T1 Gd-enhancing lesions was 0.491 at the end of the DBP (Year 2), decreasing to 0.007 at Year 3, 0.004 at Year 4, and 0.004 at Year 5; and for new or enlarging T2 lesions the unadjusted rate was 2.583 over the duration of Year 2, decreasing to 0.371 over Year 3, 0.063 over Year 4, and 0.038 over Year 5. In the OLE phase, there was no difference in MRI lesion counts at Years 3, 4, and 5 in patients receiving continuous OCR compared with those switching from IFN β -1a ($p>0.5$, all comparisons; figure 4), except for new or enlarging T2 lesions at Year 3 where the number was lower in

patients receiving continuous OCR compared with those switching from IFN β -1a (0.091 vs 0.371; $p<0.001$; figure 4B).

At 5 years (OLE Year 3), patients treated continuously with OCR compared with those switching from IFN β -1a to OCR, experienced significantly lower brain atrophy measured by change from DBP baseline in WBV, cortical GMV and WMV (adjusted rate: WBV -1.87% vs -2.15% , cGMV -2.02% vs -2.25% and WMV -1.33% vs -1.62% ; $p<0.01$ for all comparisons; figure 5A1, 5B1, and 5C1). Similarly, significant differences between patients treated continuously with OCR compared with patients switching from IFN β -1a to OCR were seen at Year 2, 3 and 4 for change from baseline in WBV, cortical GMV and WMV (adjusted rates: $p\leq 0.01$ for all comparisons; figure 5A1, 5B1, and 5C1), except for cortical GMV at Year 3 where no difference was found (adjusted rate: -1.47 vs -1.56% ; $p=0.155$; figure 5B1). When expressed as annualised percent change in volume occurring during the preceding 48 weeks the adjusted rates were generally stable during the OLE phase for patients switching from IFN β -1a to OCR and those continuing OCR (figure 5A2, 5B2, and 5C2).

NEDA in the OLE

In patients treated with OCR compared with IFN β -1a, the relative proportion of patients with NEDA was increased by 74% in the DBP (OCR 48.5% [$n=369/761$] vs IFN β -1a 27.8% [$n=210/756$]; $p<0.001$) and by 88% over the duration of the DBP and OLE periods (OCR 35.7% [$n=255/715$] vs IFN β -1a/OCR 19.0% [$n=140/738$]; $p<0.001$). During the OLE period alone, the proportion of patients with NEDA was 65.4% ($n=409/625$) in patients treated continuously with OCR compared with 55.1%

($n=310/563$) in those switching from IFN β -1a to OCR, a relative difference of 19% ($p<0.001$).

Safety in the OLE

Table 2 summarizes the safety analyses in all patients treated with OCR over a period of 5 years, which includes patients treated continuously with OCR (5 years) and patients switched from IFN β -1a (3 years). As of February 2018, 1,448 patients with MS received OCR during the DBP and associated OLE periods of the OPERA trials. The rate of adverse events (AEs) in the overall OCR exposure population was 220 (95% CI 217–224) per 100 PY; lower than the rate observed at the primary DBP analysis cut-off date (May 2015) for each group (events per 100 PY [95% CI], IFN β -1a: 296 [287–305]; OCR 290 [281–299]). The most common AEs included infusion-related reactions, urinary tract infections (UTIs), and upper respiratory tract infections. Overall, the rate of serious AEs was 6.1 (95% CI 5.5–6.8) events per 100 PY, consistent with the rate observed at the primary analysis cut-off date for each group (IFN β -1a: 6.29 [5.05–7.75]; OCR: 5.39 [4.26–6.72]). The rate of infections per 100 PY was 75.3 (95% CI 73.1–77.6), consistent with the rate observed at the primary analysis cut-off date for each group (IFN β -1a: 67.8 [95% CI 63.5–72.2]; OCR: 84.5 [95% CI 79.9–89.4]).

The most common serious AEs were classified as infections, which occurred at a rate 1.5 per 100 PY [95% CI 1.2–1.8] over the 5-year period, and this was similar to the rate observed at the primary analysis cut-off date (IFN β -1a: 1.79 [1.16–2.64]; OCR: 0.83 [0.43–1.45]). The most common serious infections were UTIs and pneumonia. Two potential serious opportunistic infections were reported in the OLE period; both patients recovered with treatment by standard therapies (systemic

Pasteurella infection in a patient with RMS following a cat bite; enterovirus-induced fulminant hepatitis in a diabetic patient with RMS, resulting in liver transplant). As of end of April 2019, no cases of progressive multifocal leukoencephalopathy (PML) were identified in the overall OCR exposure population for the pooled OPERA studies. The crude incidence rate of all malignancies per 100 PY in the overall OCR exposure population was 0.40 (0.26–0.61), and at the primary analysis cut-off date the incidence rate for IFN β -1a was 0.14 (0.02–0.52) and for OCR was 0.28 (0.08–0.71). A list of malignancies from the DBP and OLE phase of the pooled OPERA studies as of February 2018 is provided in the supplemental data (available from Dryad, supplemental data, <https://doi.org/10.5061/dryad.stqjq2bzw>).

The rate per 100 PY of AEs leading to treatment withdrawals in the overall OCR exposure population (Year 5: 1.36 [95% CI 1.08–1.70]) did not increase over time (rate observed at the primary analysis cut-off date: IFN β -1a: 3.93 [2.96–5.12]; OCR: 2.35 [1.63–3.28]).

Over 5 study years in the pooled OPERA study population, a reduction in serum immunoglobulin levels was observed. At baseline, the number (%) of patients with immunoglobulin concentrations below the lower limit of normal (LLN) were: 7 (0.5%) for IgG, 17 (1.2%) for IgA, and 7 (0.5%) for IgM. Over 5 study years, for the majority of patients, immunoglobulin levels remained above the LLN (data available from Dryad, Table e-1, <https://doi.org/10.5061/dryad.stqjq2bzw>); the number (%) of patients with a decrease below the LLN at Year 5 were: 33 (5.4%) for IgG, 31 (5.1%) for IgA, and 164 (29.5) for IgM.

Discussion

These interim results from the OPERA extension study provide several important insights on the efficacy and safety of long-term (up to 5 years) treatment with OCR in patients with relapsing MS. The low levels of disease activity observed in patients treated with OCR during the 2-year controlled period³ were sustained from Years 3 to 5, suggesting a benefit of earlier treatment and persistence of the effect with maintained therapy. In patients who switched from IFN β -1a, OCR consistently led to a rapid decrease in relapse activity and an almost complete suppression of MRI activity. Disability accrual occurred at similarly low rates in the 2 groups during the OLE phase but, at the end of Year 5, the proportion of patients with confirmed disability progression from BL of the DBP was lower in those originally treated with OCR. The safety profile observed in Years 3 to 5 was generally consistent with that observed during the controlled period, with no additional safety findings that suggest potential deleterious effects of long-term exposure to OCR.

In patients treated early and continuously with OCR, consistent and persistent effects were evident on clinical and MRI measures of inflammatory disease activity. ARR remained low over 5 years. Consistent with the effects on relapses, the near complete suppression of subclinical disease activity, as measured by MRI, observed in the DBP was maintained throughout the OLE phase, with few patients exhibiting either T1 gadolinium-enhancing lesions (0.006 lesions per scan) or new/enlarging T2 lesions (0.031 lesions per scan) at the end of Year 5. Patients who started OCR after switching from IFN β -1a experienced significant decreases in levels of disease

activity, with relapse rates and lesion counts becoming similar to those observed in patients on early and continuous OCR at Year 3 and consistently maintained through to Year 5. The effect of OCR in reducing the relapse rate is of particular relevance to the long-term prognosis, as natural history and long-term follow-up studies of MS disease-modifying therapies (DMTs) show that more frequent relapses early in the disease course, and relapses occurring over the 2- to 3-year interval of a randomized clinical trial, are associated with adverse long-term disability outcomes.⁷

The benefits of earlier and sustained OCR treatment for measures of disease progression were evidenced by lower levels of clinically evaluated CDP, with only 16.1% of patients who continued OCR experiencing 24-week CDP at the end of the OLE phase (Year 5). In patients who switched from IFN β -1a, a treatment effect of OCR was observed starting in the first year of the OLE, leading to rates of disability progression similar to those seen in patients continuing OCR in the OLE phase. However, a higher proportion of IFN β -1a-treated patients experienced 24-week CDP by the end of the OLE phase (Year 5). Those patients who initiated OCR 2 years earlier accrued significantly less disability progression compared with those switched from IFN β -1a (16.1% vs 21.3%). Similarly, by the end of the OLE phase (Year 5), a significantly higher proportion of patients initiating OCR 2 years earlier achieved improvements in disability compared with patients switching from IFN β -1a (25.8% vs 20.6%). These results add to the body of evidence that early high-efficacy treatment is more favorable than the traditional escalation approach. A recent observational study demonstrated that patients commencing high-efficacy DMTs, including OCR, early after disease onset accumulate less long-term disability compared with those exposed later in their disease.⁸⁻¹¹

OCR also slowed the rate of brain volume loss. At 5 years from DBP baseline, patients on early and continuous OCR experienced lower WBV loss during the DBP compared with IFN β -1a, and the difference between the 2 groups was maintained throughout the OLE phase. The beneficial effect was also observed in both the white matter and cortical gray matter compartments, with the exception of cortical GMV at Year 3 where the absence of a difference might be due to the reversal of pseudoatrophy affecting gray matter in patients switching from IFN β -1a to OCR.¹² In patients with MS, a parenchymal loss of $\geq 0.4\%$ per year ($\geq 2.0\%$ over a 5-year period) has been proposed as a pathological atrophy rate.¹³ The 5-year cumulative WBV loss from DBP baseline in patients treated early and continuously with OCR (-1.87%) was lower than in those that switched from IFN β -1a (-2.15%). Taken together our findings converge in demonstrating that patients with relapsing MS who start later with high efficacy treatment do not catch up on clinical and MRI outcomes reflecting residual functional loss and tissue damage.

The durable efficacy of OCR across multiple endpoints, with an early impact not only on clinical and MRI measures of inflammation but also on disease progression, was accompanied by a safety profile consistent with previous reports.³ This was reflected in the low on-study attrition rates, where almost 90% of all patients who entered the OLE phase completed Year 5, indicating that OCR was generally well tolerated. The reported rates of AEs per 100 PY with OCR during the OLE out to Year 5 continue to be generally consistent with those seen during the DBP in patients with RMS. Consistent with results of previously reported trials,^{3,14} the incidence rates of malignancies in patients treated with OCR remain within the range of placebo data from clinical trials in MS and epidemiological data for this patient population.^{15,14} A

small increase in serious infections has been previously reported during OLE observations in PPMS patients treated with OCR.¹⁶ No cases of PML occurred in the controlled treatment period of the OCR MS clinical trials (pivotal Phase III studies and the Phase II study) and to date, no cases have been observed in the ongoing OLE of these studies or in the other ongoing MS clinical trials. Outside of clinical trials, as of October 2019, there have been 8 confirmed cases of PML in patients with MS treated with OCR: 7 cases of probable carry-over PML (6 switching from natalizumab, 1 from fingolimod); in one case, the patient had not been treated with other DMTs but had contributing risk factors for PML, including old age (78 years) and pre-existing grade 1 lymphopenia (which worsened to grade 2 during treatment). No other PML cases with OCR have been reported to date (based on drug product sales as of October 2019, where an estimated 130,000 patients with RMS and PPMS have received OCR treatment for approximately 140,000 PY).¹⁶ The observed decrease in immunoglobulin levels and potential implications for patient safety, such as serious infections, needs to be considered in the context of longer follow-up data.

As with other extension studies of DMTs, definitive conclusions related to efficacy outcomes are limited by the absence of a control arm, and the influence of regression to the mean, which has been described in MS studies, cannot be excluded.¹⁷ As blinding was not maintained in the OLE phase, some rater assessment bias could have been introduced, although EDSS raters continue to be blinded to all other procedures, and MRI interpretation remains masked in the OLE phase. There is a possibility of selection bias given that participation in the extension was voluntary. However, this is unlikely to be significant as over 94% of patients in both groups who completed the DBP entered the OLE, with 88% of these patients

completing Year 5. It should also be noted that the disease duration at baseline for the majority of the patients enrolled in the OPERA I/II studies was longer than the five years defined in one study as the threshold for early MS,¹⁸ however the duration was typical of other clinical trials in the higher-efficacy DMT era. The long-term outcome of ocrelizumab therapy in patient populations with earlier MS disease course requires further study.

Studies that demonstrate the maintenance of long-term efficacy and safety of DMTs are valuable since patients with MS need to receive DMTs over the long term. The results of this analysis of 5-year data from the DBP and OLE of the pooled OPERA studies underscore persistence of the OCR treatment effect and suggest that early and continuous treatment provides sustained long-term benefit. These and other data support the early use of highly effective therapies that impact clinical and MRI measures of disease activity and progression in RMS to optimize short- and long-term patient outcomes.¹⁹

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Appendices

Appendix 1: Authors

Name	Location	Contribution
Stephen Hauser, MD	University of California, San Francisco, San Francisco, California	Design and conceptualized study; reviewed the data; drafted and revised the manuscript content
Ludwig Kappos, MD	University Hospital Basel, University of Basel, Basel	Design and conceptualized study; reviewed the data; drafted and revised the manuscript content
Douglas Arnold, MD	McGill University, Montreal, QC, Canada NeuroRx Research, Montreal, QC, Canada	Reviewed the data; drafted and revised the manuscript content
Amit Bar-Or, MD	University of Pennsylvania, Philadelphia	Drafted and revised the manuscript content
Bruno Brochet, MD	CHU de Bordeaux, Bordeaux, France	Drafted and revised the manuscript content
Robert Naismith, MD	Washington University School of Medicine, St. Louis, MO, USA	Drafted and revised the manuscript content
Anthony Traboulsee, MD	University of British Columbia, Vancouver, BC, Canada	Drafted and revised the manuscript content
Jerry Wolinsky, MD	McGovern Medical School, UTHealth, Texas	Design and conceptualized study; reviewed the data; drafted and revised the manuscript content
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Harold Koendgen, MD, PhD	F. Hoffmann-La Roche Ltd, Basel	Reviewed the data; drafted and revised the manuscript content
Victoria Levesque,	Genentech, Inc., South San Francisco, California	Drafted and revised the manuscript content

PhD		
Marianna Manfrini, MD	F. Hoffmann-La Roche Ltd, Basel	Drafted and revised the manuscript content
Fabian Model, PhD	F. Hoffmann-La Roche Ltd, Basel	Analyzed the data; drafted and revised the manuscript content
Stanislas Hubeaux, MSc	F. Hoffmann-La Roche Ltd, Basel	Analyzed the data; drafted and revised the manuscript content
Lahar Mehta, MD	Genentech, Inc., South San Francisco, California	Reviewed the data; drafted and revised the manuscript content
Xavier Montalban, MD, PhD	University of Toronto, Toronto, ON, Canada Vall d'Hebron University Hospital, Barcelona, Spain	Design and conceptualized study; reviewed the data; drafted and revised the manuscript content

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Table 1 Baseline demographics and disease characteristics for the pooled OPERA I and OPERA II populations at the start of the DBP and OLE

	DBP baseline		OLE baseline		DBP baseline EDSS score of ≥ 2.0		OLE baseline EDSS score of ≥ 2.0	
	IFN β -1a 44 μ g/ OCR 600 mg (n=829)	OCR 600 mg/ OCR 600 mg (n=827)	IFN β -1a 44 μ g/ OCR 600 mg (n=623)	OCR 600 mg/ OCR 600 mg (n=702)	IFN β -1a 44 μ g/ OCR 600 mg (n=614)	OCR 600 mg/ OCR 600 mg (n=628)	IFN β -1a 44 μ g/ OCR 600 mg (n=439)	OCR 600 mg/ OCR 600 mg (n=500)
Age, mean (SD), y	37.2 (9.2)	37.1 (9.2)	39.3 (9.2)	39.2 (9.1)	38.6 (9.0)	38.3 (9.3)	41.0 (9.0)	40.4 (9.3)
Female, n (%)	552 (66.6)	541 (65.4)	408 (65.5)	454 (64.7)	406 (66.1)	408 (65.0)	297 (67.7)	326 (65.2)
EDSS, mean (SD)	2.8 (1.3)	2.8 (1.3)	2.7 (1.5)	2.6 (1.3)	3.3 (1.1)	3.3 (1.0)	3.4 (1.3)	3.1 (1.0)
Pts with T1 Gd-enhancing lesions, n (%) ^a	327 (39.8) ^d	333 (40.7) ^e	106 (17.3) ^e	5 (0.7) ^g	233 (38.3) ^g	256 (41.2) ^d	77 (17.8) ^d	4 (0.8) ^l
No. T1 Gd-enhancing lesions, mean (SD) ^a	1.9 (5.0) ^d	1.8 (4.6) ^e	0.5 (2.1) ^e	0.02 (0.2) ^g	2.0 (5.3) ^g	1.8 (4.8) ^d	0.4 (1.4) ^d	0.02 (0.3) ^l
No. T1 hypointense lesions, mean (SD) ^b	32.9 (35.1) ^d	32.4 (35.2) ^e	35.6 (36.8) ^h	33.9 (36.1) ^h	36.9 (36.8) ^g	36.5 (37.4) ^d	39.8 (38.0) ^h	37.8 (38.4)

T2 hyperintense lesion volume, cm³, mean (SD)^c	10.2 (11.8) ^f	10.8 (14.1) ^f	9.4 (11.5) ⁱ	10.1 (13.8) ^j	11.3 (12.4) ^k	12.2 (15.0) ^f	10.6 (12.0) ^m	11.6 (15.1) ⁱ
No. T2 lesions, mean (SD)^b	51.0 (37.8) ^f	50.1 (38.8) ^f	55.5 (41.3)	50.9 (39.4)	53.9 (39.0) ^k	53.2 (39.8) ^f	59.3 (42.9)	53.2 (39.8)

Abbreviations: DBP = double-blind period; EDSS = Expanded Disability Status Scale; Gd = gadolinium; IFN = interferon; OCR = ocrelizumab; OLE = open-label extension; Pts = patients.

Demographics and disease characteristics at Week 96 of the DBP (clinical cut-off dates: OPERA I, April 2, 2015; OPERA II, May 12, 2015) are considered baseline for the OLE phase.

For MRI measurements: ^a OLE baseline is the assessment at Week 96; ^b OLE baseline is the sum of lesion counts at baseline, Week 24, Week 48, and Week 96.

^c OLE baseline is the last assessment prior to or at the start of OLE treatment.

Patients missing and excluded for calculating percentages: ^d n=7; ^e n=9; ^f n=5; ^g n=6; ^h n=1; ⁱ n=33; ^j n=44; ^k n=4; ^l n=3; ^m n=28.

Table 2 Adverse events, serious adverse events and adverse events leading to discontinuation during the DBP and OLE phase of the pooled OPERA I and OPERA II populations

Event	OPERA (pooled) controlled treatment period ^a		OPERA DBP/OLE ^b
	IFN β -1a rate per 100 PY (95% CI) ^c	OCR rate per 100 PY (95% CI) ^c	OCR rate per 100 PY (95% CI) ^c
Any adverse event^d	296 (287–305)	290 (281–299)	220 (217–224)
Adverse events leading to study treatment discontinuation	3.93 (2.96–5.12)	2.35 (1.63–3.28)	1.36 (1.08–1.70)
Infections and infestations^d	67.8 (63.5–72.2)	84.5 (79.9–89.4)	75.3 (73.1–77.6)
Urinary tract infection	9.7 (8.1–11.4)	11.6 (9.9–13.5)	11.7 (10.8–12.6)
Nasopharyngitis	8.3 (6.9–9.9)	13.0 (11.2–15.0)	11.0 (10.2–11.9)
Upper respiratory tract infection	9.4 (7.8–11.1)	13.3 (11.5–15.3)	12.6 (11.7–13.6)
Bronchitis	2.2 (1.5–3.1)	3.5 (2.6–4.6)	3.7 (3.2–4.2)
Influenza	3.3 (2.4–4.4)	3.1 (2.3–4.2)	2.7 (2.3–3.1)
Injury, poisoning and procedural complications^d	17.1 (15.0–19.4)	45.9 (42.4–49.5)	28.2 (26.8–29.6)
Infusion-related reactions	7.9 (6.5–9.5)	34.9 (31.9–38.1)	18.2 (17.1–19.3)
Nervous system	34.8 (31.8–38.0)	31.6 (28.8–34.7)	20.7 (19.5–21.9)

disorders^d			
Headache	12.4 (10.6–14.4)	9.5 (8.0–11.3)	4.7 (4.2–5.3)
Musculoskeletal and connective tissue disorders^d	25.0 (22.5–27.8)	24.3 (21.8–27.0)	18.8 (17.6–20.0)
Back pain	3.1 (2.2–4.1)	4.1 (3.1–5.3)	3.0 (2.6–3.5)
Arthralgia	3.9 (3.0–5.1)	3.5 (2.6–4.6)	2.8 (2.3–3.2)
Pain in extremity	2.9 (2.1–4.0)	3.7 (2.7–4.8)	2.3 (1.9–2.8)
General disorders and administration site conditions^d	51.3 (47.6–55.2)	17.3 (15.2–19.5)	10.6 (9.8–11.5)
Fatigue	5.7 (4.5–7.1)	5.4 (4.3–6.7)	3.5 (3.1–4.0)
Psychiatric disorders^d	14.2 (12.3–16.3)	14.4 (12.5–16.5)	8.5 (7.7–9.2)
Depression	4.2 (3.2–5.4)	4.9 (3.8–6.2)	2.9 (2.5–3.4)
Malignancies^{d,e,f}	0.14 (0.02–0.52)	0.28 (0.08–0.71)	0.40 (0.26–0.61)
Serious adverse events^d	6.29 (5.05–7.75)	5.39 (4.26–6.72)	6.1 (5.5–6.8)
Serious infections ^g	1.79 (1.16–2.64)	0.83 (0.43–1.45)	1.5 (1.2–1.8)
Number of potential serious OIs ^h	0	0	2
Fatalitiesⁱ	0.14 (0.02–0.52)	0.07 (0–0.38)	0.04 (0–0.13)

Abbreviations: CCOD = clinical cut-off date; DBP = double-blind period; IFN =

interferon; MedDRA = Medical Dictionary for Regulatory Activities; OCR =

ocrelizumab; OI = opportunistic infection; OLE = open-label extension; PY = patient

years; SOC = system organ class.

^a Includes patients who received IFN β -1a during the controlled treatment period of the OPERA I (CCOD April 2015) and OPERA II (CCOD May 2015) studies.

^b Includes patients who received any dose of OCR during the controlled treatment and associated OLE phase of the OPERA I and OPERA II studies; data from patients who were originally randomized to comparator (IFN β -1a) are included after the switch to open-label OCR treatment. CCOD for inclusion of data in this analysis was February 5, 2018.

^c Multiple occurrences of the same adverse event (except for malignancies) in one patient are counted multiple times.

^d Includes adverse events falling into the MedDRA versions 18.0 (OPERA [pooled] controlled treatment period) and 20.1 (CCOD: February 2018).

^e Malignancies are identified using adverse events falling into the standard MedDRA query 'Malignant tumours (narrow)'.

^f Reported as incidence rate per 100 PY of first malignancy.

^g Serious infections are defined using adverse events falling into the MedDRA SOC *Infections and Infestations*, and using 'Is the event non-serious or serious?' from the adverse event case report form.

^h Potential serious OIs were medically reviewed.

ⁱ A causal association between OCR and fatal events could not be established.

Figures

Figure 1 Patient disposition in the pooled OPERA I and OPERA II ITT population.

Percentages in parentheses are of the ITT population. ^a Clinical cut-off date:

February 5, 2018; patients entering the OLE phase who completed the DBP: IFN β -

1a 623/660 (94.4%) and OCR 702/726 (96.7%). ^b 88.4%, and ^c 88.7%, of patients

who entered the OLE completed Year 3. DBP = double-blind period; IFN =

interferon; ITT = intention-to-treat; OCR = ocrelizumab; OLE = open-label extension;

SFU = safety follow-up.

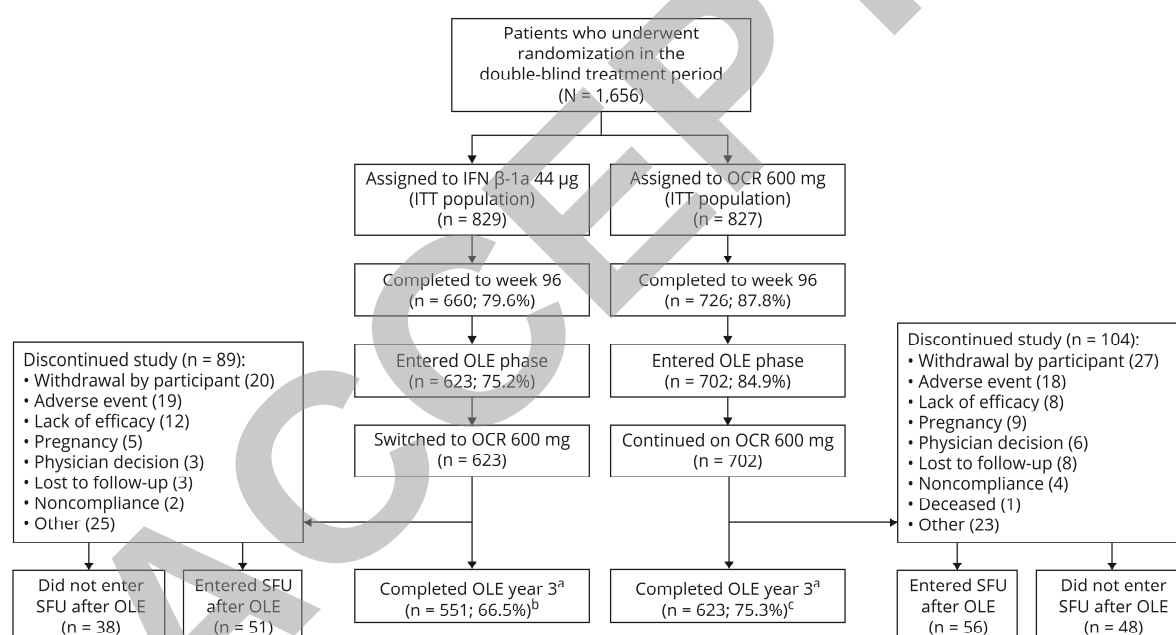


Figure 2 ARR in DBP study Years 1 and 2 and OLE Years 1–3.

Estimates are from analysis based on GEE Poisson regression model with repeated measurements using unstructured covariance matrix, adjusted by randomized treatment, study, baseline EDSS (<4.0 vs ≥4.0), geographical region (US vs ROW), year, and treatment-by-year interaction. Log-transformed exposure time is included as an offset variable. ^a The total number of relapses for all patients in the treatment group divided by the total patient years of exposure to that treatment. ^b DBP Year 1 and DBP Year 2 data include the ITT population (number of patients available); Year 3 (OLE Year 1), Year 4 (OLE Year 2), and Year 5 (OLE Year 3) data include the OLE ITT population (number of patients available). Clinical cut-off date: February 5, 2018. ARR = annualized relapse rate; DBP = double-blind period; EDSS = Expanded Disability Status Scale; IFN = interferon; ITT = intention-to-treat; OCR = ocrelizumab; OLE = open-label extension; ROW = rest of the world.

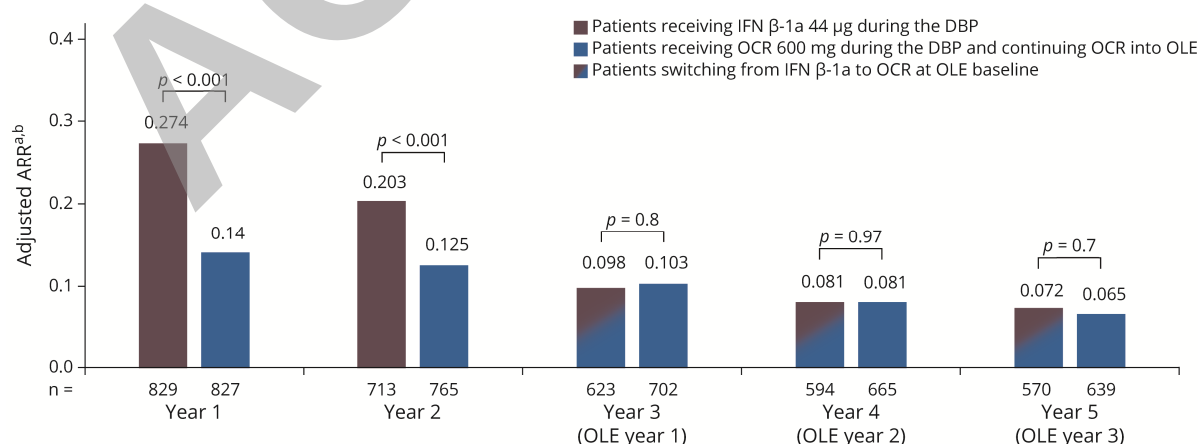


Figure 3 Time to onset of (A) CDP and (B) CDI for at least 24 weeks during DBP and OLE periods.

Curves show KM estimates of the proportion of patients with disability progression events relative to the original double-blind treatment period baseline throughout double-blind and open-label extension periods. Without imputation. ITT population. Pooled OPERA I and OPERA II population; DBP clinical cut-off dates: April 2, 2015 and May 12, 2015, respectively; OLE clinical cut-off date: February 5, 2018. Data shown up to Week 240, the last visit all ongoing patients completed. CDI = confirmed disability improvement; CDP = confirmed disability progression; DBP = double-blind period; EDSS = Expanded Disability Status Scale; HR = hazard ratio; IFN = interferon; ITT = intention-to-treat; OCR = ocrelizumab; OLE = open-label extension.

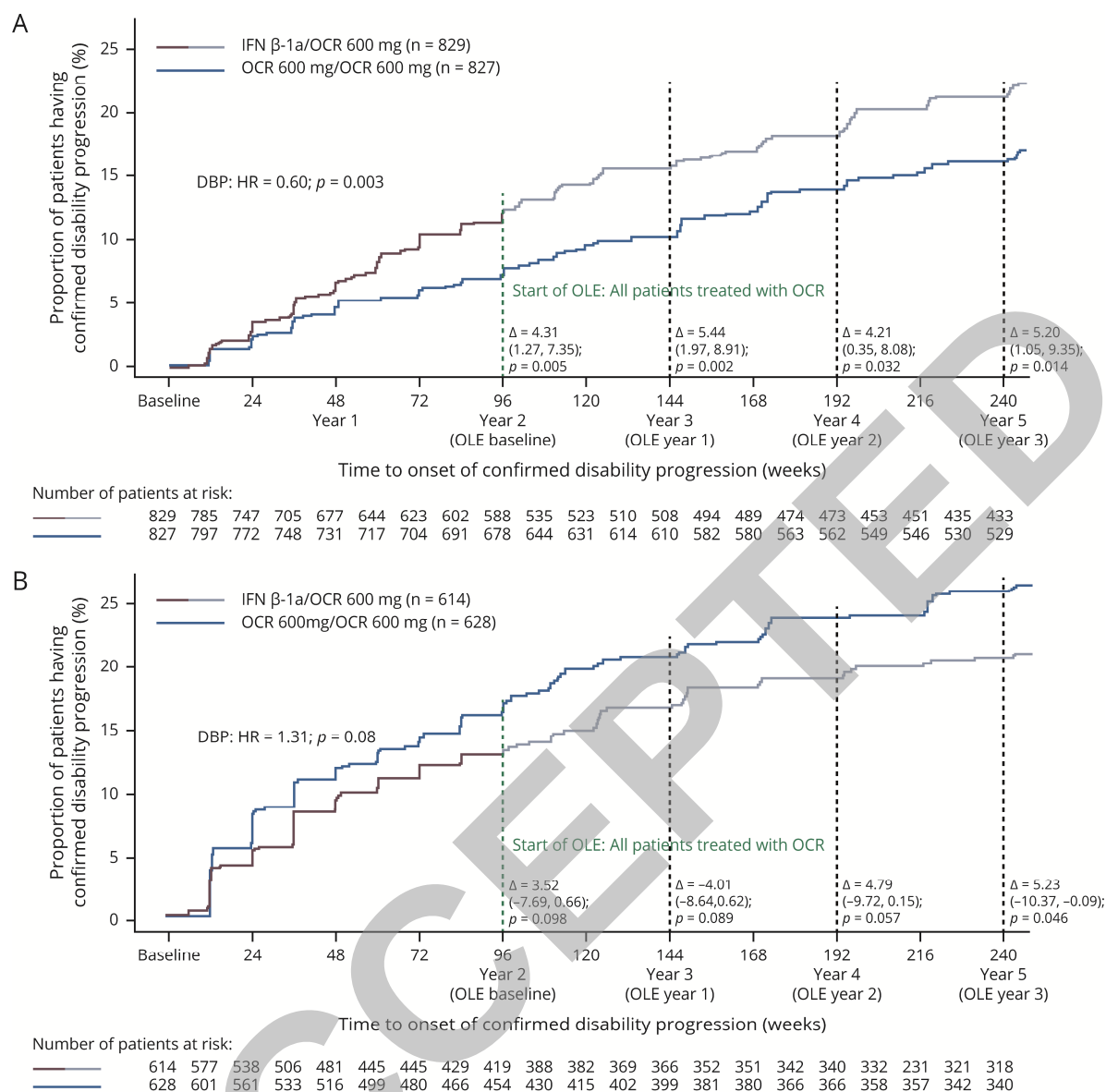


Figure 4 Total number of (A) T1 Gd-enhancing lesions and (B) new or enlarging T2 lesions in the DBP and OLE.

^a DBP Week 24, DBP Year 1 and DBP Year 2 data include the ITT population; Year 3 (OLE Year 1), Year 4 (OLE Year 2), and Year 5 (OLE Year 3) data include the OLE ITT population; clinical cut-off date: February 5, 2018. ^b Unadjusted rate.

DBP = double-blind period; Gd = gadolinium; IFN = interferon; ITT = intention-to-treat; OCR = ocrelizumab; OLE = open-label extension.

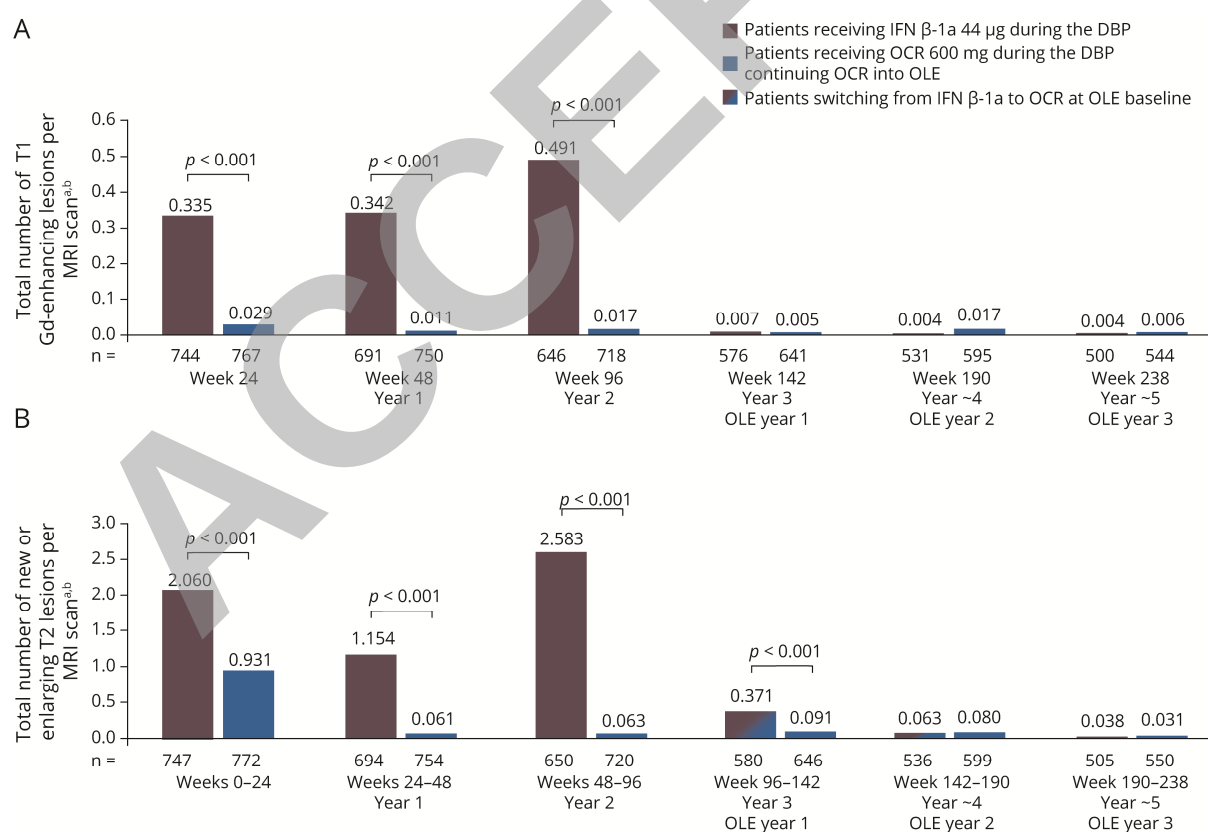
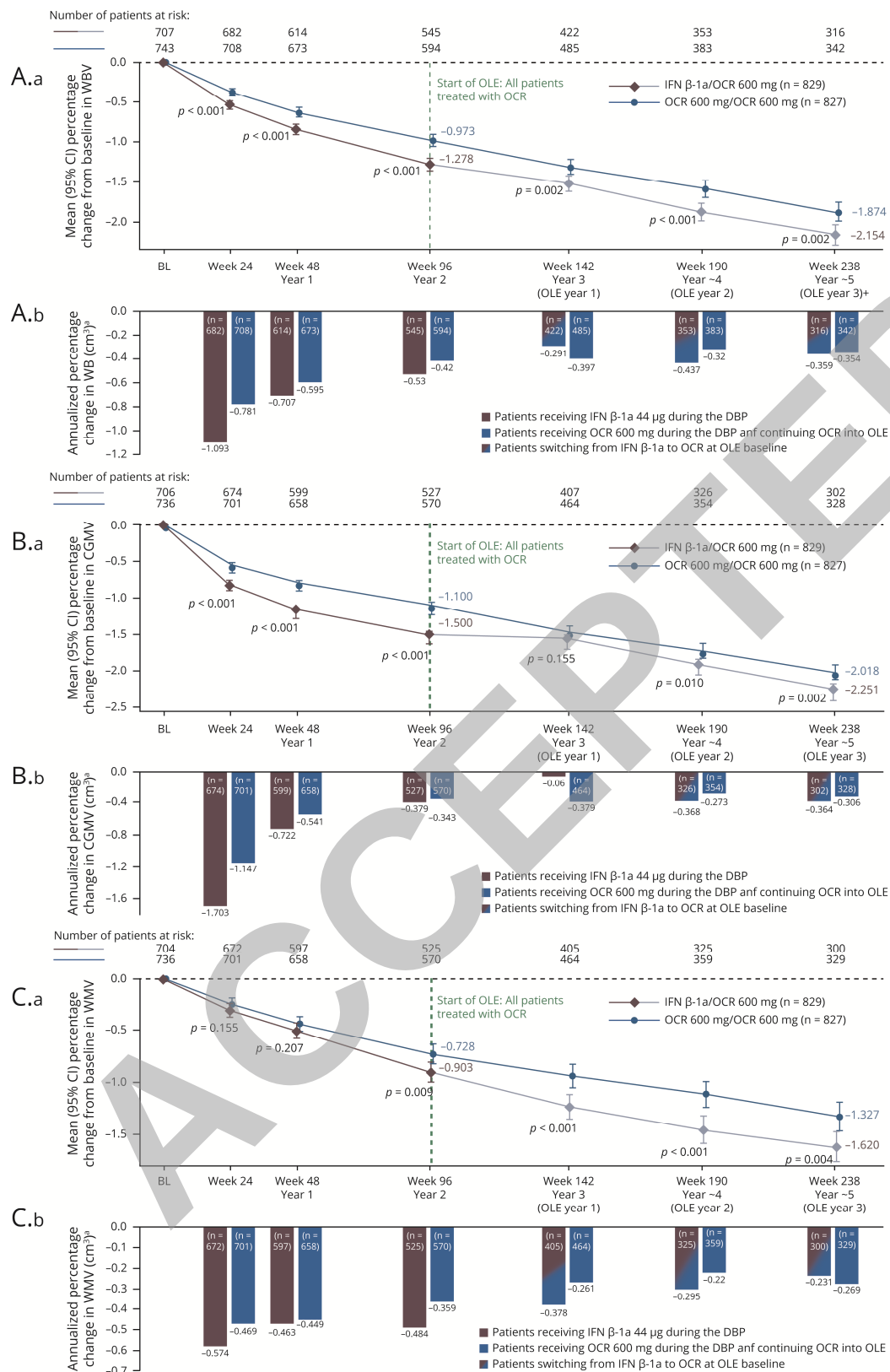


Figure 5 Percentage change (A.a, B.a, C.a, D.a) from baseline and (A.b, B.b, C.b, D.b) annualized, in A) WBV, B) CGMV, and C) WMV in the DBP and OLE.

MMRM plot, ITT population. Pooled OPERA I and OPERA II (clinical cut-off date: February 5, 2018); p values shown for difference in adjusted means. Graph includes patients with assessment at baseline and at least one post-baseline value. Estimates are from analysis based on MMRM using unstructured covariance matrix:

Percentage Change = Baseline Brain Volume + Geographical Region (US vs ROW) + Baseline EDSS (<4.0 vs ≥4.0) + Study + Week + Treatment + Treatment*Week (repeated values over Week) + Baseline Brain Volume*Week. a The bars represent the annualized change in WBV, CGMV, or WMV occurring during the time period delineated by the axis label and the preceding 24 or 48 weeks. BL = baseline; CGMV = cortical gray matter volume; DBP = double-blind period; EDSS = Expanded Disability Status Scale; IFN = interferon; ITT = intention-to-treat; MMRM = mixed-effect model of repeated measures; OCR = ocrelizumab; OLE = open-label extension; ROW = rest of world; WBV = whole brain volume; WMV = white matter volume.



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