# Brain MRI Activity and Atrophy in Ocrelizumab-Treated Relapsing Multiple Sclerosis Patients in the Open-Label Extension of the Pooled OPERA Trials


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## BACKGROUND

- 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 two identical Phase III randomized, double-blind, double-dummy trials (OPERA I [NCT01247324] and OPERA II [NCT01412333]) in relapsing multiple sclerosis (RMS), OCR has shown superior efficacy for preventing relapses and disability worsening compared with interferon (IFN) β-1a
- Following completion of the double-blind, controlled treatment phases of the OPERA I and OPERA II studies, patients were eligible to enter the open-label extension (OLE) phase to evaluate the long-term safety, tolerability and efficacy of OCR in RMS

## OBJECTIVE

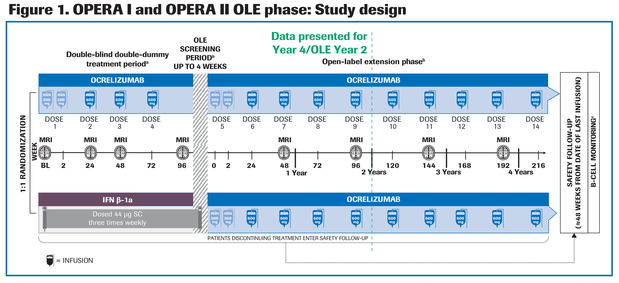
- To assess the efficacy of switching to or maintaining OCR therapy on MRI measures of disease activity and progression in the OLE period of Phase III trials in RMS

## METHODS

### *Time Frames for the OLE Phases in OPERA I and OPERA II (Figure 1)*

- Patients entering the OLE phase first entered the OLE screening phase, which lasted up to 4 weeks
- At the start of the OLE, patients from the IFN β-1a group were switched to OCR
- Clinical cut-off date for data included in the OLE analysis was February 17, 2017

**Figure 1. OPERA I and OPERA II OLE phase: Study design**




[a]Patients in the ocrelizumab group received placebo injections three times weekly, while patients in the IFN β-1a group received placebo infusions at Days 1 and 15 and Weeks 24, 48 and 72. [b]OLE was not mandatory. Patients who declined to participate in the OLE entered safety follow-up; [c]Continued monitoring occurs if B cells are not repleted.
BL, baseline; IFN, interferon; OLE, open-label extension; SC, subcutaneous.

### *Study Endpoints*

- The following endpoints are reported using the pooled OPERA I and OPERA II population:

**Lesion Activity**

- Total number of T1 gadolinium (Gd)-enhancing lesions (key secondary endpoint during the double-blind period [DBP])
- Total number of new/enlarging T2 lesions (DBP key secondary endpoint)
- MRI lesion activity was analyzed using a negative binomial distribution

**Brain Volume Change**

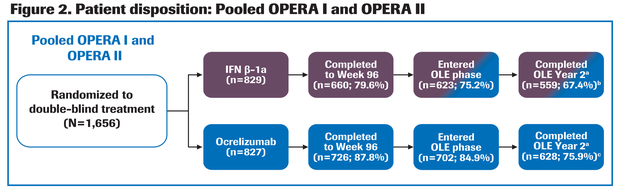
- Percentage change in whole brain volume (WBV) was calculated using Structural Image Evaluation using Normalization of Atrophy
- Percentage change in cortical gray matter volume (GMV) and white matter volume (WMV) was calculated using paired Jacobian integration
- Results are shown as the percentage change from the baseline measurement of the DBP and were analysed using mixed-effect model of repeated measures

## RESULTS

### *Patient Disposition, Demographics and Disease Characteristics*

- Patient disposition is shown in **Figure 2**
  - 559/829 (67.4%) and 628/827 (75.9%) patients who entered the DBP completed Year 4/OLE Year 2 in the IFN β-1a to OCR switch and continuous OCR groups, respectively
  - 623/660 (94.4%) and 702/726 (96.7%) patients who completed the DBP entered the OLE in the IFN β-1a to OCR switch and continuous OCR groups, respectively
  - 559/623 (89.7%) and 628/702 (89.5%) patients who entered the OLE completed Year 4 (OLE Year 2) in the IFN β-1a to OCR switch and continuous OCR groups, respectively
- Reasons for discontinuing the OLE are summarized in **Table 1**
- Patient demographics and disease characteristics for the pooled OPERA I and OPERA II studies at the baseline of the DBP and at the start of the OLE phase are presented in **Table 2**

**Figure 2. Patient disposition: Pooled OPERA I and OPERA II**




Percentage in parentheses is of the ITT population.
[a]Clinical cut-off date: February 17, 2017; [b]89.7% and [c]89.5% of patients who entered the OLE completed Year 2.
IFN, interferon; ITT, intention-to-treat; OLE, open-label extension.

**Table 1. Reasons for discontinuing the OLE**

| Reason, n (%) | Pooled OPERA I and OPERA II | |
|---|---|---|
| | IFN β-1a 44 µg/OCR 600 mg (n=623) | OCR 600 mg/OCR 600 mg (n=702) |
| Withdrawal of consent | 14 (2.2) | 21 (3.0) |
| Adverse event | 17 (2.7) | 10 (1.4) |
| Lack of efficacy | 9 (1.4) | 8 (1.1) |
| Pregnancy | 3 (0.5) | 8 (1.1) |
| Physician decision | 4 (0.6) | 6 (0.9) |
| Lost to follow-up | 1 (0.2) | 7 (1.0) |
| Noncompliance | 1 (0.2) | 3 (0.4) |
| Death | 0 (0) | 1 (0.1)[a] |
| Other | 21 (3.4) | 17 (2.4) |
| **Total** | **70 (11.2)** | **81 (11.5)** |

[a]Cause of death was esophageal cancer.
IFN, interferon; OCR, ocrelizumab; OLE, open-label extension.

**Table 2. Patient demographics and disease characteristics for the pooled OPERA I and OPERA II studies at the start of DBP and OLE**

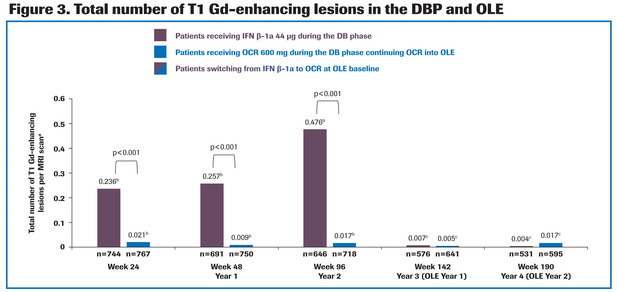
| | DBP baseline | | OLE baseline | |
|---|---|---|---|---|
| | IFN β-1a 44 µg/OCR 600 mg (n=829) | OCR 600 mg/OCR 600 mg (n=827) | IFN β-1a 44 µg/OCR 600 mg (n=623) | OCR 600 mg/OCR 600 mg (n=702) |
| **Age, years, mean (SD)** | 37.2 (9.2) | 37.1 (9.2) | 39.3 (9.2) | 39.2 (9.1) |
| **Female, n (%)** | 552 (66.6) | 541 (65.4) | 408 (65.5) | 454 (64.7) |
| **EDSS, mean (SD)** | 2.8 (1.3) | 2.8 (1.3) | 2.7 (1.5) | 2.6 (1.3) |
| **MRI** | | | | |
| Patients with T1 Gd-enhancing lesions, n (%)[a] | 327 (39.8)[d] | 333 (40.7)[e] | 106 (17.3)[e] | 5 (0.7)[g] |
| Number of 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] |
| T2 hyperintense lesion volume, cm$^3$, mean (SD)[b] | 10.2 (11.8)[f] | 10.8 (14.1)[f] | 9.4 (11.5)[h] | 10.1 (13.8)[i] |
| Number of T2 lesions, mean (SD)[c] | 51.0 (37.8)[f] | 50.1 (38.8)[f] | 55.5 (41.3) | 50.9 (39.3) |

Demographics and disease characteristics at Week 96 of the double-blind treatment period (clinical cut-off dates: OPERA I, April 2, 2015; OPERA II, May 12, 2015) are considered baseline for the OLE phase (clinical cut-off date: February 17, 2017).
For MRI measurements: [a]OLE baseline is the assessment at Week 96; [b]OLE baseline is the last assessment prior to or at the start of OLE treatment; [c]OLE baseline is the sum of lesion counts at baseline, Week 24, Week 48 and Week 96.
Patients missing and excluded for calculating percentages/means: [d]n=7; [e]n=9; [f]n=5; [g]n=6; [h]n=33; [i]n=44.
DBP double-blind period; EDSS, Expanded Disability Status Scale; Gd, gadolinium; IFN, interferon; OCR, ocrelizumab; OLE, open-label extension.

### *Total Number of T1 Gd-Enhancing Lesions in the DBP and OLE*

- The adjusted rate of total Gd-enhancing lesions in patients subsequently switching from IFN β-1a to OCR was 0.476 at 96 weeks (Year 2) (**Figure 3**)
- One year after switching (OLE Week 46 [Year 3]), the unadjusted rate of total Gd-enhancing lesions was 0.007, and this almost complete suppression was maintained at OLE Week 94 (Year 4; 0.004) (**Figure 3**)
- The almost complete suppression of Gd-enhancing lesions in patients receiving OCR in the DBP (adjusted rate 0.017 at 96 weeks [Year 2]) was maintained in those continuing to receive OCR in the OLE (unadjusted rate at OLE Week 46 [Year 3]: 0.005) and OLE Week 94 [Year 4]: 0.017) (**Figure 3**)

**Figure 3. Total number of T1 Gd-enhancing lesions in the DBP and OLE**

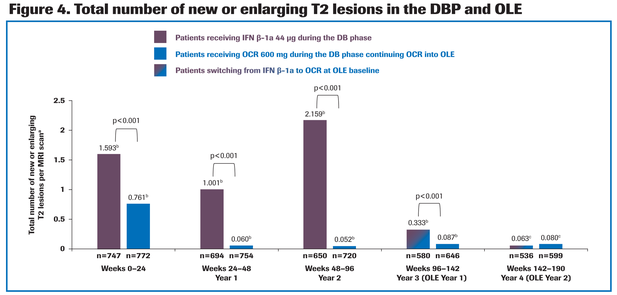



[a]DB period Week 24, DB period Year 1 and DB period Year 2 data include the ITT population; Year 3 (OLE Year 1) and Year 4 (OLE Year 2) data include the OLE ITT population; clinical cut-off date: February 17, 2017; [b]Adjusted by study, baseline T1 Gd-enhancing lesion (present or not), baseline EDSS (<4.0 vs ≥4.0) and geographical region (US vs ROW); [c]Unadjusted rate.
DB, double-blind; EDSS, Expanded Disability Status Scale; Gd, gadolinium; IFN, interferon; ITT, intention-to-treat; OCR, ocrelizumab; OLE, open-label extension; ROW, rest of world.

### *Total Number of New or Enlarging T2 Lesions in the DBP and OL*

- The adjusted rate of total new or enlarging T2 lesions in patients subsequently switching from IFN β-1a to OCR was 2.159 during Weeks 48–96 (Year 2) (**Figure 4**)
- Between Weeks 96–142 (Year 3/OLE Year 1), the adjusted rate of new or enlarging T2 lesions had decreased to 0.333 and this rate decreased further for Weeks 142–190 (Year 4/OLE Year 2; unadjusted rate 0.063) (**Figure 4**)
- The low number of new or enlarging T2 lesions in patients receiving OCR in the DBP (adjusted rate 0.052 for Weeks 48–96 [Year 2]) was maintained in those continuing to receive OCR in the OLE (adjusted rate for Weeks 96–142 [Year 3/OLE Year 1]: 0.087) and unadjusted rate for Weeks 142–190 [Year 4]: 0.080) (**Figure 4**)

**Figure 4. Total number of new or enlarging T2 lesions in the DBP and OLE**




[a]DB period Week 24, DB period Year 1 and DB period Year 2 data include the ITT population; Year 3 (OLE Year 1) and Year 4 (OLE Year 2) data include the OLE ITT population; clinical cut-off date: February 17, 2017; [b]Adjusted by study, baseline T2 lesion count, baseline EDSS (<4.0 vs ≥4.0) and geographical region (US vs ROW); [c]Unadjusted rate.
DB, double-blind; EDSS, Expanded Disability Status Scale; IFN, interferon; ITT, intention-to-treat; OCR, ocrelizumab; OLE, open-label extension; ROW, rest of world.

### *Percentage Change in WBV From Baseline to Year 4*

- Among patients switching from IFN β-1a to OCR, the adjusted mean of percentage change in WBV was –1.280 at 96 weeks (Year 2) (**Figure 5**)
- During the OLE, the adjusted mean of percentage change in WBV in patients switching from IFN β-1a to OCR was –1.513 at OLE Week 46 (Year 3/OLE Year 1) and –1.878 at OLE Week 94 (Year 4/OLE Year 2) (**Figure 5**)
- Among patients receiving continuous OCR, the adjusted mean of percentage change in WBV was –0.976 at 96 weeks (Year 2) (**Figure 5**)
- During the OLE, the adjusted mean of percentage change in WBV in patients receiving continuous OCR was –1.313 at OLE Week 46 (Year 3/OLE Year 1) and –1.572 at OLE Week 94 (Year 4/OLE Year 2) (**Figure 5**)

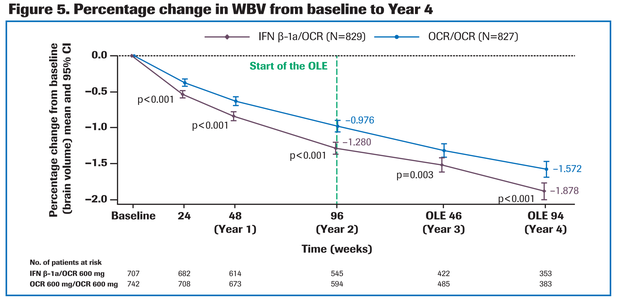
### *Percentage Change in Cortical GMV From Baseline to Year 4*

- Among patients switching from IFN β-1a to OCR, the adjusted mean of percentage change in GMV was –1.501 at 96 weeks (Year 2) (**Figure 6**)
- During the OLE, the adjusted mean of percentage change in GMV in patients switching from IFN β-1a to OCR was –1.555 at OLE Week 46 (Year 3/OLE Year 1) and –1.906 at OLE Week 94 (Year 4/OLE Year 2) (**Figure 6**)
- Among patients receiving continuous OCR, the adjusted mean of percentage change in GMV was –1.101 at 96 weeks (Year 2) (**Figure 6**)
- During the OLE, the adjusted mean of percentage change in GMV in patients receiving continuous OCR was –1.467 at OLE Week 46 (Year 3/OLE Year 1) and –1.719 at OLE Week 94 (Year 4/OLE Year 2) (**Figure 6**)

### *Percentage Change in WMV From Baseline to Year 4*

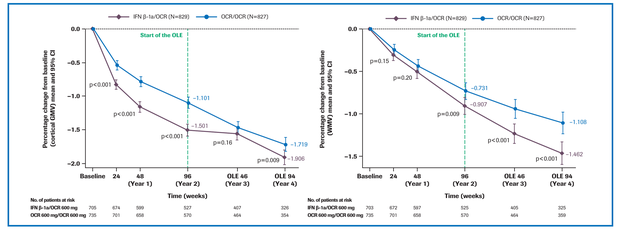
- Among patients switching from IFN β-1a to OCR, the adjusted mean of percentage change in WMV was –0.907 at 96 weeks (Year 2) (**Figure 6**)
- During the OLE, the adjusted mean of percentage change in WMV in patients switching from IFN β-1a to OCR was –1.231 at OLE Week 46 Year 3/OLE Year 1) and –1.462 at OLE Week 94 (Year 4/OLE Year 2) (**Figure 6**)
- Among patients receiving continuous OCR, the adjusted mean of percentage change in WMV was –0.731 at 96 weeks (Year 2) (**Figure 6**)
- During the OLE, the adjusted mean of percentage change in WMV in patients receiving continuous OCR was –0.941 at OLE Week 46 (Year 3/OLE Year 1) and –1.108 at OLE Week 94 (Year 4/OLE Year 2) (**Figure 6**)

**Figure 5. Percentage change in WBV from baseline to Year 4**




MMRM plot, ITT population. Pooled OPERA I and OPERA II (clinical cut-off date: February 17, 2017); 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.
EDSS, Expanded Disability Status Scale; GMV, gray matter volume; 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.

**Figure 6. Percentage change in cortical GMV and WMV from baseline to Year 4**




MMRM plots, ITT population. Pooled OPERA I and OPERA II (clinical cut-off date: February 17, 2017); p values shown for difference in adjusted means. Graphs include 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.
EDSS, Expanded Disability Status Scale; GMV, gray matter volume; IFN, interferon; ITT, intention-to-treat; MMRM, mixed-effect model of repeated measures; OCR, ocrelizumab; OLE, open-label extension; ROW, rest of world; WMV, white matter volume.

## CONCLUSIONS

- Overall, 90% of patients who entered the OLE phase of the OPERA studies completed Year 2 of the OLE
- Patients who switched from IFN β-1a to ocrelizumab in the OLE phase experienced reductions in:
  - Total number of T1 Gd-enhancing lesions
  - New/enlarging T2 lesions
- The almost complete suppression of T1 Gd-enhancing lesion activity observed in those receiving ocrelizumab in the DBP was also achieved in those switching from IFN β-1a to ocrelizumab in the OLE and maintained in those receiving continuous ocrelizumab
- At Year 4 (Year 2 of the OLE), the benefits accrued on total brain, gray matter and white matter volume loss from the earlier initiation and continued treatment with ocrelizumab were maintained compared with patients who switched from IFN β-1a to ocrelizumab when entering the OLE

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## DISCLOSURES

A Traboulsee has received research support from Sanofi Genzyme, Roche, Chugai, Novartis and Biogen; has received consulting fees from Sanofi Genzyme, Roche, Teva Neuroscience, Novartis, Biogen and EMD Serono; and has received honoraria for his involvement in speaker bureau activities for Sanofi Genzyme and Teva Neuroscience. DL Arnold has received personal fees for consulting from Acorda, Biogen, F Hoffmann-La Roche Ltd, MedImmune, Mitsubishi, Novartis, Receptos and Sanofi-Aventis; grants from Biogen and Novartis; and an equity interest in NeuroRx Research. L Kappos' institution, the University Hospital Basel, has received research support and payments that were used exclusively for research support for L. Kappos' activities as principal investigator and member or chair of planning and steering committees or advisory boards for trials sponsored by Actelion, Addex, Almirall, Bayer HealthCare Pharmaceuticals, CLC Behring, F. Hoffmann-La Roche Ltd and Genentech, Inc., GeNeuro SA, Genzyme, Merck Serono, Mitsubishi Pharma, Novartis, Octapharma, Ono Pharmaceutical, Pfizer, Receptos, Sanofi, Santhera, Siemens, Teva, UCB and XenoPort; has received license fees for Neurostatus products; and has received research grants from the European Union, Gianni Rubatto Foundation, Novartis Research Foundation, Roche Research Foundation, Swiss Multiple Sclerosis Society and Swiss National Research Foundation. SL Hauser serves on the board of trustees for Neurona and on scientific advisory boards for Annexon, Bionure and Symbiotix and has received travel reimbursement and writing assistance from F. Hoffmann-La Roche Ltd for CD20-related meetings and presentations. X Montalban has received speaking honoraria and travel expense reimbursement for participation in scientific meetings, been a steering committee member of clinical trials or served on advisory boards of clinical trials for Actelion, Almirall, Bayer, Biogen, F. Hoffmann-La Roche Ltd, Genzyme, Merck, Novartis, Octapharma, Receptos, Sanofi, Teva and Trophos. JS Wolinsky has served on advisory boards and data monitoring or steering committees, has held consulting agreements or has received speaker honoraria from AbbVie, Alkermes, Biogen, Bionest, Clene Nanomedicine, EMD Serono, F Hoffmann-La Roche Ltd, Forward Pharma, Genentech, Inc., MedDay Pharmaceuticals, Novartis, Sanofi Genzyme, Takeda, Teva, and has received royalties for monoclonal antibodies outlicensed to Chemicon International through UTHealth. V Levesque is an employee of Genentech, Inc. P Villoslada is an employee of Genentech, Inc. and shareholder of F Hoffmann-La Roche Ltd. S Belachew is an employee and shareholder of F Hoffmann-La Roche Ltd. F Model is an employee of F Hoffmann-La Roche Ltd. S Hubeaux is an employee and shareholder of F Hoffmann-La Roche Ltd. A Bar-Or has served on scientific advisory boards for Biogen, F Hoffmann-La Roche Ltd and Genentech, Inc., GlaxoSmithKline, Guthy-Jackson/GGF, MedImmune, Merck/EMD Serono, Mitsubishi Tanabe, Ono, Receptos and Sanofi Genzyme and has received research support from Biogen, Novartis and Sanofi Genzyme.

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