Open-Label Phase III Extension Studies to Evaluate the Long-Term Safety and Efficacy of Ocrelizumab in Relapsing MS and Primary Progressive MS

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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 and OPERA II) in relapsing multiple sclerosis (RMS), OCR has shown superior efficacy compared with interferon β-1a (IFN β-1a)[3] (**Figure 1**)
- Further, OCR met the primary efficacy outcome in the Phase III, randomized, double-blind, placebo-controlled study (ORATORIO) in primary progressive MS (PPMS)[4] (**Figure 2**)
- Following completion of the double-blind, controlled treatment phases of the OPERA I and OPERA II and ORATORIO studies, patients were eligible to enter open-label extension (OLE) phases to evaluate long-term OCR safety, tolerability and efficacy

METHODS

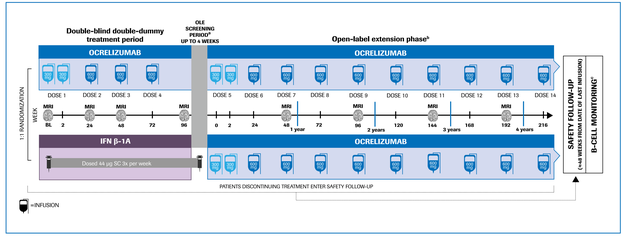
Time Frames for the Open-Label Extension Phases

- **OPERA I and OPERA II**
  - — Patients entering the OLE phase first entered the OLE screening phase, which lasted up to 4 weeks
  - — Patients unwilling to proceed to the OLE phase were entered into the safety follow-up phase for 48 weeks starting from the date of the patient's latest visit
- **ORATORIO**
  - — The OLE phase began following the availability of the blinded primary analysis of ORATORIO
  - — Patients who were not eligible to continue into the OLE phase were encouraged to enter the safety follow-up phase for 48 weeks starting from the date of the patient's latest visit

Key Inclusion Criteria for OPERA I and OPERA II and ORATORIO Open-Label Extension Phases

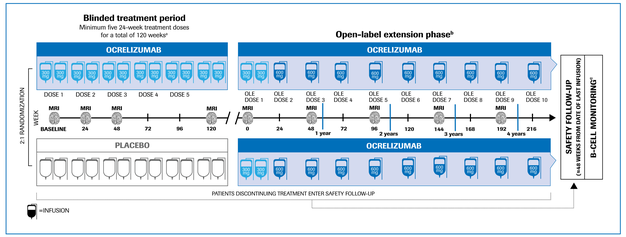
- Completion of the blinded treatment period
- Consent from investigators who determine that the patient may benefit from OCR treatment based on the assessments performed during the treatment period
- Written informed consent from the patient to enter the OLE phase
- Patient meets OCR treatment/retreatment criteria, in which they are free from the following conditions and laboratory abnormalities:
  - — Life-threatening (CTCAE Grade 4) infusion-related event that occurred during a previous OCR infusion
  - — Any significant or uncontrolled medical condition or treatment-emergent, clinically significant laboratory abnormality
  - — Active infection
  - — Absolute neutrophil count <1.5×10^9/μL
  - — CD4 cell count <250/μL
  - — Hypogammaglobulinemia immunoglobulin G <3.3 g/L

Figure 1. OPERA I and OPERA II study design



Patients received methylprednisolone prior to each ocrelizumab infusion.
[a]During OLE screening, patients received IFN β-1a or IFN β-1a placebo until first infusion of dose 5.
[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.
OLE, open-label extension; SC, subcutaneous.

Figure 2. ORATORIO study design



Patients received methylprednisolone prior to each ocrelizumab infusion.
[a]The blinded treatment period continued until the last patient completed 120 weeks and a target of 253 confirmed disability progression events was reached.
[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.
OLE, open-label extension.

Key Safety and Efficacy Assessments

- Safety assessments for OPERA I, OPERA II, and ORATORIO studies will include:
  - — Routine safety laboratory assessments: hematology, chemistry and urinalysis
  - — Concomitant medications and procedures will be reported at each scheduled and unscheduled visit
  - — Antibody titers against common antigens (mumps, rubella, varicella, and *Streptococcus pneumoniae*) will be performed
- Key efficacy assessments for OPERA I, OPERA II, and ORATORIO studies will include:
  - — Patients will be evaluated for relapses by the treating investigator at each scheduled visit and, if necessary, at unscheduled visits to confirm relapses occurring between the visits. If a relapse is suspected, the Expanded Disability Status Scale (EDSS) should also be performed in addition to completing the MS relapse electronic case report form
  - — Neurological examination will be performed at every planned and unscheduled visit. All patients with new neurological symptoms suggestive of MS worsening or of a relapse should have EDSS performed by examining investigator
  - — EDSS score will be performed in all patients by the examining investigator every 12 weeks. Additional EDSS assessments may be performed between visits (i.e. during an MS relapse, neurological worsening, etc). Disability progression is defined as a ≥1.0-point (where baseline EDSS is ≤5.5) or ≥0.5-point (where baseline EDSS is >5.5) increase from the baseline EDSS score that is not attributable to another etiology
  - — Brain MRI scans will be performed at the start of the OLE phase (if none were performed in the previous 12 weeks), thereafter annually, and at OLE withdrawal visits (if none were performed in the previous 4 weeks)
  - — SF-36 quality-of-life assessments will be performed annually

RESULTS

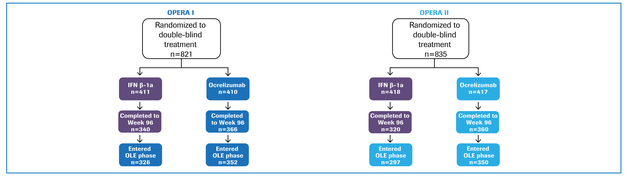
Open-Label Extension Enrollment

Table 1. OPERA I and OPERA II open-label extension phase

	OPERA I	OPERA II
Number of patients enrolled	678	647
First patient in	July 2013	August 2013
Last patient in	December 2014	February 2015

- In OPERA I, 678 of 706 patients (96%) who completed the 96-week double-blind treatment phase entered the OLE phase:
  - — 326 patients randomized to IFN β-1a (96% of 340 patients who completed the 96-week double-blind treatment phase)
  - — 352 patients randomized to OCR (96% of 366 patients who completed the 96-week double-blind treatment phase)
- In OPERA II, 647 of 680 patients (95%) who completed the 96-week double-blind treatment phase entered the OLE phase:
  - — 297 patients randomized to IFN β-1a (93% of 320 patients who completed the 96-week double-blind treatment phase)
  - — 350 patients randomized to OCR (97% of 360 patients who completed the 96-week double-blind treatment phase)

Figure 3. OPERA I and OPERA II open-label extension phase enrolled patients



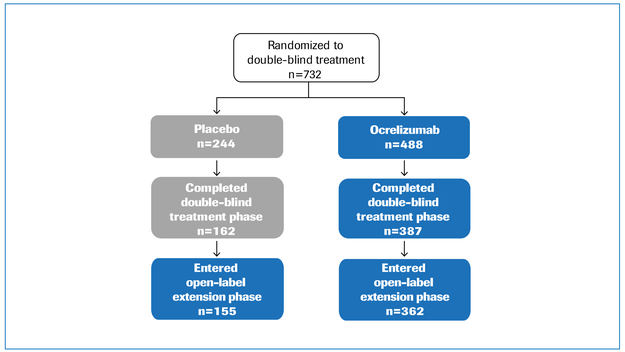
OLE, open-label extension.

Table 2. ORATORIO open-label extension phase

	ORATORIO
Number of patients enrolled	549
First patient in	November 2015
Last patient in	April 2016

- In ORATORIO, 517 of 549 patients (94%) who completed the double-blind treatment phase entered the OLE phase:
  - — 155 patients randomized to placebo (96% of 162 patients who completed the double-blind treatment phase)
  - — 362 patients randomized to OCR (94% of 387 patients who completed the double-blind treatment phase)

Figure 4. ORATORIO open-label extension phase enrolled patients



CONCLUSIONS

- **Long-term safety, tolerability and efficacy of ocrelizumab in RMS and PPMS will continue to be assessed in the OLE phases of OPERA I, OPERA II and ORATORIO studies**
- **The great majority of patients who completed double-blind treatment phases entered the OLE phases (96%, 95% and 94% for OPERA I, OPERA II and ORATORIO studies, respectively)**
- **The open-label extension phase will provide long-term data regarding ocrelizumab in patients with RMS and PPMS**

DISCLOSURES

R Kuhelj, G Deol-Bhullar and M Garas are employees and/or shareholders of F. Hoffmann-La Roche Ltd. P Chin is an employee and/or shareholder of Genentech, Inc. SL Hauser serves on the scientific advisory boards for Annexon, Symbiotix, Bionure; he has also received travel reimbursement and writing assistance from F. Hoffman-La Roche Ltd for CD20-related meetings and presentations. X Montalban has received speaking honoraria and travel expense reimbursement for participation in scientific meetings, has been a steering committee member of clinical trials or participated in advisory boards of clinical trials in the past years with Actelion, Almirall, Bayer, Biogen, Genzyme, Merck, Novartis, Octapharma, Receptos, F. Hoffmann-La Roche Ltd, Sanofi, Teva and Trophos.

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