A Phase III, Open-Label Study to Evaluate the Effect of Ocrelizumab on Immune Responses in Patients With Relapsing Multiple Sclerosis

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BACKGROUND

- Ocrelizumab (OCR) is a humanized monoclonal antibody that selectively depletes CD20$^+$ B cells, while preserving the capacity for B-cell reconstitution and preexisting humoral immunity
- Vaccinations against infections are an important part of the management of patients with multiple sclerosis (MS)[1–3]
- No formal vaccination study has been conducted in OCR-treated patients; this study aims to characterize the humoral immune responses to vaccines in OCR-treated patients with relapsing MS (RMS)
- This study uses five vaccines to evaluate different immune response pathways (**Table 1**)

Table 1. Vaccines used within study

Vaccine	Immune response pathway
TT	To assess the T-cell dependent anamnestic humoral response
23-PPV	To assess a mostly T-cell independent or pure 'B cell' humoral response
13-PCV	To assess the impact of the 23-PPV vaccine followed by the booster 13-PCV compared to 23-PPV vaccine alone
KLH	To explore the B cell dependent immune response to a neo-antigen
Influenza	To test the ability to mount a humoral response

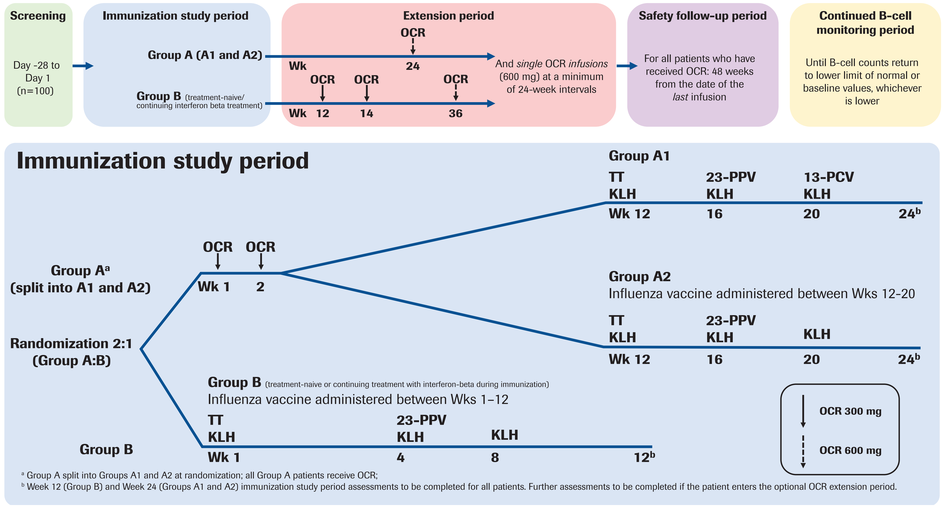
KLH, keyhole limpet hemocyanin; 13-PCV, booster 13-valent conjugate pneumococcal vaccine; 23-PPV, 23-valent pneumococcal polysaccharide vaccine; TT, tetanus toxoid–containing vaccine.

METHODS

Study Design

- In this Phase IIIb, multicenter, randomized, open-label study, approximately 100 patients will be randomized (2:1) to receive OCR 600 mg (administered as two 300 mg infusions on Days 1 and 15)
- Group A will receive OCR preimmunization; Group B will remain treatment-naive or continue with interferon β treatment during immunization (**Figure 1**)
- Group B will be immunized with tetanus toxoid (TT)–containing adsorbed vaccine on day 1; 23-valent pneumococcal polysaccharide vaccine (23-PPV) on day 28; keyhole limpet hemocyanin (KLH) on days 1, 28 and 56, and influenza vaccine during weeks 1–12
- Group A will be immunized ≥12 weeks after first OCR administration: TT at Week 12, 23-PPV at Week 16 and KLH at Weeks 12, 16, and 20
- Group A will be further divided to receive booster 13-valent conjugate pneumococcal vaccine (13-PCV; Group A1) or influenza vaccine (Group A2)

Figure 1. Study design



KLH, keyhole limpet haemocyanin; OCR, ocrelizumab; 13-PCV, booster 13-valent conjugate pneumococcal vaccine; 23-PPV, 23-valent pneumococcal polysaccharide vaccine; TT, tetanus toxoid–containing vaccine; Wk, week.

- Key inclusion criteria
  - RMS diagnosis (2010 revised McDonald criteria)[4]
  - 18–55 years
  - Received ≥1 previous immunization against
    - TT or
    - tetanus and diphtheria (DT/Td), or
    - tetanus, diphtheria, and acellular pertussis (DTaP/Tdap)
  - Expanded Disability Status Scale score of 0–5.5
- Key exclusion criteria
  - Known hypersensitivity to any component of the TT-containing adsorbed vaccine, pneumococcal polysaccharide/conjugate vaccine, or influenza vaccine
  - Receipt of any PPV <5 years prior to screening or a live vaccine <6 weeks prior to randomization
  - Previous exposure to KLH
  - Immunization with any tetanus-containing vaccine <2 years prior to screening

Key Secondary Outcome Measures

- TT response
  - The proportion of patients treated with OCR (Groups A1 and A2) and not treated with OCR (Group B) with a positive response (IgG) to TT vaccine at 4 weeks postimmunization
- 23-PPV
  - The proportion of patients treated with OCR (Groups A1 and A2) and not treated with OCR (Group B) with positive responses against an individual antipneumococcal antibody serotype measured 4 weeks postimmunization
    - A positive response is defined as developing a 2-fold increase in level or a >1µg/mL rise in level compared with preimmunization levels
- KLH
  - Mean levels of anti-KLH antibody (IgG) in patients treated with OCR (Groups A1 and A2) and not treated with OCR (Group B) measured immediately prior to the first administration and 4 weeks after the last administration of KLH
- Pneumococcal conjugate booster response in Groups A1 and B
  - The proportion of patients treated with OCR in Group A1 with positive responses against an individual antipneumococcal antibody serotype (23 serotypes) measured 4 weeks after the booster 13-PCV vaccine
    - A positive response is defined as developing a 2-fold increase in level or a >1µg/mL rise in level compared with preimmunization levels
- Influenza vaccine response
  - The proportion of patients treated with OCR who achieve seroprotection (specific hemagglutination inhibition titers >1:40) at 4 weeks postimmunization compared with patients not treated with OCR

Immunophenotyping Outcome Measures

- Measures of humoral and cellular immunity include:
  - Total B-cell (CD19$^+$) counts; B-cell subset (memory, naive and plasma) counts
  - Total T-cell (CD3$^+$) counts; T-helper-cell (CD3$^+$CD4$^+$) counts; cytotoxic T cell (CD3$^+$CD8$^+$) counts
  - Natural killer cells (CD3$^-$CD16/56$^+$)

RESULTS

Primary Outcome Measure

- To compare positive TT response (Immunoglobulin G [IgG]) 8 weeks postimmunization in patients treated with OCR (Groups A1 and A2) with patients not treated with OCR (Group B)
  - A positive response to the booster immunization is defined as an antibody titer ≥0.2 IU/mL (preimmunization titers <0.1 IU/mL) or a 4-fold increase in antibody titer (preimmunization titers ≥0.1 IU/mL)

CONCLUSIONS

- **This study will evaluate the effect of ocrelizumab on immune responses against clinically relevant vaccines and further help to guide immunization recommendations**

DISCLOSURES

L Millar, H Bennett, J Evershed and C Li are employees of F Hoffmann-La Roche Ltd. M Gerber and H Garren are employees and shareholders of F Hoffmann-La Roche Ltd.

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