# Effect of Ocrelizumab on Vaccine Responses in Patients With Multiple Sclerosis


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## BACKGROUND

- Ocrelizumab (OCR) is a high-efficacy treatment approved for relapsing multiple sclerosis (RMS)[1] and is the first approved treatment for primary progressive multiple sclerosis
- OCR selectively depletes CD20+ B cells while preserving the capacity for B-cell reconstitution and pre-existing humoral immunity[2–5]
- In the Phase III OPERA I and OPERA II studies in patients with RMS, pre-existing antibody titres against common viral and bacterial antigens were similar in OCR and high-dose interferon (IFN) β-1a recipients at baseline, and were maintained throughout the 96-week double-blind treatment period[6]
- There is a need to further understand the impact of OCR on the response to vaccines

## OBJECTIVE

- VELOCE (NCT02545868) is a Phase IIIb study being conducted in the USA and Canada to evaluate the effects of OCR on humoral responses to selected vaccines (**Table 1**) in patients with RMS

**Table 1. Vaccines and neoantigen used in VELOCE**

| VELOCE vaccines/neoantigen[a] | Response pathway |
|---|---|
| Tetanus toxoid–containing vaccine | Mainly T-cell–dependent response to a known antigen |
| 23-valent pneumococcal polysaccharide vaccine | Mainly B-cell–dependent response |
| 13-valent pneumococcal conjugate vaccine | Response to a booster of 23-PPV |
| Seasonal influenza (inactivated)[b] | Response to a clinically relevant vaccine |
| Keyhole limpet haemocyanin | Humoral response to a neoantigen |

[a]Commercially available vaccines were used; all vaccines were administered in the deltoid muscle as a single intramuscular injection (KLH was administered subcutaneously); [b]Locally available tri- or quadrivalent World Health Organization-recommended seasonal influenza vaccines (2015/2016 or 2016/2017) for the Northern Hemisphere were used.
KLH, keyhole limpet haemocyanin; PPV, 23-valent pneumococcal polysaccharide vaccine.

## METHODS

### *Study Endpoints*

- Primary endpoint: proportion of patients with a positive response (immunoglobulin G [IgG]) to tetanus toxoid (TT)-containing vaccine 8 weeks after TT booster vaccine administration
  - Assessed at 4 weeks post-vaccination as a secondary endpoint
- Secondary endpoints included:
  - **23-valent pneumococcal polysaccharide vaccine (23-PPV) and 13-valent pneumoccal conjugate vaccine (13-PCV)**: proportion of patients with a positive response against an individual pneumococcal serotype 4 weeks after vaccination
  - **Influenza vaccine**: proportion of patients treated with OCR who achieve seroprotection at 4 weeks post-vaccination compared with patients in the Control group
  - **Keyhole limpet haemocyanin (KLH)**: mean levels of anti-KLH antibody (IgG and IgM) in all patients during the immunisation study period (ISP; immediately prior and 4, 8 and 12 weeks after the last administration of KLH)

### *Study Design*

- VELOCE has five study periods, which include: screening, immunisation, optional OCR extension, safety follow-up and continued B-cell monitoring (**Figure 1**)
- Patients were randomised (2:1) to receive one dose of OCR 600 mg (per prescribing information), or remain on IFN β or no disease-modifying therapy (DMT; Control group) during the ISP
  - Patients in the OCR group were assigned to OCR 1 or OCR 2 at randomisation
- Vaccinations in the OCR group were started at Week 12 when patients were B-cell depleted; vaccinations in the Control group were started on Day 1

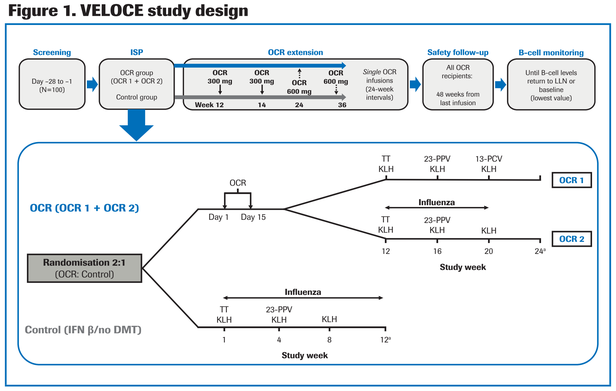
### *Inclusion/Exclusion Criteria*

- Patients were aged 18–55 years, had a diagnosis of RMS (McDonald Criteria, 2010) and a baseline Expanded Disability Status Scale score at screening of 0–5.5
- Patients had received ≥1 vaccination with a TT-containing vaccine >2 years prior to screening
- Patients were excluded if they had received any pneumococcal vaccine <5 years prior to screening or a live vaccine <6 weeks prior to randomisation, or had previous exposure to KLH

### *Analysis Population*

- We report findings from the Observed Cases population (all patients completing the ISP) during the ISP (first patient, first visit: 27 October 2015; last patient, last visit: 14 February 2017 [effective clinical cut-off date])
- There was no formal assessment of non-inferiority; comparisons and 95% CIs were calculated via the normal approximation method

**Figure 1. VELOCE study design**




[1]ISP duration: OCR group (OCR 1+ OCR 2), 24 weeks; Control group, 12 weeks.
13-PCV, 13-valent pneumococcal conjugate vaccine; 23-PPV, 23-valent pneumococcal polysaccharide vaccine; DMT, disease-modifying therapy; IFN, interferon; ISP, immunisation study period; KLH, keyhole limpet haemocyanin; LLN, lower limit of normal; OCR, ocrelizumab; TT, tetanus toxoid-containing vaccine.

## RESULTS

### *Baseline Demographic and Disease Characteristics*

- Baseline demographic and disease characteristics were generally well balanced (**Table 2**)
  - There was a lower proportion of female patients in the OCR group than in the Control group
  - The mean number of T1 gadolinium-enhancing lesions at baseline was higher in patients in the OCR group than in the Control group
- Twelve patients (35%) randomised to the Control group remained on IFN β during the ISP

**Table 2. Baseline demographic and disease characteristics**

| Parameter | OCR 600 mg (all) N=68 | Control (IFN β/no DMT) N=34 |
|---|---|---|
| Age, years, mean (SD) | 39.7 (8.9) | 41.4 (7.9) |
| Female, n (%) | 45 (66.2) | 27 (79.4) |
| Caucasian, n (%) | 64 (94.1) | 30 (88.2) |
| BMI, kg/m², mean (SD) | 28.9 (6.7)[a] | 26.6 (5.7)[b] |
| Duration since MS symptom onset, years, mean (SD) | 8.9 (7.1) | 9.5 (5.9) |
| Duration since RMS diagnosis, years, mean (SD) | 6.6 (6.6) | 7.1 (5.2) |
| Baseline EDSS score, mean (SD) | 2.7 (1.3) | 2.3 (1.4) |
| Number of T1 gadolinium-enhancing lesions, mean (SD) | 2.9 (10.9)[c] | 0.6 (2.7) |
| Number of T2 lesions, mean (SD) | 57.9 (45.4)[d] | 45.5 (28.6) |
| T2 lesion volume, cm³, mean (SD) | 10.8 (13.3)[d] | 7.5 (8.2) |

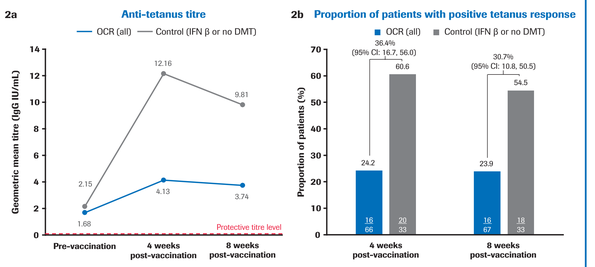
[a]n=64; [b]n=33; [c]n=65; [d]n=66.
BMI, body mass index; DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; IFN, interferon; MS, multiple sclerosis; OCR, ocrelizumab; RMS, relapsing multiple sclerosis.

- Vaccination/passive immunisation histories in the OCR and Control groups were comparable
- All patients completed the ISP and entered the optional OCR extension period; all patients randomised to OCR received a single dose (600 mg)

### *Response (IgG) to Tetanus Toxoid-Containing Vaccine*

- Pre-vaccination geometric mean anti-tetanus (IgG) antibody levels were comparable between treatment groups (**Figure 2a**)
- Geometric mean IgG levels 4 and 8 weeks post-vaccination were lower in patients receiving OCR, compared with those in the Control group (**Figure 2a**)
- The proportion of patients with a positive response at 4 and 8 weeks was lower in those who received OCR versus Control (**Figure 2b**)
- All patients with a known response were seroprotected (IgG ≥0.1 IU/mL) 4 and 8 weeks after vaccination, including three patients not seroprotected prior to vaccination (all OCR)

**Figure 2. Response (IgG) to tetanus toxoid–containing vaccine**

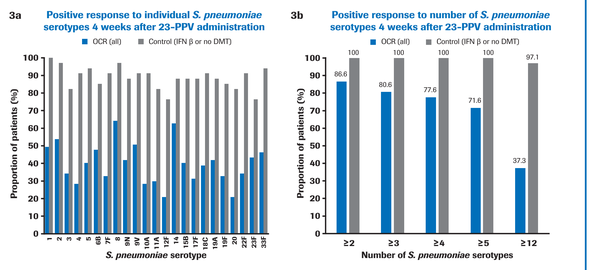



Positive response defined as a 4-fold increase in antibody titres measured 8 weeks after vaccination compared with pre-vaccination levels (pre-vaccination titre level ≥0.1 IU/mL) or an antibody titre ≥0.2 IU/mL if pre-vaccination titre was <0.1 IU/mL.
DMT, disease-modifying therapy; IFN, interferon; IgG, immunoglobulin G; OCR, ocrelizumab.

### *Response (IgG) to Pneumococcal Vaccine*

- Serotype specific geometric mean antibody levels at 4 and 8 weeks post-vaccination were lower in OCR recipients, including those receiving the 13-PCV booster 4 weeks after 23-PPV (Group OCR1), versus those in the Control group
- Post-vaccination positive responses to individual *Streptococcus pneumoniae* serotypes in 23-PPV were lower in the OCR group versus the Control group (4 weeks, –62.8% to –25.5%; **Figure 3a**)
- The 13-PCV booster administered 4 weeks after 23-PPV in the OCR1 group did not markedly enhance the response to the 12 serotypes in common with 23-PPV (data not shown)

**Figure 3. Response (IgG) to pneumococcal vaccine**




Positive response: 2-fold increase or a >1 µg/mL rise in titre level (IgG), compared with pre-vaccination levels.
23-PPV, 23-valent pneumococcal polysaccharide vaccine; DMT, disease-modifying therapy; IFN, interferon; IgG; immunoglobulin G; OCR, ocrelizumab.

- The proportion of positive responders in the OCR group decreased with each increase in number of serotypes (**Figure 3b**)

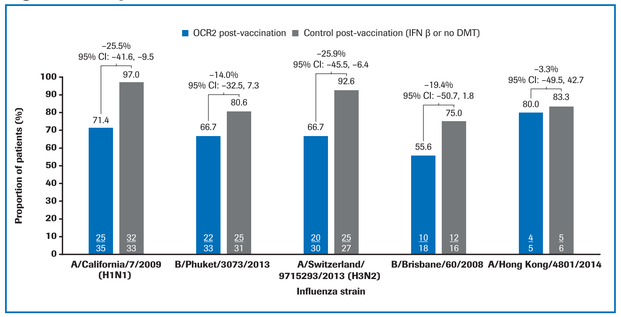
### *Seroprotection to Individual Influenza Strains*

- The proportion of patients with seroprotective haemagglutination inhibition titres immediately prior to vaccination was higher in patients in the OCR2 group, compared with those in the Control group
- Seroprotective titres 4 weeks post-vaccination against five influenza strains (in influenza vaccines of seasons 2015/2016 and 2016/2017) ranged from 55.6% to 80.0% in patients receiving OCR and 75.0% to 97.0% in Control patients (**Figure 4**)

### *IgM and IgG Responses to Keyhole Limpet Haemocyanin Neoantigen*

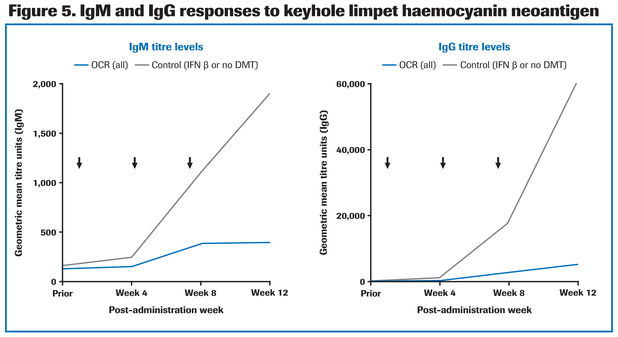
- Pre-administration geometric mean levels of IgM and IgG across treatment groups were comparable (OCR: IgM, 100 units; IgG, 274 units; Control: IgM, 130 units; IgG, 235 units)
- Post-administration responses (4, 8 and 12 weeks) were lower in OCR recipients versus Control (**Figure 5**)
  - After repeated KLH administration, a stronger boosting effect was observed in the Control group, compared with those receiving OCR

**Figure 4. Seroprotection to individual influenza strains**




Pre-vaccination seroprotection levels were higher in patients receiving OCR vs those in the Control group for all individual serotypes (A/California/7/2009: 54.3% vs 33.3%; B/Phuket/3073/2013: 48.5% vs 29.0%; A/Switzerland/9715293/2013: 60.0% vs 40.7%; B/Brisbane/60/2008: 50.0% vs 43.8%; A/Hong Kong/4801/2014: 20.0% vs 16.7%). Seroprotection defined as a specific haemagglutination inhibition titre >40.
DMT, disease-modifying therapy; IFN, interferon; OCR, ocrelizumab.

**Figure 5. IgM and IgG responses to keyhole limpet haemocyanin neoantigen**




↓ KLH administration.
DMT, disease-modifying therapy; IFN, interferon; IgG; immunoglobulin G; IgM, immunoglobulin M; KLH, keyhole limpet haemocyanin; OCR, ocrelizumab.

### *Safety*

- The overall safety profile of OCR was consistent with pooled Phase III safety data[1,7]
- No new safety signals were identified; no serious adverse event or adverse event leading to withdrawal from treatment was reported during the ISP
- Safety findings from the VELOCE study are presented as part of a combined OCR safety report in **ePresentation EPR1105** (Hauser SL, *et al.*)

## CONCLUSIONS

- Data from the Phase III OPERA I and OPERA II studies show that pre-existing humoral immunity is not affected by ocrelizumab treatment[6]
- In the VELOCE study, humoral responses were attenuated at all time points in patients who were B-cell depleted having received ocrelizumab, compared with those who did not
- Patients were nonetheless able to mount humoral responses to the vaccines and neoantigen studied
  - Cellular immune responses were not assessed
- These data confirm the current prescribing recommendations for vaccinations
  - Administer all vaccinations according to guidelines at least 6 weeks prior to initiation of ocrelizumab
- Patients should still receive seasonal influenza vaccinations since a potentially protective humoral response, even if attenuated, can be expected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The data on this poster have previously been presented at the 2018 Annual Meeting of the Consortium of Multiple Sclerosis Centers (CMSC); 30 May–2 June 2018; Nashville, TN, USA.


## DISCLOSURES

D Stokmaier is an employee of F. Hoffmann-La Roche Ltd. K Winthrop is a consultant for GlaxoSmithKline plc, F. Hoffmann-La Roche Ltd and Pfizer Inc. C Chognot is an employee of F. Hoffmann-La Roche Ltd. J Evershed is an employee of F. Hoffmann-La Roche Ltd. M Manfrini is an employee of F. Hoffmann-La Roche Ltd. J McNamara is an employee of John McNamara Consulting 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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