Low Disease Activity Over 4 Years of Ocrelizumab Therapy in Treatment-Naive Patients With Early-Stage Relapsing-Remitting Multiple Sclerosis: The Phase IIIb ENSEMBLE Study

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ENSEMBLE (NCT03085810)

Presented at the 75th Annual Meeting of the American Academy of Neurology, April 22-27, 2023, Boston, MA, USA
Program number P004.S46
**Disclosures**

**R Bermel** has served as a consultant for AstraZeneca, Biogen, EMD Serono/Merck, Genzyme/Sanofi, Genentech/Roche, LabCorp, Eli Lilly, Novartis, TG Therapeutics and Viela Bio/Horizon. He receives research support from Biogen, Genentech and Novartis; and shares rights to intellectual property underlying the Multiple Sclerosis Performance Test, currently licensed to Qr8 Health and Biogen.

**HP Hartung** has received honoraria for consulting, serving on steering committees and speaking at scientific symposia with approval by the Rector of Heinrich-Heine University Düsseldorf from Bayer, Biogen, BMS Celsgene, F. Hoffmann-La Roche Ltd, GenNeuro SA, Genzyme, MedImmune, Merck-Serono, Novartis, Octapharma, Sanofi-Genzyme, Teva, TG Therapeutics and Viela Bio.

**B Brochet** or his institution has received honoraria for consulting, speaking at scientific symposia or serving on advisory boards from Biogen Idec., BMS, Merck-Serono, Novartis, Roche and Sanofi-Genzyme.

**RHB Benedict** has received research support from Biogen, Bristol Myers Squibb, F. Hoffmann-La Roche Ltd, Genzyme, Genentech, Novartis, National Institutes of Health, National Multiple Sclerosis Society and VeraSci; consultancy fees from Immunic Therapeutics, Latin American Committee for Treatment and Research in Multiple Sclerosis, Merck, Novartis and Sanofi; speaking support from Biogen, Bristol Myers Squibb and EMD Serono; and royalties from Psychological Assessment Resources, Inc.

**T Berger** has participated in meetings sponsored by and received honoraria (lectures, advisory boards, consultations) from pharmaceutical companies marketing treatments for multiple sclerosis: Almirall, Bayer, Biogen, Biologix, Bionorica, BMS/Celsgene, GW/Jazz Pharma, Horizon, Janssen-Cilag, MedDay, Merck, Novartis, Octapharma, Roche, SANDOZ, Sanofi-Genzyme, TG PharmaSciences, Teva-Ratiopharm and UCB. His institution has received financial support in the last 12 months by unrestricted research grants (Biogen, BMS/Celsgene, Merck, Novartis, Roche and Sanofi-Genzyme) and for participation in clinical trials in multiple sclerosis sponsored by Alexion, Biogen, BMS/Celsgene, Merck, Novartis, Octapharma, Roche, Sanofi-Genzyme and Teva.

**WM Carroll** has received honoraria for serving on steering committees, advisory boards and for speaking at scientific meetings from Bayer, Biogen Idec., Merck, Novartis, Roche and Sanofi-Genzyme.

**T Volmer** has received compensation for consultancy from Biogen Idec., Genentech/F. Hoffmann-La Roche Ltd and Novartis; and has received research support from Rocky Mountain Multiple Sclerosis Center, Celsgene, Biogen Idec., AnokiON, Genentech/F. Hoffmann-La Roche Ltd, GW Pharma and TG Therapeutics.

**T Holmey** has received honoraria/consultancy fees from Biogen Idec., Merck, Novartis, Roche, Bristol Myers Squibb, Santan and Sanofi-Genzyme.

**R Karabudak** received honoraria for consulting, lectures and advisory boards from Sanofi-Genzyme, Roche, Novartis, Merck-Serono, Gen Ilac TR and Teva.

**J Killestein** has carried out contracted research for F. Hoffmann-La Roche Ltd, Biogen, Teva, Merck, Novartis and Sanofi-Genzyme.

**C Nos** has received funding for registration for scientific meeting from Novartis.

**F Patti** received personal compensation for speaking activities and serving on the advisory board by Almirall, Bayer, Biogen, Celsgene, Merck, Novartis, Roche, Sanofi-Genzyme and Teva. He also received research grants by Biogen, Merck, FISM (Fondazione Italiana Sclerosi Multipla), RELOAD Onlus Association and University of Catania.

**A Perrin Ross** has received honoraria/consultancy fees for serving on advisory boards from Alexion, Biogen Idec., EMD Serono, Merck, Mallinckrodt, Novartis, Roche, Sanofi-Genzyme, Genentech, Inc., Horizon, Janssen, BMS, TG Therapeutics and Greenwich Biosciences.

**L Vanopdenbosch** has received compensation for lectures and consultancy from Biogen, F. Hoffmann-La Roche Ltd, Novartis, Merck-Serono and Sanofi-Genzyme.

**J Wuerfel** was an employee of MIAC AG and is an employee of F. Hoffmann-La Roche Ltd. He has received grants from EU (Horizon2020), Else Kröner-Fresenius Foundation and Novartis Foundation; and his former institution received consultancy fees from Actelion, Bayer, Biogen, F. Hoffmann-La Roche Ltd, Genzyme/Sanofi, Idorsia, lnmuneBio, Novartis and Teva.

**T Künzel** is an employee of F. Hoffmann-La Roche Ltd.

**I Kulyk** is an employee of F. Hoffmann-La Roche Ltd.

**MS Freedman** has received research or educational grants from Sanofi-Genzyme Canada; honoraria/consultancy fees from Alexion, Atara Biotherapeutics, Bayer HealthCare, Beigene, BMS (Cellgene), EMD Inc., F. Hoffmann-La Roche Ltd, Janssen (J&J), Merck-Serono, Novartis, Sanofi-Genzyme and Teva Canada Innovation; is a member of a company advisory board, board of directors or other similar group for Alexion, Atara Biotherapeutics, Bayer HealthCare, Beigene, BMS (Cellgene), Celestra, F. Hoffmann-La Roche Ltd, Janssen (J&J), McKesson, Merck-Serono, Novartis and Sanofi-Genzyme; and has participated in a company sponsored speaker’s bureau for Sanofi-Genzyme and EMD Serono.

Sponsored by F. Hoffmann-La Roche Ltd; editorial assistance was provided by Articulate Science, UK, and funded by F. Hoffmann-La Roche Ltd.
Background

Early high-efficacy treatment of MS may provide long-term clinical benefits and improve disease outcomes.

OCR is an anti-CD20 monoclonal antibody approved for the treatment of RMS and PPMS.

As a high-efficacy therapy, OCR reduces disease activity and the risk of long-term disability progression in patients with RMS.

ENSEMBLE (NCT03085810) was a prospective, 4-year, multicenter, interventional, open-label, single-arm Phase IIIb study investigating OCR as a therapy for early-stage RRMS.

Objectives: To evaluate the effectiveness and safety of OCR over 4 years in treatment-naive patients with early-stage RRMS.

MS, multiple sclerosis; OCR, ocrelizumab; PPMS, primary progressive multiple sclerosis; RMS, relapsing multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis.

Methods

PATIENT POPULATION

RRMS diagnosis (McDonald 2010)¹

Age 18–55 years, inclusive

Disease duration ≤3 years (early-stage MS)

EDSS⁰ 0.0–3.5 inclusive

One or more relapses or MRI activity in prior 12 months

Treatment naive

Screening (up to 4 weeks)

Baseline

Week 8 MRI rebaselining

Week 24

Week 48 interim analysis

Week 72

Week 96 interim analysis

Week 122

Week 144

Week 168

Week 192 4-year primary analysis

OCR 300 mg IV x 2 (Days 1 & 15) for first dose followed by 600 mg IV every 24 weeks for 4 years (192 weeks; maximum of 8 doses)

MRI

KEY ENDPOINT

NEDA is a composite measure of the absence of:

Relapses

24W-CDP

T1w-CELs

New/enlarging T2w-Ls

In ENSEMBLE, MRI measurements were rebaselined at Week 8

ADDITIONAL ENDPOINTS

ARR

24W-CDP

Mean change in EDSS from baseline

Safety

⁰Baseline EDSS is defined as the average of the EDSS scores at screening and baseline visit. If one of the EDSS scores from screening or baseline visits was missing, the other was used for baseline EDSS.

Results: Baseline demographics and disease characteristics; and patient disposition

Baseline demographics and disease characteristics were consistent with a young, early-stage RRMS population. A relatively high retention rate was observed across the study.

Baseline EDSS is defined as the average of the EDSS scores at screening and baseline visit. If one of the EDSS scores from screening or baseline visits was missing, the other was used for baseline EDSS.

<table>
<thead>
<tr>
<th>Variable</th>
<th>ITT population (N=678)</th>
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<tbody>
<tr>
<td>Mean age, year (SD)</td>
<td>32.4 (9.1)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
</tr>
<tr>
<td>Male/female</td>
<td>240 (35.4) / 438 (64.6)</td>
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<tr>
<td>Race, n (%)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>555 (81.9)</td>
</tr>
<tr>
<td>Unknown</td>
<td>88 (13.0)</td>
</tr>
<tr>
<td>Mean duration since MS symptom onset, year (SD)</td>
<td>1.10 (0.84)</td>
</tr>
<tr>
<td>Mean duration since RRMS diagnosis, year (SD)</td>
<td>0.36 (0.40)</td>
</tr>
<tr>
<td>Mean EDSS at baseline* (SD)</td>
<td>1.71 (0.95)</td>
</tr>
<tr>
<td>EDSS at baseline category,* n (%)</td>
<td></td>
</tr>
<tr>
<td>&lt;2.5 / ≥2.5</td>
<td>508 (74.9) / 170 (25.1)</td>
</tr>
<tr>
<td>Number of relapses in the year prior to enrollment, n (%)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>38 (5.6)</td>
</tr>
<tr>
<td>1</td>
<td>438 (64.6)</td>
</tr>
<tr>
<td>2</td>
<td>166 (24.5)</td>
</tr>
<tr>
<td>3</td>
<td>27 (4.0)</td>
</tr>
<tr>
<td>≥4</td>
<td>9 (1.3)</td>
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</tbody>
</table>

Missing, n=6 (0.9%)
Discontinued study, n=119 (17.6%)
- Adverse event, 18 (2.7%)
- Death, 6 (0.9%)
- Withdrawal by participant, 44 (6.5%)
- Physician decision, 11 (1.6%)
- Lost to follow-up, 9 (1.3%)
- Lack of efficacy, 4 (0.6%)
- Pregnancy, 2 (0.3%)
- Commercial OCR available, 2 (0.3%)
- Study terminated by sponsor, 1 (0.1%)
- Other, 22 (3.2%)

Patients who underwent treatment with OCR 600 mg (ITT population)
N=678 (100.0%)

Patients who completed 4-year study period
N=553 (81.6%)

*Baseline EDSS is defined as the average of the EDSS scores at screening and baseline visit. If one of the EDSS scores from screening or baseline visits was missing, the other was used for baseline EDSS.
EDSS, Expanded Disability Status Scale; ITT, intention-to-treat; MS, multiple sclerosis; OCR, ocrelizumab; RRMS, relapsing-remitting multiple sclerosis; SD, standard deviation.
The majority of patients (66.4%) treated with first-line OCR maintain NEDA over 4 years.

INDIVIDUAL COMPONENTS OF NEDA

- No evidence of clinical activity: 77.9% (462/593)
- No evidence of MRI activity: 85.0% (504/593)

- No 24W-CDP: 81.8% (485/593)
- No relapses: 90.9% (539/593)
- No T1w-CEls: 90.6% (537/593)
- No N/E T2w-Ls: 90.4% (536/593)

*NEDAb 66.4% (394/593)

*Patients that discontinued early but experienced an event of disease activity before OCR discontinuation were included in the analysis.

24W-CDP, 24-week confirmed disability progression; EDSS, Expanded Disability Status Scale; NEDA, no evidence of disease activity; N/E T2w-L, new/enlarging T2 weighted lesion; OCR, ocrelizumab; T1w-CEL, T1-weighted contrast-enhancing lesion.
**Results: ARR**

Disease activity at the group level was minimal in patients treated with first-line OCR, equivalent to one relapse every 50 years.

**Adjusted ARR**

\[
\text{Adjusted ARR}^a = 0.020
\]  
(95% CI: 0.015, 0.027)

- Total number of relapses, \( n = 54 \)
- Total patient years followed, \( n = 2,385 \)
- Unadjusted ARR, 0.023

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*Adjusted by duration since MS symptom onset, presence of T1w-CELs at screening, presence of relapses in the last year. Log-transformed exposure time is included as an offset variable. ARR, annualized relapse rate; CI, confidence interval; MS, multiple sclerosis; OCR, ocrelizumab; T1w-CEL, T1-weighted contrast-enhancing lesion.*
Results: 24W-CDP

The majority of patients treated with first-line OCR (84.1%) had no disease progression over 4 years.
The majority of patients treated with first-line OCR (82.1%) maintained stable or improving EDSS scores over 4 years.

Results: EDSS

82.1%
(461/562)
EDSS stable/improved

Absolute change from baseline in EDSS score at 4 years

- Improved: 22.8% (128/562)
- Stable: 59.3% (333/562)
- Worsened: 18.0% (101/562)

EDSS, Expanded Disability Status Scale; OCR, ocrelizumab.

*Absolute change from baseline in EDSS score: Improved, <−0.5; stable, ≤0.5 and ≥−0.5; worsened, >0.5. Patients with missing EDSS scores were excluded.
Safety results were consistent with the known OCR profile, with no new safety signals.

- Fatalities included two cases of COVID-19, two cases of COVID-19 pneumonia, one case of pneumonia and one case of immune reconstitution inflammatory syndrome.
- AEs leading to discontinuation included six neoplasms, three infections, three IRRs and two investigations, as well as disorders of each of the following (one each): Blood, general disorders, immune system, muscle, psychiatric, reproductive and skin disorders.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Ocrelizumab (N=678)</th>
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<tbody>
<tr>
<td></td>
<td>Total number of patients with event, n (%)</td>
</tr>
<tr>
<td>Adverse events</td>
<td>647 (95.4)</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>105 (15.5)</td>
</tr>
<tr>
<td>Deaths &lt;sup&gt;a&lt;/sup&gt;</td>
<td>6 (0.9)</td>
</tr>
<tr>
<td>Infusion-related reactions</td>
<td>351 (51.8)</td>
</tr>
<tr>
<td>Infections</td>
<td>510 (75.2)</td>
</tr>
<tr>
<td>Serious infections</td>
<td>47 (6.9)</td>
</tr>
<tr>
<td>AEs leading to study drug discontinuation &lt;sup&gt;b&lt;/sup&gt;</td>
<td>21 (3.1)</td>
</tr>
<tr>
<td>SAEs leading to study drug discontinuation</td>
<td>13 (1.9)</td>
</tr>
<tr>
<td>AEs leading to dose modification/interruption</td>
<td>11 (1.6)</td>
</tr>
<tr>
<td>SAEs leading to dose modification/interruption</td>
<td>2 (0.3)</td>
</tr>
<tr>
<td>AEs Grade 3 and above</td>
<td>133 (19.6)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Fatalities included two cases of COVID-19, two cases of COVID-19 pneumonia, one case of pneumonia and one case of immune reconstitution inflammatory syndrome.

<sup>b</sup>AEs leading to discontinuation included six neoplasms, three infections, three IRRs and two investigations, as well as disorders of each of the following (one each): Blood, general disorders, immune system, muscle, psychiatric, reproductive and skin disorders.

AE, adverse event; IRR, infusion-related reaction; OCR, ocrelizumab; SAE, serious adverse event.
Results: Safety overview

ADVERSE EVENTS
- AEs were reported in 647/678 patients (95.4%)
- The most common AEs\(^a\) (occurring in >20% patients):
  - Nasopharyngitis 29.2%
  - Headache 27.3%
  - IRRs 51.8%

Of the 51.8% IRRs (n=351):
- 13 were Grade 3
- None were Grade 4 or above

SERIOUS ADVERSE EVENTS
- SAEs were reported in 105/678 patients (15.5%)
- The most common SAEs (occurring in >0.5% patients):
  - COVID-19 (pneumonia) 2.1%
  - MS relapse 1.0%
  - Pneumonia 0.9%

Serious IRRs were reported in 0.4% patients\(^b\)
- 51 SIs were reported in 47 patients (6.9%),
  the most commonly reported cases (≥5 patients):
  - COVID-19 (9)
  - Pneumonia (6)
  - COVID-19 pneumonia (5)

Safety results were consistent with the known OCR profile, with no new safety signals

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\(^a\)AEs defined by preferred terms; \(^b\)the three serious IRRs were: 1) Pruritus and stridor, Grade 3, resolved, drug withdrawn; 2) Diarrhea, dry mouth, palpitations, nausea, tachycardia, Grade 3, resolved, dose not changed; 3) Cough, eye pain, laryngeal discomfort, tachycardia, Grade 3, resolved, dose not changed. None of the three patients were randomized to shorter infusion.

AE, adverse event; IRR, infusion-related reaction; MS, multiple sclerosis; OCR, ocrelizumab; SAE, serious adverse event; SI, serious infection.
Conclusions

Disease activity, based on clinical and MRI measures, was minimal in most patients treated with ocrelizumab over 4 years.

Disability progression remained stable or showed improvements in most patients.

Safety results were consistent with the known ocrelizumab safety profile, with no new safety signals.

The positive benefit–risk profile observed in ENSEMBLE supports the use of ocrelizumab as a first-line therapy in newly diagnosed patients with early RRMS, to control disease activity and reduce long-term disability progression.

**Acknowledgments:** We would like to thank all patients, their families and the investigators who participated in this study.

**RRMS:** relapsing-remitting multiple sclerosis.