Efficacy and Safety of Ocrelizumab in Relapsing Multiple Sclerosis: Results of the Phase III, Interferon β-1a–controlled OPERA I and OPERA II Studies

F Lublin,DL Arnold, AV Bar-Or, G Comi, SL Hauser, K Selmaï, A Traboulsee, P Chin, P Fontoura, H Garren, G Klingenschmidt, D Masterman, L Kappos, HP Hartung \(^1\) on behalf of the OPERA I and OPERA II investigators

The Multiple Sclerosis Research Centre of the University of Cambridge

**BACKGROUND**

- The monitoring program for the ongoing multiple sclerosis (MS) patient database allows assessment of treatment efficacy and safety over time.
- Ocrelizumab (ORC ) is a humanized anti-CD20 monoclonal antibody that has been shown to reduce disease activity in relapsing-remitting multiple sclerosis (RRMS).
- In previous trials, ORC was associated with a reduced incidence of clinical disease activity compared to interferon β-1a (IFN-β-1a).

**OBJECTIVES**

- To evaluate the efficacy and safety of ORC in two identical Phase III randomized, double-blind, double-dummy trials (OPERA I and OPERA II).
- To compare ORC with IFN-β-1a in terms of clinical endpoint reductions and disease-modifying activity.

**METHODS**

- Phase III, double-blind, randomized, controlled clinical trials (OPERA I and OPERA II).
- Patients with RRMS (EDSS 0.0–5.5) were randomized (1:1) to receive ORC 600 mg via intravenous infusion every 24 weeks or subcutaneous IFN-β-1a 44 µg every 48 weeks.
- Primary endpoint: Adjusted annualized relapse rate (ARR) at 96 weeks.
- Secondary endpoints: Disability progression, brain MRI endpoints, and overall NEDA status.

**RESULTS**

**Baseline Demographics and Disease Characteristics**

- Baseline characteristics were well balanced between OPERA I and OPERA II studies, and between treatment arms (Table 1).

**Disability Progression**

- A significant result at a two-sided alpha <0.05 would demonstrate a superior effect of ORC in reducing ARR compared to IFN-β-1a.
- The adjusted ARR at 96 weeks was significantly lower in the ORC group compared to IFN-β-1a (p<0.0001; Table 2).
- Disability progression (CDP) was evaluated in OPERA I and OPERA II studies (Figure 5).
- The proportion of patients having CDP through Week 96 was significantly lower in the ORC group compared to IFN-β-1a (p<0.0001; Table 2).

**Brain MRI Endpoints**

- Brain MRI endpoints included the number of new or gadolinium-enhancing T1 lesions and the number of new T2 lesions.
- The median number of T1 gadolinium-enhancing lesions at Week 96 was significantly lower in the ORC group compared to IFN-β-1a (Table 3).
- The median number of T2 lesions at Week 96 was significantly lower in the ORC group compared to IFN-β-1a (Table 3).

**No Evidence of Disease Activity (NEDA)**

- In an analysis of all patients in the ITT population, ORC increased the proportion of patients that achieved NEDA vs IFN-β-1a (p<0.0001; Table 4).

**CONCLUSIONS**

- ORC significantly reduced clinical disease activity compared to IFN-β-1a in OPERA I and OPERA II studies.
- ORC also significantly reduced disability progression compared to IFN-β-1a in OPERA I and OPERA II studies.

**ACKNOWLEDGMENTS**

- The authors would like to thank all patients, their families, and the investigators who participated in this study.

**REFERENCES**


**Table 1. Baseline demographics and disease characteristics**

<table>
<thead>
<tr>
<th>OPERA I</th>
<th>OPERA II</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EDSS</strong></td>
<td>2.5 (0.7)</td>
</tr>
<tr>
<td><strong>T1 Gd+</strong></td>
<td>3.7 (4.6)</td>
</tr>
<tr>
<td><strong>T2</strong></td>
<td>6.3 (6.0)</td>
</tr>
<tr>
<td><strong>Relapses in previous 12 months</strong></td>
<td>6.7 (6.1)</td>
</tr>
</tbody>
</table>

**Table 2. AEs over the 96-week treatment period**

<table>
<thead>
<tr>
<th>AEs</th>
<th>OPERA I</th>
<th>OPERA II</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Injection-site reaction</strong></td>
<td>5 (1.8)</td>
<td>2 (0.6)</td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td>207 (25.1)</td>
<td>204 (24.7)</td>
</tr>
</tbody>
</table>

**Table 3. AEs over the 96-week treatment period**

<table>
<thead>
<tr>
<th>AEs</th>
<th>OPERA I</th>
<th>OPERA II</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Injection-site reaction</strong></td>
<td>5 (1.8)</td>
<td>2 (0.6)</td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td>207 (25.1)</td>
<td>204 (24.7)</td>
</tr>
</tbody>
</table>

**Table 4. No Evidence of Disease Activity (NEDA)**

<table>
<thead>
<tr>
<th>NEDA Status</th>
<th>OPERA I</th>
<th>OPERA II</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NEDA</strong></td>
<td>96%</td>
<td>96%</td>
</tr>
</tbody>
</table>

**DISCLOSURES**

- The authors declare no conflicts of interest.

**Figures**

- Figure 1: OPERA I and OPERA II study design.
- Figure 2: Protocol-defined AEs by 96 weeks.
- Figure 3: Annualized relapse rates from baseline to Week 96.
- Figure 4: Relative reductions in the sum of 10 gadolinium-enhancing lesions and the median number of new T2 lesions between Week 0 and Week 96 compared to IFN-β-1a.
- Figure 5: Percent change in whole brain volume from baseline to Week 96.

**Supplementary Information**

- Additional data and tables are available in the supplementary information section.