INTRODUCTION

Chimeric (OCRx) is a humanized monoclonal antibody that selectively targets CD20-expressing B cells and has been approved for treatment of relapsing and primary progressive forms of multiple sclerosis (RRMS and PPMS, respectively).1

OCRx is administered subcutaneously as a 300-mg infusion.

- In the OPERA and ORATORIO studies,2–4 all patients received the first dose as two 300-mg intravenous infusions 16 days apart. Patients in the ORATORIO trial continued to receive divided dosing every 24 weeks whereas OPERA patients received subsequent doses as single 600-mg infusions every 24 weeks.
- For the US EU-PA application,5 all patients follow the OPERA dosage schedule.

Infusion-Related Reactions (IRR) in Pivotal Studies

- In pivotal trials of OCR in patients with RRMS (OPERA I [NCT01727324], OPERA II [NCT02312327] and PRMS [OP345972]) IRRs were among the most common adverse events (AEs), similar to findings from clinical trials of other monoclonal antibody treatments6–9:
  - IRRs were defined as any event that occurred during infusion or within 24 hours after infusion.10
  - IRRs were graded by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.0 as mild (Grade 1: asymptomatic or mild symptoms), moderate (Grade 2: moderate, local, or noninvasive intervention indicated), severe (Grade 3: severe or medically significant), life-threatening (Grade 4: life-threatening consequences, urgent intervention indicated) or death related to AE.11
  - Serious IRRs were defined as events that were life-threatening, required hospitalization or prehospitalization, resulted in permanent or significant disability or incapacity or were otherwise considered medically significant or required intervention to prevent the occurrence of the previously listed outcomes.

- In ORATORIO, IRRs occurred in 1% of patients, with no serious IRRs reported in 210 patients treated with OCR.

- In OPERA, IRRs occurred in 2% of patients, with one patient experiencing a Grade 3 IRR.

- Serious IRRs were reported in one OCR-treated patient from the pooled OPERA studies (Grade 4 bronchospasm) in association with the initial OCR infusion and five OCR-treated patients in ORATORIO (psychiatric, cardiac, cutaneous, respiratory and systemic reactions).

- To minimize the occurrence of IRRs, pre-infusion prophylaxis was required for all participants of the pivotal trials,7–10 including 15 minutes before and an antihistamine (30–60 minutes before), with a recommendation for additional analgesic treatment minutes before and an antihistamine (30–60 minutes before), with a recommendation for additional analgesic treatment

Optimizing the Infusion Duration of OCR Treatment

- Aside from the potential for IRRs, another important consideration with infusion therapies is duration of the infusion, since optimizing the infusion duration of OCR treatment is a key consideration in the design of a study to evaluate the safety of administering OCR.

METHODS

Eligibility Criteria

- This open-label, randomized study includes patients aged 18 to 55 years with RRMS enrolled at 17 centers in the US and 15 centers in Europe.

- Patients are divided into two cohorts (Figure 2).

- Patients in Cohort 1 receive the first 600-mg infusion of OCR on Day 1 over 4 hours and the second 600-mg infusion of OCR on Day 2 over 2 hours.

- Patients in Cohort 2 receive the first 300-mg infusion of OCR on Day 1 over 2.5 hours and the second 300-mg infusion of OCR on Day 2 over 2 hours.

- The primary endpoint is the rate and frequency of NCI CTCAE Grade 3 and 4 IRRs in Cohort 1.

- Secondary endpoints include the rate and frequency of Grade 3 and 4 IRRs in Cohort 2 and the rate and frequency of Grade 1–2 IRRs in both cohorts.

Table 1. Recommended infusion schedule for OCR treatment per the US label

<table>
<thead>
<tr>
<th>Time, min</th>
<th>Dose</th>
<th>Number of doses</th>
<th>Cumulative dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–15</td>
<td>300mg</td>
<td>1</td>
<td>300mg</td>
</tr>
<tr>
<td>15–30</td>
<td>300mg</td>
<td>1</td>
<td>600mg</td>
</tr>
<tr>
<td>30–120</td>
<td>300mg</td>
<td>1</td>
<td>900mg</td>
</tr>
<tr>
<td>120–150</td>
<td>300mg</td>
<td>1</td>
<td>1200mg</td>
</tr>
<tr>
<td>150–240</td>
<td>300mg</td>
<td>1</td>
<td>1500mg</td>
</tr>
<tr>
<td>TOTAL</td>
<td></td>
<td></td>
<td>1800mg</td>
</tr>
</tbody>
</table>

Table 2. Schedule of assessments

<table>
<thead>
<tr>
<th>Time, min</th>
<th>Dose</th>
<th>Number of doses</th>
<th>Cumulative dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–15</td>
<td>300mg</td>
<td>1</td>
<td>300mg</td>
</tr>
<tr>
<td>15–30</td>
<td>300mg</td>
<td>1</td>
<td>600mg</td>
</tr>
<tr>
<td>30–120</td>
<td>300mg</td>
<td>1</td>
<td>900mg</td>
</tr>
<tr>
<td>120–150</td>
<td>300mg</td>
<td>1</td>
<td>1200mg</td>
</tr>
<tr>
<td>150–240</td>
<td>300mg</td>
<td>1</td>
<td>1500mg</td>
</tr>
<tr>
<td>TOTAL</td>
<td></td>
<td></td>
<td>1800mg</td>
</tr>
</tbody>
</table>

REFERENCES