Number-Needed-to-Treat Analyses Comparing Clinical Disease Outcomes and Disability Improvement in RMS Patients Treated With Alemtuzumab or Ocrelizumab

Aaron Boster1, Bart Van Wijmennek2, Raed Allrouhni2, Giancarlo Conm3, Regina Berkovich4, Guillermo Izquierdo2, Daniel Kantor5, Christopher LaGanke6, Volker Limbricht7, Richard AL Macdonell8, Heinz Wiendl9, Maria Melanson10, Karthinathan Thangavelu10, Mark S Freedman11; on behalf of the CAMMS223, CARE-MS I, and CARE-MS II Investigators

1Onsite Neurological Physicians, Columbus, OH, USA; 2Rehabilitation & MS-Centre Overbeek, BIOMED, Hasselt University, Hasselt, Belgium; 3Amir Hospital, Shang, Kuwait; 4University Vita-Salute San Raffaele, Milan, Italy; 5University of Southern California, Keck School of Medicine, Los Angeles, CA; 6Vroman Neurology, Inc., Park City, UT, USA; 7Novartis North Central Neurology Associates, Calman, AL, USA; 8Myeloneurology and Palliative Care, Cologne, Germany; 9Austin Health and Florey Institute of Neuroscience and Mental Health, Melbourne, VIC, Australia; 10University of Manitoba, Winnipeg, MB, Canada; 11Sanofi, Cambridge, MA, USA; 12University of Ottawa and the Ottawa Hospital Research Institute, Ottawa, ON, Canada

OBJECTIVE

• To analyze the number needed to treat (NNT) to prevent clinical disease events and improve disability (alemtuzumab) versus placebo or ocrelizumab for treatment-naive relapsing-remitting patients with multiple sclerosis (RRMS)

INTRODUCTION

• Alemtuzumab (a humanized anti-CD52 monoclonal antibody) and ocrelizumab (a humanized anti-CD20 monoclonal antibody) have demonstrated statistically significant improvements in clinical efficacy outcomes in active RRMS patients against the same comparator, SC IFNB-1a, in randomized clinical trials over 2 or 3 years or 96 weeks (CAMMS223, CARE-MS I, and CARE-MS II)3-6 (CAMMS223 [NCT00050778]; CARE-MS I [NCT00632307]; CARE-MS II [NCT01291230]; OPERA I [NCT01473204]; OPERA II [NCT01411233]).

• These differences across studies in patient populations, study sites, and trial designs generally have had an inadequate response to 2 or more therapies indicated for the treatment of MS. In the EU, it is defined as a relapsing-remitting disease with active disease defined by clinical or imaging features. This material may contain terminology that some readers may consider offensive. Readers’ discretion is advised.

• Differences across studies in patient populations, study sites, and trial designs have limited the ability to make direct comparisons between studies. Therefore, indirect comparisons are needed to indirectly compare alemtuzumab and ocrelizumab efficacy.

METHODS

Patients and Procedures

• CAMMS223, CARE-MS I and II, and OPERA I and II were randomized, clinical studies of alemtuzumab or ocrelizumab versus placebo in treatment-naive relapsing-remitting interferon-beta-1a (SC IFNB-1a; CAMMS223, CARE-MS I and II) and ocrelizumab versus SC IFNB-1a (OPERA I and II) in patients with relapsing–remitting multiple sclerosis (RRMS)

• Alemtuzumab 12 mg/day IV (baseline: 5 consecutive days) followed by 2 additional days (alemtuzumab 10 mg/kg IV on day 9) and 16 weeks in a phase 3 trial (NCT00632307). Alemtuzumab was given at the same time every year for 2 years with an interval of 2 years between courses.

• Ocrelizumab 300 mg IV on day 1 and 2 of Course 1; 200 mg IV on day 1 and 2 of Courses 2 to 4.

• Ocrelizumab treatment in CARE-MS II was delayed by 5 years (baseline: 2013) compared to CARE-MS I (baseline: 2008).

• OPERA I: 24 weeks (CAMMS223, CARE-MS II and OPERA I); OPERA II: 96 weeks (OPERA II only) versus SC IFNB-1a (24 weeks in OPERA I and II; 96 weeks in OPERA II).

• OPERA I: 2011; OPERA II: 2013

• Total of 786 CAMMS223/CARE-MS I: 628 CAMMS223/CARE-MS II: 323 OPERA I: and 630 OPERA II patients were included in the NNT analysis

• Within studies, patient populations were well matched for demographic characteristics including age, sex, and history of prior therapy.

• Baseline Expanded Disability Status Scale (EDSS) scores (CAMMS223/CARE-MS I: 2.8 ± 1.2 and 2.8 ± 1.2; CARE-MS II: 2.8 ± 1.2 and 2.8 ± 1.2; OPERA I: 2.8 ± 1.2 and 2.8 ± 1.2; OPERA II: 2.7 ± 1.2). Baseline EDSS was similar across studies.

RESULTS

Table 1. CAMMS223, CARE-MS I, and OPERA I and II Study Designs

<table>
<thead>
<tr>
<th>Study Design</th>
<th>CAMMS223</th>
<th>CARE-MS I</th>
<th>CARE-MS II</th>
<th>OPERA I</th>
<th>OPERA II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 1</td>
<td>randomised</td>
<td>1 (11)</td>
<td>1 (11)</td>
<td>1 (11)</td>
<td>1 (11)</td>
</tr>
<tr>
<td>Phase 2</td>
<td>randomised</td>
<td>2 (22)</td>
<td>2 (22)</td>
<td>2 (22)</td>
<td>2 (22)</td>
</tr>
<tr>
<td>Active RIMs available</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Active RIMs</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
</tr>
</tbody>
</table>

Patients

• Overall NNT was calculated in the intention-to-treat population (ITT-1, ITT-2, per protocol, and univariate treatment in CARE-MS II only).

• NNT is calculated in the ITT-1 population and only includes patients who have had at least one relapse from baseline on treatment (100% per protocol ITT-1).

• NNT is calculated in the ITT-2 population and only includes patients who have not stopped treatment due to adverse events (94% per protocol ITT-2).

Figure 1. NNT to Prevent 1 Relapse

Table 2. NNT Comparisons

<table>
<thead>
<tr>
<th>Study Design</th>
<th>CAMMS223</th>
<th>CARE-MS I</th>
<th>CARE-MS II</th>
<th>OPERA I</th>
<th>OPERA II</th>
</tr>
</thead>
<tbody>
<tr>
<td>NNT to Prevent 1 Relapse</td>
<td>Alemtuzumab 12 mg</td>
<td>0.151*</td>
<td>0.286*</td>
<td>0.156*</td>
<td>0.153*</td>
</tr>
<tr>
<td>NNT to Prevent 1 Relapse</td>
<td>Ocrelizumab 600 mg</td>
<td>0.152*</td>
<td>0.283*</td>
<td>0.155*</td>
<td>0.153*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study Design</th>
<th>CAMMS223</th>
<th>CARE-MS I</th>
<th>CARE-MS II</th>
<th>OPERA I</th>
<th>OPERA II</th>
</tr>
</thead>
<tbody>
<tr>
<td>NNT to Achieve 6-Month CDA in 1 Patient</td>
<td>Alemtuzumab 12 mg</td>
<td>24.0 ± 10.6</td>
<td>40.4 ± 14.0</td>
<td>24.0 ± 10.6</td>
<td>27.0 ± 14.0</td>
</tr>
<tr>
<td>NNT to Achieve 6-Month CDA in 1 Patient</td>
<td>Ocrelizumab 600 mg</td>
<td>25.0 ± 10.5</td>
<td>15.0 ± 14.0</td>
<td>25.0 ± 10.5</td>
<td>14.0 ± 14.0</td>
</tr>
</tbody>
</table>

Figure 3. NNT to Prevent CDA in 1 Patient

Figure 4. NNT to Achieve 6-Month CDA in 1 Patient

CONCLUSIONS

• NNT values to prevent 1 relapse, to prevent CDA, to prevent CDA, and to achieve CDA in 1 patient versus SC IFNB-1a were lower for patients receiving alemtuzumab than for patients receiving ocrelizumab.

• NNT values provide indirect comparative treatment efficacy trials based on absolute risk difference versus relative risk reduction, which may be impacted by overall event rates and differences in severity disease between populations.

• Further data derived from real-world clinical experience will be important to confirm these findings.

REFERENCES