Ocrelizumab Efficacy in PPMS Patients in the Presence/Absence of T1 Gadolinium-Enhancing Lesions at Baseline in a Phase III Placebo-Controlled Trial

J Wolinsky, DL Arnold, A Bar-Or, J de Seze, G Giovannoni, B Hemmer, K Rammohan, P Chin, P Fontoura, H Garren, D Masterman, A Sauter, X Montalban
on behalf of the ORATORIO clinical investigators
NCT01194570
The 2016 Annual Meeting of the Consortium of Multiple Sclerosis Centers
National Harbor, MD, USA, June 1-4, 2016
Oral Presentation DX06

Learning objectives

• To review the primary and key secondary efficacy outcomes of ORATORIO, a randomized, parallel-group, double-blind, placebo-controlled Phase III study of ocrelizumab in primary progressive multiple sclerosis (PPMS)

• To explore the efficacy of ocrelizumab versus placebo in PPMS patients with and without T1 gadolinium-enhancing lesions at baseline

• To assess the overall safety and benefit-risk profile of ocrelizumab versus placebo in PPMS patients in ORATORIO

Primary progressive multiple sclerosis (PPMS): Epidemiology and unmet needs

• More than 2.3 million people worldwide affected by MS

• 10% have PPMS

• No cure for MS

• PPMS is characterized by a progressive course from disease onset

• Relapses and contrast-enhancing lesions may occur in PPMS

• PPMS median age of onset > 40 years

• Men and women affected equally

• No approved therapies for PPMS

• Previous trials have failed to demonstrate efficacy in slowing of disability progression in patients with PPMS

• PPMS is a disabling condition with very high unmet medical need
**ORATORIO: Phase III PPMS**

**Study design**

- Diagnosis of PPMS (2005 revised McDonald criteria)
- Age 18–55 years
- EDSS 3.0–6.5
- CSF: elevated IgG index or >1 oligoclonal bands
- No history of RRMS, SPMS, or PRMS
- No treatment with other MS DMTs at screening

**Blinded Treatment Period**

Minimum five 24-week treatment doses for a total of 120 weeks

**Randomization**

2:1 Randomization

- Stratified by age (≤45 vs >45) and region (USA vs ROW).

**Patients discontinuing treatment**

15.6% of patients discontinued treatment due to lack of efficacy or adverse events.

**SAFETY FOLLOW-UP**

≥48 weeks from date of last infusion

**B-CELL MONITORING**

Continued monitoring occurred if B cells were not repleted.

**Study objectives and endpoints**

**Objectives**

- To evaluate the efficacy and safety of ocrelizumab compared with placebo in patients with PPMS

**Primary endpoint**

- 12-week confirmed disability progression (CDP)

**Secondary endpoints**

- 24-week CDP
- Change in timed 25-foot walk
- Change in T2 lesion volume
- Percent change in whole brain volume
- SF-36 Physical Component Score

**Overall Study Population**

24% reduction in risk of CDP

HR (95% CI): 0.76 (0.59, 0.98); p-value (log rank)=0.03*

**Significant reduction in risk of 12-week confirmed disability progression**

**ORATORIO: MS disease history and baseline characteristics**

<table>
<thead>
<tr>
<th>Placebo N=244</th>
<th>Ocrelizumab N=488</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years</strong></td>
<td>44.4 (8.3)</td>
</tr>
<tr>
<td><strong>Female, n (%)</strong></td>
<td>124 (50.8)</td>
</tr>
<tr>
<td><strong>Time since MS symptom onset, years</strong></td>
<td>6.1 (3.6)</td>
</tr>
<tr>
<td><strong>Time since MS diagnosis, years</strong></td>
<td>2.8 (3.3)</td>
</tr>
<tr>
<td><strong>MS disease-modifying treatment naive, n (%)</strong></td>
<td>214 (87.7)</td>
</tr>
<tr>
<td><strong>EDSS, mean (SD)</strong></td>
<td>4.7 (1.2)</td>
</tr>
</tbody>
</table>
| **MRI**
| Patients with T1 Gad+ lesions, n (%) | 60 (24.7) | 133 (27.5) |
| Brain T2 hyperintense lesion volume, cm³, mean (SD) | 10.9 (13.0) | 12.7 (15.1) |
| Normalized brain volume, cm³, mean (SD) | 1469.9 (88.7) | 1462.9 (83.9) |

**Evaluation of efficacy in patient subgroups with and without T1 gadolinium-enhancing lesions at baseline is a key area of interest**

**No disease-modifying treatments in the previous 2 years.**

EDSS, Expanded Disability Status Scale; Gad+, gadolinium-enhancing; MRI, magnetic resonance imaging; MS, multiple sclerosis; SD, standard deviation.
Significant reduction in risk of 12-week confirmed disability progression

Overall Study Population

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=244)</th>
<th>Ocrelizumab (N=488)</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall population</td>
<td>244</td>
<td>96</td>
<td>0.76</td>
<td>(0.59, 0.98)</td>
</tr>
<tr>
<td>With T1 Gd+ lesions</td>
<td>60</td>
<td>27</td>
<td>0.65</td>
<td>(0.40, 1.06)</td>
</tr>
<tr>
<td>Without T1 Gd+ lesions</td>
<td>183</td>
<td>68</td>
<td>0.84</td>
<td>(0.62, 1.13)</td>
</tr>
</tbody>
</table>

Analysis based on ITT population; p-value based on log-rank test stratified by geographic region and age. Patients with initial disability progression who discontinued treatment early with no confirmatory EDSS assessment were considered as having confirmed disability progression.

CDP, confirmed disability progression; CI, confidence interval; EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; HR, hazard ratio; ITT, intent to treat.

24% reduction in risk of CDP
HR (95% CI): 0.76 (0.59, 0.98); p-value (log rank)=0.03*

Significant reduction in risk of 24-week confirmed disability progression

Overall Study Population

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=244)</th>
<th>Ocrelizumab (N=488)</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall population</td>
<td>244</td>
<td>87</td>
<td>0.75</td>
<td>(0.58, 0.98)</td>
</tr>
<tr>
<td>With T1 Gd+ lesions</td>
<td>60</td>
<td>23</td>
<td>0.67</td>
<td>(0.40, 1.14)</td>
</tr>
<tr>
<td>Without T1 Gd+ lesions</td>
<td>183</td>
<td>63</td>
<td>0.81</td>
<td>(0.59, 1.10)</td>
</tr>
</tbody>
</table>

Analysis based on ITT population; p-value based on log-rank test stratified by geographic region and age. Patients with initial disability progression who discontinued treatment early with no confirmatory EDSS assessment were considered as having confirmed disability progression.

CDP, confirmed disability progression; CI, confidence interval; EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; HR, hazard ratio; ITT, intent to treat.

25% reduction in risk of CDP
HR (95% CI): 0.75 (0.58, 0.98); p-value (log rank)=0.04*

Secondary endpoint

29% relative reduction
p=0.04*

Analysis based on ITT population; p-value based on ranked ANCOVA at 120-week visit adjusted for baseline timed 25-foot walk, geographic region and age with missing values replaced by LOCF. Point estimates and 95% CIs based on mixed analysis on log-transformed ratio adjusted for baseline timed 25-foot walk, geographic region and age.

CI, confidence interval; Gd+, gadolinium-enhancing; ITT, intent to treat; LOCF, last observation carried forward; MMRM, mixed-effect model repeated measure.
Significant reduction in change in timed 25-foot walk from baseline to Week 120

Overall Study Population

% Change From Baseline (Mean, 95% CI)

Placebo n=174 Ocrelizumab n=397

Patients With T1 Gd+ Lesions at Baseline

% Change From Baseline

Placebo n=39 Ocrelizumab n=106

Patients Without T1 Gd+ Lesions at Baseline

% Change From Baseline

Placebo n=134 Ocrelizumab n=288

Secondary endpoint
*Analysis based on ITT population; p-value based on ranked ANCOVA, qf 120-week visit adjusted for baseline timed 25-foot walk, geographic region and age with missing values imputed by LOCF. Point estimates and 95% CI based on MMRM analysis on log-transformed data adjusted for baseline timed 25-foot walk, geographic region and age. CI, confidence interval; Gd+, gadolinium-enhancing; ITT, intent-to-treat; LOCF, last observation carried forward.

MMRM: mixed-effect model repeated measure.

13

Significant reduction in T2 hyperintense lesion volume from baseline to Week 120

Overall Study Population

% Change From Baseline (Mean, 95% CI)

Placebo n=183 Ocrelizumab n=400

Patients With T1 Gd+ Lesions at Baseline

% Change From Baseline

Placebo n=39 Ocrelizumab n=107

Patients Without T1 Gd+ Lesions at Baseline

% Change From Baseline

Placebo n=144 Ocrelizumab n=291

Secondary endpoint
*Analysis based on ITT population; p-value based on ranked ANCOVA, qf 120-week visit adjusted for baseline T2 lesion volume, geographic region and age with missing values imputed by LOCF. Point estimates and 95% CI based on MMRM analysis on log-transformed data adjusted for baseline T2 lesion volume, geographic region and age. ANCOVA, analysis of covariance; CI, confidence interval; Gd+, gadolinium-enhancing; ITT, intent-to-treat; LOCF, last observation carried forward.

MMRM: mixed-effect model repeated measure.

14

Significant reduction in T2 hyperintense lesion volume from baseline to Week 120

Overall Study Population

% Change From Baseline (Mean, 95% CI)

Placebo n=150 Ocrelizumab n=325

% Change in Whole Brain Volume From Week 24

(Mean, 95% CI)

Overall Study Population

Placebo n=183 Ocrelizumab n=400

Secondary endpoint
*Analysis based on ITT population with Week 24 and at least one post-Week 24 assessment; p-value based on MMRM at 120-week visit adjusted for Week 24 brain volume, geographic region and age.

CI, confidence interval; Gd+, gadolinium-enhancing; ITT, intent-to-treat; MMRM, mixed-effect model repeated measure.

15

16
**Significant reduction in rate of whole brain volume loss from Week 24 to Week 120**

**Change in Whole Brain Volume From Week 24 (Mean, 95% CI)**

- **Patients Without T1 Gd+ Lesions at Baseline**
  - Placebo n=150
  - Ocrelizumab n=325
  - Mean Change: -0.4, 95% CI: (0.0, -0.8)
- **Patients With T1 Gd+ Lesions at Baseline**
  - Placebo n=31
  - Ocrelizumab n=83
  - Mean Change: -1.0, 95% CI: (-0.6, -1.4)

**Overall Study Population**

- Placebo n=119
- Ocrelizumab n=241
- Mean Change: -0.8, 95% CI: (0.0, -1.6)

Significant reduction in rate of whole brain volume loss from Week 24 to Week 120.

Secondary endpoint: *Analysis based on ITT population with Week 24 and at least one post-Week 24 assessment; p-value based on MMRM at 120-week visit adjusted for Week 24 brain volume, geographic region and age. CI, confidence interval; Gd+, gadolinium-enhancing; ITT, intent-to-treat; MMRM, mixed-effect model repeated measure.

**Change in SF-36 Physical Component Summary score from baseline to Week 120**

**Overall Study Population**

- Placebo n=128
- Ocrelizumab n=292
- Mean Change: 17.5%, relative reduction 0.38 (95% CI: -1.05, 1.80); p=0.02*

Secondary endpoint: *Analysis based on ITT population with assessment at baseline and at least one post-baseline value; p-value based on MMRM at the 120-week visit adjusted for baseline SF-36 PCS score, geographic region and age. CI, confidence interval; Gd+, gadolinium-enhancing; ITT, intent-to-treat; MMRM, mixed-effect model of repeated measures; PCS, physical component summary; SF-36, short form (36).

**AEs by system organ class reported by ≥10% of patients in either treatment arm until clinical cut-off date**

<table>
<thead>
<tr>
<th>Category</th>
<th>Placebo (n=239)</th>
<th>Ocrelizumab (n=486)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary endpoints</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall patients with ≥1 AE</td>
<td>215 (90.0)</td>
<td>462 (95.1)</td>
</tr>
<tr>
<td><strong>Infections and Infestations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infections and Infestations*</td>
<td>162 (47.8)</td>
<td>339 (49.9)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>65 (37.2)</td>
<td>110 (22.4)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>54 (28.3)</td>
<td>96 (17.3)</td>
</tr>
<tr>
<td>Influenza</td>
<td>21 (12.3)</td>
<td>54 (11.3)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>14 (8.4)</td>
<td>53 (11.9)</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>12 (6.8)</td>
<td>30 (6.1)</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>12 (6.8)</td>
<td>30 (6.1)</td>
</tr>
<tr>
<td><strong>Injury, Poisoning and Procedural Complications</strong></td>
<td>104 (43.5)</td>
<td>263 (54.1)</td>
</tr>
<tr>
<td><strong>Musculoskeletal and Connective Tissue Disorders</strong></td>
<td>98 (41.4)</td>
<td>181 (37.2)</td>
</tr>
<tr>
<td><strong>Nervous System Disorders</strong></td>
<td>79 (33.1)</td>
<td>174 (35.8)</td>
</tr>
<tr>
<td><strong>General Disorders and Administration-Site Conditions</strong></td>
<td>60 (25.1)</td>
<td>130 (26.7)</td>
</tr>
<tr>
<td><strong>Gastrointestinal Disorders</strong></td>
<td>60 (25.1)</td>
<td>126 (25.9)</td>
</tr>
<tr>
<td><strong>Psychiatric Disorders</strong></td>
<td>59 (24.7)</td>
<td>89 (18.3)</td>
</tr>
<tr>
<td><strong>Skin and Subcutaneous Tissue Disorders</strong></td>
<td>44 (18.4)</td>
<td>97 (20.4)</td>
</tr>
<tr>
<td><strong>Respiratory, Thoracic and Mediastinal Disorders</strong></td>
<td>35 (14.6)</td>
<td>97 (19.9)</td>
</tr>
<tr>
<td><strong>Metabolism and Nutrition disorders</strong></td>
<td>28 (11.7)</td>
<td>56 (11.3)</td>
</tr>
<tr>
<td><strong>Renal and Urological Disorders</strong></td>
<td>30 (12.6)</td>
<td>31 (10.3)</td>
</tr>
<tr>
<td><strong>Infectious</strong></td>
<td>28 (10.9)</td>
<td>54 (11.1)</td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td>25 (8.4)</td>
<td>55 (11.9)</td>
</tr>
</tbody>
</table>

*For infections and infestations SOC only, events reported by at least 5% of patients in one treatment arm are presented.*

AE, adverse event; SOC, system organ class.
Infusion-related reactions (IRRs) by dose and severity until clinical cut-off date

<table>
<thead>
<tr>
<th>Dose</th>
<th>Placebo</th>
<th>Ocrelizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>1 SAE</td>
<td>11 SAE</td>
</tr>
<tr>
<td>Day 15</td>
<td>30 SAE</td>
<td>19 SAE</td>
</tr>
</tbody>
</table>

SAEs by system organ class reported by ≥1% of patients in either treatment arm until clinical cut-off date

<table>
<thead>
<tr>
<th>Category</th>
<th>Placebo (n=239)</th>
<th>Ocrelizumab (n=46)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall patients with ≥1 SAE</td>
<td>45 (22.2)</td>
<td>49 (20.4)</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>14 (6.8)</td>
<td>30 (6.2)</td>
</tr>
<tr>
<td>Injury, Poisoning, and Procedural Complications</td>
<td>1 (4.4)</td>
<td>11 (3.9)</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td>9 (3.8)</td>
<td>18 (3.7)</td>
</tr>
<tr>
<td>Neoplasms benign, Malignant and Unspecified (including cysts and polyps)</td>
<td>7 (2.9)</td>
<td>8 (1.6)</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>1 (0.4)</td>
<td>10 (2.1)</td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue Disorders</td>
<td>4 (1.7)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td>3 (1.3)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Renal and Urinary Disorders</td>
<td>3 (1.3)</td>
<td>6 (1.3)</td>
</tr>
</tbody>
</table>

Five deaths were reported:
- 0.4% in the placebo arm: road traffic accident
- 0.8% in the ocrelizumab arm: pulmonary embolism, pneumonia, pancreas carcinoma, pneumonia aspiration

Thirteen malignancies were reported:
- 0.8% in the placebo arm: one cervix adenocarcinoma in situ and one basal cell carcinoma
- 2.3% in the ocrelizumab arm: four breast cancers, one endometrial adenocarcinoma, one angiofollicular lymphoma, one histiocytoma, one metastatic pancreas cancer, and three basal cell carcinomas

Ocrelizumab is the first treatment to show efficacy in PPMS

- Ocrelizumab met the primary and key secondary clinical and MRI endpoints
- Efficacy of ocrelizumab versus placebo in patients with and without T1 Gd+ lesions at baseline was consistent with that in the overall study population
  - However, the ORATORIO study was not powered to demonstrate efficacy differences between these subgroups
- Overall, the proportion of patients experiencing AEs and SAEs associated with ocrelizumab, including serious infections, was similar to placebo
- As expected with IV monoclonal antibodies, a higher proportion of patients in the ocrelizumab group reported infusion-related reactions, the majority of which were mild to moderate in severity
- The imbalance observed in the incidence of malignancies needs to be contextualized with the totality of MS data and epidemiology data; no conclusion can be made based on this low number
- The benefit-risk profile of ocrelizumab in ORATORIO supports it as a potential therapeutic approach in PPMS

Acknowledgements: Investigators and patients involved in the ORATORIO study

SAEs: serious adverse events; Gd+: gadolinium-enhancing; IV: intravenous; MS: multiple sclerosis; PPMS: primary progressive MS; AE: adverse event.