ECTRIMS 2015, Barcelona

Roche Investor Science Conference Call
Monday, 12 October 2015
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2. legislative and regulatory developments and economic conditions;
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4. fluctuations in currency exchange rates and general financial market conditions;
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Agenda

Welcome
Karl Mahler, Head of Investor Relations

Roche in Neuroscience
Ahmed Elhusseiny, Global Therapy Area Head, Neuroscience and Rare Diseases

RMS and PPMS – overview and treatment landscape today
Paulo Fontoura, M.D. Ph.D., Global Head, Clinical Development Neuroscience

Results of ocrelizumab phase 3 studies in RMS and PPMS
Stephen Hauser, M.D., Chair of Neurology, University of California San Francisco

Q&A
Karl Mahler, Head of Investor Relations
Welcome

Karl Mahler
Head of Investor Relations, Roche
# Expanding into new therapeutic areas

## Roche non-oncology development

### Phase I
- **NME fibrosis**
- **NME autoimmune diseases**
- **NME inflammatory diseases**
- **DBO β-lactamase inh bacterial infections**
- **NME infectious diseases**
- **therapeutic vaccine HBV**
- **Lucentis sust. delivery**
- **VEGF-ANG2 MAb wAMD**
- **TAU MAb Alzheimer’s**
- **Nav1.7 inh pain**
- **SNM2 splicer spinal muscular atrophy**
- **α-synuclein MAb Parkinson’s disease**

### Phase II
- **Actemra systemic sclerosis**
- **lebri +/- Esbriet IPF**
- **lebrikizumab atopic dematitis**
- **danoprevir HCV**
- **FluA MAb influenza**
- **TLR7 agonist HBV**
- **sembraagiline Alzheimer’s**
- **GABRA5 NAM Down syndrome**
- **bitopertin OCD**
- **olesoxime spinal muscular atrophy**
- **basimglurant TRD**
- **V1 receptor ant. autism**
- **crenezumab Alzheimer’s**

### Phase III
- **MabThera pemphigus vulgaris**
- **Actemra giant cell arteritis**
- **lebrikizumab severe asthma**
- **etrolizumab ulcerative colitis**
- **etrolizumab Crohn’s disease**
- **lampalizumab geographic atrophy**
- **gantenerumab Alzheimer’s**
- **ocrelizumab RMS**
- **ocrelizumab PPMS**

<table>
<thead>
<tr>
<th>Immunology</th>
<th>Infectious Diseases</th>
<th>Ophthalmology</th>
<th>Neuroscience</th>
</tr>
</thead>
</table>

Status as of July 23, 2015
Multiple Sclerosis market expanding

Improvements over Standard of Care driving market

Global value sales (lc) USDm

Source: IMS Data 2015Q1 Database; * Includes Imusera sales
### Presentations planned

<table>
<thead>
<tr>
<th>Event</th>
<th>Presentations</th>
</tr>
</thead>
</table>
| **San Francisco, 18-21 Nov**  | • **atezolizumab**  
  - mM: P1 vemurafenib combo  
  • cobimetinib + Zelboraf BRAF  
  +mM: coBRIM OS data          |
| **San Antonio, 19-22 Nov**    | • **atezolizumab**  
  - GBM: P1                      |
| **Orlando, 5-8 Dec**          | • **venetoclax**  
  - CLL: P2 R/R p17del  
  • Gazyva  
  - NHL: P3 GADOLIN update  
  - CLL: P3 GREEN update       |
| **San Antonio, 8-12 Dec**     | • **atezolizumab**  
  - TNBC: P1b abraxane combo    |
Roche in Neuroscience

Ahmed Elhusseiny
*Global Therapy Area Head, Neuroscience and Rare Diseases*
Neuroscience is the 2nd largest therapeutic area by value

Oncology/Immunomodulator: 18%
CNS: 16%
Systemic anti-infectives: 13%
Alimentary Tract + Metabol: 13%
Cardiovascular system: 11%
Respiratory System: 6%
Others: 23%

Source: IMS MIDAS, Evaluate Pharma
An area of significant unmet medical needs and huge socioeconomic burdens

- Economic Burden: 3-4% of GDP in the EU
- 13% of global disease burden
- 33-50% of disability claims
- $6 Trillion total direct/in-direct costs by 2030
- 700M cases of mental & neurological disorders reported annually worldwide

Roche in Neuroscience

13 NMEs in clinical development
Multiple sclerosis is expected to become the 3rd biggest indication in 2020 by value

<table>
<thead>
<tr>
<th>2014</th>
<th>Sales in CHF bn</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type II diabetes</td>
<td>34</td>
</tr>
<tr>
<td>Hypertension</td>
<td>21</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>21</td>
</tr>
<tr>
<td>HIV treatment</td>
<td>18</td>
</tr>
<tr>
<td><strong>Multiple sclerosis</strong></td>
<td><strong>18</strong></td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>16</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>16</td>
</tr>
<tr>
<td>Asthma</td>
<td>14</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>12</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>11</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>2020</th>
<th>Sales in CHF bn</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type II diabetes</td>
<td>51</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>23</td>
</tr>
<tr>
<td><strong>Multiple sclerosis</strong></td>
<td><strong>22</strong></td>
</tr>
<tr>
<td>Breast cancer</td>
<td>22</td>
</tr>
<tr>
<td>HIV treatment</td>
<td>22</td>
</tr>
<tr>
<td>NSCLC (lung cancer)</td>
<td>20</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>20</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>17</td>
</tr>
<tr>
<td>Hypertension</td>
<td>14</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>14</td>
</tr>
</tbody>
</table>

Source: Evaluate Pharma
Multiple sclerosis market evolution
New therapies are changing treatment landscape

Evolution of global MS market

ABC7Rs with over 50% share in 2014

Source: Evaluate Pharma Multiples Sclerosis report, September 2015
ABC7Rs include: interferon beta-1a, interferon beta-1b, glatiramer acetate, interferon beta-1a, interferon beta-1a, peginterferon beta-1a
Multiple sclerosis market in patient numbers
*Treated PPMS subset estimated to grow*

- PPMS incidence rate of ~10-15% of total MS market
- Approximately one third of the patients are on some off label therapy\(^2\)
- Treated PPMS patient pool estimated to grow with approved treatment option

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**Total MS market size\(^1\)**

<table>
<thead>
<tr>
<th></th>
<th>Number of patients (in thousands)</th>
</tr>
</thead>
<tbody>
<tr>
<td>US</td>
<td>468</td>
</tr>
<tr>
<td>EU</td>
<td>580</td>
</tr>
</tbody>
</table>

\(^1\)Evaluate Pharma Multiples Sclerosis Report October 2015
\(^2\)Roche internal estimate- no approved therapy
\(^3\)Market size estimate ongoing
RMS and PPMS – overview and treatment landscape today

Paulo Fontoura, MD PhD
Global Head, Clinical Development Neuroscience
RMS and PPMS

Distinct diseases with different need

• Characterized by clearly defined attacks of worsening neurologic function followed by increasing disability later
• Patients usually diagnosed in 20s and 30s
• 12 approved treatment options demonstrated reduction in relapses, progression and number of brain MRI lesions
• Safer high efficacy medicines are needed for earlier treatment

RMS

• Characterized by steady progression of disability from beginning, mostly without relapses
• About 15% of overall MS cases
• Patients usually diagnosed in 40s and 50s
• To date there is no approved disease-modifying treatment, several medicines have failed Ph3 trials

PPMS
Range of treatment options in RMS
Number of agents with varying efficacy/safety profiles

ABCRs=Avonex®, Betaseron®, Copaxone®, Rebiff®
Study designs differ for various RMS agents

Complicating efficacy comparison across studies

### Placebo-controlled studies

<table>
<thead>
<tr>
<th></th>
<th>Natalizumab</th>
<th>Fingolimod</th>
<th>Dimethyl fumarate</th>
<th>Teriflunomide (14mg)</th>
<th>Interferon beta-1a² 44 vg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ARR</strong></td>
<td>-68%</td>
<td>-54%</td>
<td>-53%/44%</td>
<td>-31%/ -36%</td>
<td>-32%</td>
</tr>
<tr>
<td><strong>CDP(12w)</strong></td>
<td>-42%</td>
<td>-30%/n.s.</td>
<td>-38%/n.s.</td>
<td>-30%/ -31%</td>
<td>-30%</td>
</tr>
<tr>
<td><strong>CDP(24w)</strong></td>
<td>-54%</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

### Active comparator-controlled studies

<table>
<thead>
<tr>
<th></th>
<th>Alemtuzumab vs. interferon beta-1a²</th>
<th>Daclizumab vs. interferon beta-1a¹</th>
<th>Ocrelizumab vs. interferon beta-1a²</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ARR</strong></td>
<td>-55%/-49%</td>
<td>-45%</td>
<td>-46%/-47%</td>
</tr>
<tr>
<td><strong>CDP(12w)</strong></td>
<td>NA</td>
<td>n.s.</td>
<td>-40% (-37% and -43%)</td>
</tr>
<tr>
<td><strong>CDP(24w)</strong></td>
<td>-42%/n.s.</td>
<td>NA</td>
<td>-40% (-37% and -43%)</td>
</tr>
</tbody>
</table>

Not an exhaustive list of all studies

Data source: NEJM, Lancet, product labels; ARR=annualized relapse rate, CDP=confirmed disability progression

¹Avonex®; ²Rebif®; n.s.=not significant
PPMS – challenging disease
Randomised studies failed to demonstrate benefit

Number of different MS agents are used in PPMS off-label despite lack of efficacy data
ORATORIO

First study with positive primary and secondary outcome data
**ORCHESTRA program**

**Ocrelizumab development in RMS and PPMS**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Relapsing multiple sclerosis (RMS)</th>
<th>Primary progressive multiple sclerosis (PPMS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase/study</td>
<td>Phase III OPERA I</td>
<td>Phase III OPERA II</td>
</tr>
<tr>
<td># of patients</td>
<td>N=800</td>
<td>N=800</td>
</tr>
</tbody>
</table>
| Design | • 96-week treatment period:  
  • **ARM A**: Ocrelizumab 2x 300 mg iv followed by 600 mg iv every 24 weeks  
  • **ARM B**: Interferon β-1a 44ug s.c. 3/weekly | • 96-week treatment period:  
  • **ARM A**: Ocrelizumab 2x 300 mg iv followed by 600 mg iv every 24 weeks  
  • **ARM B**: Interferon β-1a 44ug s.c. 3/weekly | • 120-week treatment period:  
  • **ARM A**: Ocrelizumab 2x 300 mg iv every 24 weeks  
  • **ARM B**: Placebo |
| Primary endpoint | • Annualized relapse rate at 96 weeks versus Rebif | • Annualized relapse rate at 96 weeks versus Rebif | • Sustained disability progression versus placebo by Expanded Disability Status Scale (EDSS) |

The ORCHESTRA program included several state of the art methodology elements:

- Double-blind/double dummy design in OPERA 1 and 2
- Active comparator with high efficacy ABCR
- Robust evaluation of efficacy including clinically meaningful endpoints and MRI methods (allowing evaluation of NEDA, atrophy)
Continued high unmet medical need in MS

**Key areas of unmet medical need in MS**

1. DMT’s offering optimal disease control in relapsing forms of MS with favorable safety profiles
2. Neuroprotective / reparative therapies
3. Therapies for progressive MS
4. Better symptomatic control – cognition, fatigue
5. Predictive prognostic, diagnostic, therapeutic response markers

Source: adapted from Decision Resources, Cognos Study, Multiple Sclerosis, January 2015

DMT=disease modifying therapy
Results of ocrelizumab phase 3 studies in RMS and PPMS

Stephen Hauser, MD
Chair of Neurology, University of California San Francisco
Efficacy and Safety of Ocrelizumab in Relapsing Multiple Sclerosis – Results of the Phase III Double-blind, Interferon beta-1a-controlled OPERA I and II Studies

SL Hauser, GC Comi, H-P Hartung, K Selmaï, A Traboulsee, A Bar-Or, DL Arnold, G Klingelschmitt, F Lublin, H Garren, L Kappos, on behalf of the OPERA I and II clinical investigators

OPERA I, NCT01247324; OPERA II, NCT01412333

31st Congress of the European Committee for Treatment and Research in Multiple Sclerosis 2015

Platform presentation number 190
B cells can contribute to the pathophysiology of MS

Targeting CD20⁺ B cells may preserve B cell reconstitution and long-term immune memory

B-cell Reconstitution

PLASMA CELLS

Ocrelizumab is a humanised monoclonal antibody that selectively depletes CD20⁺ B cells

OPERA I and II: Two identical studies evaluating the efficacy and safety of ocrelizumab in RMS

**Double-blind Double-dummy Treatment Period**

- **Ocrelizumab**
  - Dose 1: 300 mg i.v. x 2 (days 1 & 15)
  - Doses 2-4: 600 mg i.v. x 1

- **IFN β-1a**
  - Dosed 44 μg s.c. 3 × per week

**1:1 Randomisation**

- RMS diagnosis
- 18–55 yrs
- ≥2 clinical relapses within last 2 yrs or 1 relapse in last yr
- EDSS of 0.0–5.5

**OLE screening period**

- Continued monitoring occurs if B cells are not repleted.

**Safety follow-up**

≈48 weeks from date of last infusion

**B-cell monitoring‡**

EDSS, Expanded Disability Status Scale; IFN, interferon; i.v., intravenous; OLE, open-label extension; RMS, relapsing multiple sclerosis; s.c., subcutaneous.
Objectives

• To evaluate the efficacy and safety of ocrelizumab compared with IFN β-1a in patients with RMS

Primary endpoint

• Annualised relapse rate (ARR) at 96 weeks

Key secondary endpoints

• 12- and 24-week confirmed disability progression (CDP)
• Number of T1 Gd-enhancing lesions (weeks 24, 48 and 96)
• Number of new and/or enlarging T2 lesions (weeks 24, 48 and 96)
Over 85% of patients in the ocrelizumab arms completed the OPERA I and OPERA II studies

<table>
<thead>
<tr>
<th></th>
<th>OPERA I</th>
<th>OPERA II</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IFN β -1a 44 μg</td>
<td>Ocrelizumab 600 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ITT*, n</td>
<td>411</td>
<td>410</td>
</tr>
<tr>
<td>Treated, n</td>
<td>409</td>
<td>408</td>
</tr>
<tr>
<td>Withdrawn, n (%)</td>
<td>69 (17)</td>
<td>42 (10)</td>
</tr>
<tr>
<td>Entered safety follow-up, n (%)</td>
<td>42 (17)</td>
<td>25 (6.1)</td>
</tr>
<tr>
<td>Completed, n (%)</td>
<td>340 (83)</td>
<td>366 (89)</td>
</tr>
<tr>
<td>Entered safety follow-up, n (%)</td>
<td>12 (4)</td>
<td>17 (5)</td>
</tr>
<tr>
<td>Entered open-label extension, n (%)</td>
<td>326 (96)</td>
<td>352 (96)</td>
</tr>
</tbody>
</table>

*All randomised patients will be included in the ITT population. Patients prematurely withdrawing from the study for any reason and for whom an assessment was not performed for whatever reason will still be included in the ITT analysis. AE, adverse event; IFN, interferon; ITT, intent to treat.
<table>
<thead>
<tr>
<th></th>
<th>OPERA I</th>
<th>OPERA II</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IFN β -1a 44 μg n=411</td>
<td>IFN β -1a 44 μg n=418</td>
</tr>
<tr>
<td></td>
<td>Ocrelizumab 600 mg n=410</td>
<td>Ocrelizumab 600 mg n=417</td>
</tr>
<tr>
<td>Age, yr, mean (SD)</td>
<td>36.9 (9.3)</td>
<td>37.4 (9.0)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>272 (66.2)</td>
<td>280 (67.0)</td>
</tr>
<tr>
<td>Time since onset, yr, mean (SD)</td>
<td>6.3 (6.0)</td>
<td>6.7 (6.1)</td>
</tr>
<tr>
<td>Time since diagnosis, yr, mean (SD)</td>
<td>3.7 (4.6)</td>
<td>4.1 (5.1)</td>
</tr>
<tr>
<td>Relapses previous 12 months, mean (SD)</td>
<td>1.3 (0.6)</td>
<td>1.3 (0.7)</td>
</tr>
<tr>
<td>Previously untreated*, n (%)</td>
<td>292 (71.4)</td>
<td>314 (75.3)</td>
</tr>
<tr>
<td>EDSS, mean (SD)</td>
<td>2.8 (1.3)</td>
<td>2.8 (1.4)</td>
</tr>
<tr>
<td>Patients with Gd* lesions, n (%)</td>
<td>155 (38.1)</td>
<td>172 (41.4)</td>
</tr>
<tr>
<td>Number Gd* T1 lesions, mean (SD)</td>
<td>1.9 (5.2)</td>
<td>2.0 (4.9)</td>
</tr>
<tr>
<td>Number T2 lesions, mean (SD)</td>
<td>51.1 (39.9)</td>
<td>51.0 (39.0)</td>
</tr>
</tbody>
</table>

*Untreated with disease-modifying therapy in 2 years prior to study entry.

EDSS, Expanded Disability Status Scale; Gd*, gadolinium enhancing; IFN, interferon; SD, standard deviation; yr, year.
**Primary endpoint:**
Significant reduction in ARR compared with IFN β -1a

**ITT**
*Adjusted ARR calculated by negative binomial regression and adjusted for baseline EDSS score (<4.0 vs ≥4.0), and geographic region (US vs ROW).
ARR, annualised relapse rate; EDSS, Expanded Disability Status Scale; IFN, interferon; ROW, rest of the world.

**OPERA I**
- **46% ARR reduction vs IFN β -1a**
  - p<0.0001

**OPERA II**
- **47% ARR reduction vs IFN β -1a**
  - p<0.0001
Secondary endpoints: Significant reduction in CDP in the pre-specified pooled analysis of OPERA I and OPERA II

Time to 12-week CDP

- **IFN-β-1a 44 μg (n=829)**
- **Ocrelizumab 600 mg (n=827)**

Risk reduction: 40%

HR (95% CI): 0.60 (0.45, 0.81); p=0.0006

Time to 24-week CDP

- **IFN-β-1a 44 μg (n=829)**
- **Ocrelizumab 600 mg (n=827)**

Risk reduction: 40%

HR (95% CI): 0.60 (0.43, 0.84); p=0.0025

**ITT**

CDP, confirmed disability progression; CI, confidence interval; HR, hazard ratio; IFN, interferon; OCR, ocrelizumab.
Exploratory analysis by study: Consistent reduction in 12- and 24-week CDP

**OPERA I**

- **IFN-β-1a 44 µg (n=411)**
- **Ocrelizumab 600 mg (n=410)**

For ≥12 weeks:
- **Risk reduction: 43%**
- HR (95% CI): 0.57 (0.37, 0.90); p=0.0139

For ≥24 weeks:
- **Risk reduction: 43%**
- HR (95% CI): 0.57 (0.34, 0.95); p=0.0278

**OPERA II**

- **IFN-β-1a 44 µg (n=418)**
- **Ocrelizumab 600 mg (n=417)**

For ≥12 weeks:
- **Risk reduction: 37%**
- HR (95% CI): 0.63 (0.42, 0.92); p=0.0169

For ≥24 weeks:
- **Risk reduction: 37%**
- HR (95% CI): 0.63 (0.40, 0.98); p=0.0370

**ITT**
- CDP, confirmed disability progression; CI, confidence interval; HR, hazard ratio; IFN, interferon; OCR, ocrelizumab.
**Secondary endpoint:** Significant reduction in number of T1 Gd⁺ lesions compared with IFN β -1a

- **OPERA I**
  - Mean Number of T1 Gd-enhancing Lesions per MRI Scan:
  - IFN β-1a 44 µg (n=411): 0.286
  - Ocrelizumab 600 mg (n=410): 0.016
  - 94% Reduction vs IFN β-1a, p<0.0001

- **OPERA II**
  - Mean Number of T1 Gd-enhancing Lesions per MRI Scan:
  - IFN β-1a 44 µg (n=418): 0.416
  - Ocrelizumab 600 mg (n=417): 0.021
  - 95% Reduction vs IFN β-1a, p<0.0001

*ITT
*Adjusted by means calculated by negative binomial regression and adjusted for baseline T1 Gd lesion (present or not), baseline EDSS (<4.0 vs ≥4.0) and geographical region (US vs ROW).

EDSS, Expanded Disability Status Scale; Gd⁺, gadolinium enhancing; IFN, interferon; MRI, magnetic resonance imaging; ROW, rest of the world.
**Exploratory endpoint:**
Reduction in mean T1 Gd⁺ lesions compared with IFN β -1a

**OPERA I**

<table>
<thead>
<tr>
<th>Week</th>
<th>IFN β-1a 44 μg</th>
<th>Ocrelizumab 600 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td>0.372</td>
<td>0.382</td>
</tr>
<tr>
<td>48</td>
<td>0.357</td>
<td>0.377</td>
</tr>
<tr>
<td>96</td>
<td>0.335</td>
<td>0.359</td>
</tr>
</tbody>
</table>

91% p<0.0001

**OPERA II**

<table>
<thead>
<tr>
<th>Week</th>
<th>IFN β-1a 44 μg</th>
<th>Ocrelizumab 600 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td>0.372</td>
<td>0.385</td>
</tr>
<tr>
<td>48</td>
<td>0.334</td>
<td>0.373</td>
</tr>
<tr>
<td>96</td>
<td>0.311</td>
<td>0.359</td>
</tr>
</tbody>
</table>

97% p<0.0001

ITT
*Adjusted by means calculated by negative binomial regression and adjusted for baseline T1 Gd lesion (present or not), baseline EDSS (<4.0 vs ≥4.0) and geographical region (US vs ROW).

EDSS, Expanded Disability Status Scale; Gd⁺, gadolinium enhancing; IFN, interferon; MRI, magnetic resonance imaging; ROW, rest of the world.
Secondary endpoint: Significant reduction in number of new and/or enlarging T2 hyperintense lesions compared with IFN β-1a

**OPERA I**

- **IFN β-1a 44 μg (n=411)**
- **Ocrelizumab 600 mg (n=410)**

- Mean New or Enlarging T2 Hyperintense Lesions per MRI Scan:
  - **1.413**
  - **0.323**

- **77% Reduction vs IFN β-1a**
  - p<0.0001

**OPERA II**

- **IFN β-1a 44 μg (n=418)**
- **Ocrelizumab 600 mg (n=417)**

- Mean New or Enlarging T2 Hyperintense Lesions per MRI Scan:
  - **1.904**
  - **0.325**

- **83% Reduction vs IFN β-1a**
  - p<0.0001

*Adjusted by means calculated by negative binomial regression and adjusted for baseline T2 lesion count, baseline EDSS (<4.0 vs ≥4.0) and geographical region (US vs ROW).

EDSS, Expanded Disability Status Scale; IFN, interferon; MRI, magnetic resonance imaging; ROW, rest of the world.
**Exploratory endpoint:** Reduction in total new and/or enlarging T2 hyperintense lesions compared with IFN β-1a

**OPERA I**

- **IFN β-1a 44 μg**
- **Ocrelizumab 600 mg**

**Mean Number Per Patient Per MRI Scan**

- **Week 24:** IFN β-1a 373, Ocrelizumab 385
- **Week 48:** IFN β-1a 357, Ocrelizumab 378
- **Week 96:** IFN β-1a 336, Ocrelizumab 360

- **Week 24:** 41% reduction, p=0.0002
- **Week 48:** 94% reduction, p<0.0001
- **Week 96:** 98% reduction, p<0.0001

**ITT**

*Adjusted by means calculated by negative binomial regression and adjusted for baseline T2 lesion count, baseline EDSS (<4.0 vs ≥4.0) and geographical region (US vs ROW).

EDSS, Expanded Disability Status Scale; IFN, interferon; MRI, magnetic resonance imaging; ROW, rest of the world.
### Exploratory endpoints compared with IFN β-1a:

#### Change in brain volume

**OPERA I**

Percentage Change in Brain Volume from Baseline to Week 96

- **%Change From Baseline to Week 96 (Mean, 95% CI)**

  - **IFN β-1a 44 μg**
  - **Ocrelizumab 600 mg**

  - 23.5% reduction in rate of brain volume loss vs IFN β-1a

  - p<0.0001

#### No evidence of disease activity (NEDA)

**OPERA I**

NEDA

- 64% improvement vs IFN β-1a

  - p<0.0001

**NEDA** is defined as: no protocol-defined relapses, no CDP events, no new or enlarging T2 lesions, and no Gd+ T1 lesions

---

**ITT**

Exploratory endpoints

*Compared using the Cochran–Mantel–Haenszel test stratified by geographic region (US vs ROW) and baseline EDSS score (<4.0 vs ≥4.0). EDSS, Expanded Disability Status Scale; Gd+, gadolinium enhancing; IFN, interferon; ROW, rest of the world.
Exploratory endpoints compared with IFN β-1a:

Change in brain volume

**OPERA II**
Percentage Change in Brain Volume from Baseline to Week 96

<table>
<thead>
<tr>
<th>Week</th>
<th>%Change From Baseline to Week 96 (Mean, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>24</td>
<td>-0.4</td>
</tr>
<tr>
<td>48</td>
<td>-0.8</td>
</tr>
<tr>
<td>96</td>
<td>-1.2</td>
</tr>
</tbody>
</table>

23.8% reduction in rate of brain volume loss vs IFN β-1a
p=0.0001

No evidence of disease activity (NEDA)

**OPERA II**
NEDA

89% improvement vs IFN β-1a
p<0.0001

NEDA is defined as: no protocol-defined relapses, no CDP events, no new or enlarging T2 lesions, and no Gd+ T1 lesions

**ITT**
Exploratory endpoints

*Compared using the Cochran–Mantel–Haenszel test stratified by geographic region (US vs ROW) and baseline EDSS score (<4.0 vs ≥4.0).

EDSS, Expanded Disability Status Scale; Gd+, gadolinium enhancing; IFN, interferon; ROW, rest of the world.
# Adverse events over 96 weeks

<table>
<thead>
<tr>
<th>Category</th>
<th>IFN β-1a 44 μg (n=826)</th>
<th>Ocrelizumab 600 mg (n=825)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total number of patients with ≥1 AE</strong></td>
<td>688 (83.3)</td>
<td>687 (83.3)</td>
</tr>
<tr>
<td><strong>Total number of patients with ≥1 AE occurring at a frequency ≥5% in either arm</strong></td>
<td>539 (65.3)</td>
<td>544 (65.9)</td>
</tr>
<tr>
<td><strong>Injury, Poisoning and Procedural Complications</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Infusion-related reaction</td>
<td>155 (18.8)</td>
</tr>
<tr>
<td></td>
<td>General Disorders and Administration-site Conditions</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Infusion-related reaction</td>
<td>80 (9.7)</td>
</tr>
<tr>
<td></td>
<td>Influenza-like illness</td>
<td>396 (47.9)</td>
</tr>
<tr>
<td></td>
<td>Injection-site erythema</td>
<td>177 (21.4)</td>
</tr>
<tr>
<td></td>
<td>Fatigue</td>
<td>127 (15.4)</td>
</tr>
<tr>
<td></td>
<td>Injection-site reaction</td>
<td>64 (7.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Infections and Infestations</strong></td>
<td>433 (52.4)</td>
</tr>
<tr>
<td></td>
<td>Upper respiratory tract infection</td>
<td>87 (10.5)</td>
</tr>
<tr>
<td></td>
<td>Nasopharyngitis</td>
<td>84 (10.2)</td>
</tr>
<tr>
<td></td>
<td>Urinary tract infection</td>
<td>100 (12.1)</td>
</tr>
<tr>
<td></td>
<td>Sinusitis</td>
<td>45 (5.4)</td>
</tr>
<tr>
<td></td>
<td>Bronchitis</td>
<td>29 (3.5)</td>
</tr>
<tr>
<td></td>
<td><strong>Nervous System Disorders</strong></td>
<td>252 (30.5)</td>
</tr>
<tr>
<td></td>
<td>Headache</td>
<td>124 (15.0)</td>
</tr>
<tr>
<td></td>
<td><strong>Psychiatric Disorders</strong></td>
<td>144 (17.4)</td>
</tr>
<tr>
<td></td>
<td>Depression</td>
<td>54 (6.5)</td>
</tr>
<tr>
<td></td>
<td>Insomnia</td>
<td>38 (4.6)</td>
</tr>
<tr>
<td></td>
<td><strong>Musculoskeletal and Connective Tissue Disorders</strong></td>
<td>207 (25.1)</td>
</tr>
<tr>
<td></td>
<td>Back pain</td>
<td>37 (4.5)</td>
</tr>
<tr>
<td></td>
<td>Arthralgia</td>
<td>51 (6.2)</td>
</tr>
</tbody>
</table>

Table includes only pooled AEs occurring in ≥5% of patients in at least one treatment group and the corresponding system organ classes. AE, adverse event; IFN, interferon.
Serious adverse events were low over 96 weeks

<table>
<thead>
<tr>
<th>n (%)</th>
<th>IFN β -1a 44 μg (n=826)</th>
<th>Ocrelizumab 600 mg (n=825)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall patients with ≥1 SAE</td>
<td>72 (8.7)</td>
<td>57 (6.9)</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>24 (2.9)</td>
<td>11 (1.3)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>11 (1.3)</td>
<td>8 (1.0)</td>
</tr>
<tr>
<td>Injury, poisoning, and procedural complications</td>
<td>10 (1.2)</td>
<td>6 (0.7)</td>
</tr>
</tbody>
</table>

During OPERA I and OPERA II, three deaths occurred
- IFN β -1a 44 μg arm: suicide, mechanical ileus
- Ocrelizumab 600 mg arm: suicide

Six malignancies were reported:
- IFN β -1a 44 μg arm: mantle cell lymphoma and squamous cell carcinoma
- Ocrelizumab 600 mg arm: renal cancer, melanoma and two breast cancers

IFN, interferon; SAE, serious adverse event.
Most common AE associated with ocrelizumab was infusion-related reactions (IRR)
Mostly mild-to-moderate in severity*, †

*Numbers in columns represent the proportion of patients experiencing a grade of IRR.
†Grading per Common Terminology Criteria.

Note: All received 100 mg i.v. methylprednisolone.
AE, adverse event; IFN, interferon.

• 11 patients (1.3%) withdrew from ocrelizumab treatment due to an IRR during the first infusion
In OPERA I and OPERA II, ocrelizumab was effective in relapsing MS and had a favourable safety profile over 96 weeks

- Compared with IFN β-1a, ocrelizumab significantly reduced:
  - ARR
  - 12- and 24-week CDP
  - T1 Gd⁺ lesions
  - New and/or enlarging T2 lesions

- In exploratory analyses compared with IFN β-1a, ocrelizumab:
  - Reduced brain volume loss
  - Increased proportion of patients with NEDA

- Overall, in OPERA I and OPERA II, ocrelizumab had a similar safety profile compared with IFN β-1a over 96 weeks

- OPERA I and OPERA II showed that targeting CD20⁺ B cells with ocrelizumab is a potential therapeutic approach in relapsing MS

CDP, confirmed disability progression; Gd⁺, gadolinium enhancing; IFN, interferon.
Range of treatment options in RMS
Number of agents with varying efficacy/safety profiles

Legend
Injectable
Oral
MAB

Alemtuzumab
Natalizumab
(DCV+)

Daclizumab

Fingolimod

Teriflunomide

Dimethyl fumarate

Unmet need

Safer/Use

More

Less

Efficacy

Less/Later

SAFETY/USE

More/Earlier

ABCRs=Avonex®, Betaseron®, Copaxone®, Rebiff®
Efficacy and Safety of Ocrelizumab in Primary Progressive Multiple Sclerosis – Results of the Phase III, Double-blind, Placebo-controlled ORATORIO Study

X Montalban, B Hemmer, K Rammohan, G Giovannoni, J de Seze, A Bar-Or, DL Arnold, A Sauter, D Masterman, P Chin, H Garren, J Wolinsky, on behalf of the ORATORIO clinical investigators

NCT01194570

31st Congress of the European Committee for Treatment and Research in Multiple Sclerosis 2015

Platform presentation number 228
ORATORIO: Phase III Study in primary progressive MS (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

2:1 Randomisation

- Patients received methylprednisolone prior to each ocrelizumab infusion or placebo infusion.
- The blinded treatment period may be extended until database lock.
- 2:1 randomisation stratified by age (≤45 vs >45) and region (US vs ROW).
- Continued monitoring occurs if B cells are not repleted.

BL, baseline; CSF, cerebrospinal fluid; DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; i.v., intravenous; MRI, magnetic resonance imaging.

ORATORIO: 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)

Key secondary endpoints

• 24-week CDP
• Timed 25-foot walk (baseline to Week 120)
• T2 lesion volume (baseline to Week 120)
• Whole brain volume (Week 24 to Week 120)

Montalban X, et al. AAN 2015; Poster P7.017.
80% of patients in the ocrelizumab arm completed the ORATORIO study

Randomised

Placebo: 244
Ocrelizumab 600 mg: 488

Treated

Placebo: 239
Ocrelizumab 600 mg: 486

Withdrawn at clinical cut-off date

Placebo: 80 (33% of treated)
Ocrelizumab 600 mg: 96 (20% of treated)

Entered safety follow-up

Placebo: 45 (56% of withdrawn)
Ocrelizumab 600 mg: 61 (64% of withdrawn)

Ongoing

Placebo: 159 (67% of treated)
Ocrelizumab 600 mg: 390 (80% of treated)
### MS disease history and baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Placebo n=244</th>
<th>Ocrelizumab 600 mg n=488</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, yr, mean (SD)</strong></td>
<td>44.4 (8.3)</td>
<td>44.7 (7.9)</td>
</tr>
<tr>
<td><strong>Female, n (%)</strong></td>
<td>124 (50.8)</td>
<td>237 (48.6)</td>
</tr>
<tr>
<td><strong>Time since symptom onset, yr, mean (SD)</strong></td>
<td>6.1 (3.6)</td>
<td>6.7 (4.0)</td>
</tr>
<tr>
<td><strong>Time since diagnosis, yr, mean (SD)</strong></td>
<td>2.8 (3.3)</td>
<td>2.9 (3.2)</td>
</tr>
<tr>
<td><strong>MS disease-modifying treatment naive, n (%)</strong></td>
<td>214 (87.7)</td>
<td>433 (88.7)</td>
</tr>
<tr>
<td><strong>EDSS, mean (SD)</strong></td>
<td>4.7 (1.2)</td>
<td>4.7 (1.2)</td>
</tr>
<tr>
<td><strong>MRI</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with Gd⁺ lesions, n (%)</td>
<td>60 (24.7)</td>
<td>133 (27.5)</td>
</tr>
<tr>
<td>Number of Gd⁺ T1 lesions, mean (SD)</td>
<td>0.6 (1.6)</td>
<td>1.2 (5.1)</td>
</tr>
<tr>
<td>T2 lesion volume, cm³, mean (SD)</td>
<td>10.9 (13.0)</td>
<td>12.7 (15.1)</td>
</tr>
<tr>
<td>Normalised brain volume, cm³, mean (SD)</td>
<td>1469.9 (88.7)</td>
<td>1462.9 (83.9)</td>
</tr>
</tbody>
</table>

*ITT*

EDSS, Expanded Disability Status Scale; Gd, gadolinium; MRI, magnetic resonance imaging; MS, multiple sclerosis; SD, standard deviation; yr, year.
Primary endpoint: Significant reduction in 12-week CDP

Time to 12-week Confirmed Disability Progression

- Placebo (n=244)
- Ocrelizumab 600 mg (n=488)

24% reduction in risk of CDP
HR (95% CI): 0.76 (0.59, 0.98); p=0.0321

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; EDSS, Expanded Disability Status Scale; HR, hazard ratio; ITT, intent to treat.
**Secondary endpoint:** Significant reduction in 24-week CDP

Time to 24-week Confirmed Disability Progression

- **Placebo (n=244)**
- **Ocrelizumab 600 mg (n=488)**

### Analysis

- **25% reduction in risk of CDP**
- **HR (95% CI): 0.75 (0.58, 0.98); p=0.0365**

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; EDSS, Expanded Disability Status Scale; HR, hazard ratio; ITT, intent to treat.
Secondary endpoint: Significant reduction in the progression rate of walking time

Percent Change in Timed 25-Foot Walk From Baseline to Week 120

*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 imputed by LOCF. Point estimates and 95% CIs based on MMRM analysis on log-transformed data adjusted for baseline timed 25-foot walk, geographic region and age.

CI, confidence interval; HR, hazard ratio; ITT, intent to treat; LOCF, last observation carried forward.
**Secondary endpoint**: Significant reduction in T2 lesion volume from baseline to Week 120

On placebo, T2 lesion volume increases by 7.4%.
Ocrelizumab 600 mg decreases T2 lesion volume by 3.4%.

*Analysis based on ITT population; p-value based on ranked ANCOVA at 120-week visit adjusted for baseline T2 lesion volume, geographic region and age with missing values imputed by LOCF. Point estimates and 95% CIs based on MMRM analysis on log-transformed data adjusted for baseline T2 lesion volume, geographic region and age.

CI, confidence interval; ITT, intent to treat; LOCF, last observation carried forward.
**Secondary endpoint:** Significant reduction in the rate of whole brain volume loss

**Percent Change of Whole Brain Volume from Week 24 to Week 120**

- **Placebo (n=244)**
- **Ocrelizumab 600 mg (n=488)**

*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; ITT, intent to treat.
### 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 600 mg (n=486)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall patients with ≥1 AE</strong></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>Nasopharyngitis</td>
<td>65 (27.2)</td>
<td>110 (22.6)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>54 (22.6)</td>
<td>96 (19.8)</td>
</tr>
<tr>
<td>Influenza</td>
<td>21 (8.8)</td>
<td>56 (11.5)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>14 (5.9)</td>
<td>53 (10.9)</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>12 (5.0)</td>
<td>30 (6.2)</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>12 (5.0)</td>
<td>20 (4.1)</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 (41.0)</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>99 (20.4)</td>
</tr>
<tr>
<td><strong>Respiratory, Thoracic and Mediastinal Disorders</strong></td>
<td>35 (14.6)</td>
<td>87 (17.9)</td>
</tr>
<tr>
<td><strong>Metabolism and Nutrition disorders</strong></td>
<td>28 (11.7)</td>
<td>56 (11.5)</td>
</tr>
<tr>
<td><strong>Renal and Urinary Disorders</strong></td>
<td>30 (12.6)</td>
<td>51 (10.5)</td>
</tr>
<tr>
<td><strong>Vascular Disorders</strong></td>
<td>26 (10.9)</td>
<td>54 (11.1)</td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td>20 (8.4)</td>
<td>58 (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; SAE, serious adverse event.
SAEs by system organ class reported by ≥1% of patients in either treatment arm until clinical cut-off date

<table>
<thead>
<tr>
<th>n (%)</th>
<th>Placebo (n=239)</th>
<th>Ocrelizumab 600 mg (n=486)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall patients with ≥1 SAE</td>
<td>53 (22.2)</td>
<td>99 (20.4)</td>
</tr>
<tr>
<td>Infections and Infestations</td>
<td>14 (5.9)</td>
<td>30 (6.2)</td>
</tr>
<tr>
<td>Injury, Poisoning, and Procedural Complications</td>
<td>11 (4.6)</td>
<td>19 (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>3 (1.3)</td>
<td>10 (2.1)</td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue Disorders</td>
<td>6 (2.5)</td>
<td>6 (1.2)</td>
</tr>
<tr>
<td>General Disorders and Administration-site Conditions</td>
<td>3 (1.3)</td>
<td>6 (1.2)</td>
</tr>
<tr>
<td>Renal and Urinary Disorders</td>
<td>3 (1.3)</td>
<td>5 (1.0)</td>
</tr>
</tbody>
</table>

Five deaths were reported:
- 1 (0.4%) in the placebo arm: road traffic accident
- 4 (0.8%) in the ocrelizumab arm: pulmonary embolism, pneumonia, pancreas carcinoma, pneumonia aspiration

Thirteen malignancies were reported:
- 2 (0.8%) in the placebo arm: one cervix adenocarcinoma in situ and one basal cell carcinoma
- 11 (2.3%) in the ocrelizumab arm: four breast cancers, one endometrial adenocarcinoma, one anaplastic lymphoma, one histiocytoma, one metastatic pancreas cancer, and three basal cell carcinomas

SAE, serious adverse event.
Infusion-related reactions (IRRs) by dose and severity until clinical cut-off date

1 patient (0.2 %) withdrew from ocrelizumab treatment due to an IRR at the first infusion.
Infusion-related reactions (IRRs) by dose and severity until clinical cut-off date

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Infusion-related reactions (IRRs) by dose and severity until clinical cut-off date

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Infusion-related reactions (IRRs) by dose and severity until clinical cut-off date

1 patient (0.2%) withdrew from ocrelizumab treatment due to an IRR at the first infusion
In ORATORIO, ocrelizumab was effective in PPMS and had an overall safety profile similar to placebo

- ORATORIO data show that B cells may play a role in PPMS pathophysiology

- Initial analysis showed that, compared with placebo, ocrelizumab significantly reduced:
  - 12- and 24-week CDP
  - Change in timed 25-foot walk
  - Change in T2 lesion volume
  - Brain volume loss

- Throughout the mean treatment duration of approximately 3 years, ocrelizumab showed a favourable safety profile:
  - Overall, the proportion of patients experiencing AEs and SAEs associated with ocrelizumab, including serious infections, was similar to placebo
  - Most common adverse events were mild-to-moderate infusion-related reactions
  - Complete safety analyses are ongoing, including investigation of imbalance in malignancies

AE, adverse event; CDP, confirmed disability progression; PPMS, primary progressive multiple sclerosis; SAE, serious adverse event.
Q&A

Karl Mahler
Head of Investor Relations, Roche
Doing now what patients need next