Efficacy of Cladribine Tablets 3.5 mg/kg in Patients with Highly Active Relapsing Multiple Sclerosis (RMS): Pooled Analysis of the Double-Blind Cohort from CLARITY and ONWARD

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Disclosures

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- **G. Giovannoni:** serves on advisory boards for Merck, Biogen Idec, and Vertex Pharmaceuticals; has received speaker honoraria and consulting fees from Bayer Schering Pharma, FivePrime, GlaxoSmithKline, GW Pharma, Merck, Biogen Idec, Pfizer Inc, Protein Discovery Laboratories, Teva Pharmaceutical Industries Ltd, Sanofi-Aventis, UCB, Vertex Pharmaceuticals, Genzyme Corporation, Ironwood, and Novartis; serves on the Merck speakers bureau; and received research support unrelated to this study from Biogen Idec, Merck, Novartis, and Ironwood

- **X. Montalban:** has been a steering committee member of clinical trials or participated in advisory boards of clinical trials with Actelion, Bayer, Biogen, Celgene, Genzyme, Merck, Novartis, Oryzon, Roche, Sanofi-Genzyme and Teva Pharmaceutical

- **D. Damian** and **F. Dangond:** are employees of EMD Serono, Inc., a business of Merck KGaA, Darmstadt, Germany

The CLARITY study: NCT00213135. The ONWARD study: NCT00436826
Introduction and Objective

• Patients with RMS and HDA are at higher risk of disability progression
• The CLARITY study evaluated the efficacy and safety of Cladribine Tablets 3.5 mg/kg in patients with RMS\(^1\)
• The ONWARD study evaluated the safety and tolerability of Cladribine Tablets added to IFN-\(\beta\) in patients with RMS who experienced \(\geq 1\) relapse while on IFN-\(\beta\)^2

OBJECTIVE

To use a pooled analysis of data from CLARITY and ONWARD to assess the efficacy of Cladribine Tablets 3.5 mg/kg in subgroups of patients selected using 2 sets of HDA criteria

HDA, high disease activity; IFN, interferon; RMS, relapsing multiple sclerosis

Methods

• HDA patients were retrospectively selected using two sets of criteria based on relapse history, prior treatment, and MRI characteristics at baseline:

**HRA**
Patients with ≥ 2 relapses in the year before study entry, regardless of treatment status

**HRA + DAT**
Patients with ≥ 2 relapses in the year before study entry, regardless of treatment status

+ Patients with 1 relapse in the year before study entry while on DMD therapy and ≥ 1 T1 Gd+ or ≥ 9 T2 lesions

*DAT*, disease activity on treatment; *DMD*, disease modifying drug; *Gd+*, gadolinium enhancing; *HRA*, high relapse activity; *MRI*, magnetic resonance imaging
Methods

• Data from the 2-year, double-blind periods of CLARITY and ONWARD were pooled
• The efficacy of Cladribine Tablets 3.5 mg/kg vs placebo was assessed in HDA patients (HRA and HRA + DAT) and the overall population (all patients)
• In addition to HDA subgroups, efficacy was also assessed in the non-HDA counterpart groups
• All HDA analyses were post hoc
• All comparisons with P < 0.05 should be regarded as nominally significant

DAT, disease activity on treatment; HDA, high disease activity; HRA, high relapse activity
Clinical outcomes in HDA patients were better than, or as good as, the overall group and non-HDA patients.
ARR and T1 Gd+ outcomes were similar between the HDA, non-HDA and overall groups.

**Table:**

<table>
<thead>
<tr>
<th>DAT, disease activity on treatment; EDSS, Expanded Disability Status Scale; Gd+, gadolinium enhancing; HDA, high disease activity; HRA, high relapse activity</th>
<th>Overall</th>
<th>n</th>
<th>Relative Risk (95% CI)</th>
<th>Interaction P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relapse</td>
<td>Overall</td>
<td>1067</td>
<td>0.43 (0.35; 0.52)</td>
<td>0.03125</td>
</tr>
<tr>
<td></td>
<td>HRA</td>
<td>314</td>
<td>0.33 (0.23; 0.47)</td>
<td>0.03125</td>
</tr>
<tr>
<td></td>
<td>Non-HRA</td>
<td>753</td>
<td>0.49 (0.38; 0.63)</td>
<td>0.0625</td>
</tr>
<tr>
<td></td>
<td>HRA + DAT</td>
<td>459</td>
<td>0.40 (0.30; 0.53)</td>
<td>0.125</td>
</tr>
<tr>
<td></td>
<td>Non-HRA + DAT</td>
<td>608</td>
<td>0.47 (0.35; 0.61)</td>
<td>0.25</td>
</tr>
<tr>
<td></td>
<td>Overall</td>
<td>1040</td>
<td>0.10 (0.076; 0.140)</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>HRA</td>
<td>305</td>
<td>0.08 (0.050; 0.135)</td>
<td>0.03125</td>
</tr>
<tr>
<td></td>
<td>Non-HRA</td>
<td>735</td>
<td>0.12 (0.080; 0.175)</td>
<td>0.0625</td>
</tr>
<tr>
<td></td>
<td>HRA + DAT</td>
<td>448</td>
<td>0.09 (0.058; 0.144)</td>
<td>0.125</td>
</tr>
<tr>
<td></td>
<td>Non-HRA + DAT</td>
<td>592</td>
<td>0.12 (0.080; 0.181)</td>
<td>0.25</td>
</tr>
</tbody>
</table>

**Diagram:**

- **Relative Risk of Annualised Relapse**
  - Overall
  - HRA
  - Non-HRA
  - HRA + DAT
  - Non-HRA + DAT

- **New T1 Gd+ Lesions**
  - Overall
  - HRA
  - Non-HRA
  - HRA + DAT
  - Non-HRA + DAT

**Legend:**
-favours Cladribine Tablets
-favours placebo
Conclusions

• HDA and non-HDA patients treated with Cladribine Tablets 3.5 mg/kg experienced significantly better relapse, progression and MRI outcomes vs with placebo.

• The treatment effect of Cladribine Tablets 3.5 mg/kg on clinical and MRI outcomes was generally as good, or even greater, for the HDA compared with the non-HDA counterparts.

HDA, high disease activity; MRI, magnetic resonance imaging