INTRODUCTION

- The Phase III CLARITY study in patients with relapsing remitting multiple sclerosis (RRMS) demonstrated that Cladribine Tablets 10 mg (3.5 mg/kg cumulative dose over 2 years; referred to as Cladribine Tablets 3.5 mg/kg), given as two short (4 or 5 days) weekly treatments annually over 2 years, significantly reduced relapse rates, disease progression and outcomes assessed by magnetic resonance imaging (MRI) versus placebo.1

- Patients completing CLARITY could enter the CLARITY Extension study (Figure 1), where they were re-randomised to Cladribine Tablets or placebo.

- The effects of Cladribine Tablets were shown to be durable, as efficacy was sustained in years 3 and 4 in patients that received no further active treatment.2

- Patients with RRMS who show an increased rate of relapse or MRI activity can be described as having high disease activity (HDA) and are at higher risk of disease progression.3

OBJECTIVE

- The aim of this post hoc analysis was to determine whether the clinical efficacy of Cladribine Tablets 3.5 mg/kg in CLARITY was sustained for those patients switched to placebo in CLARITY Extension (years 3 and 4), in a subgroup of patients with HDA at CLARITY study baseline.

METHODS

- The CLARITY study enrolled patients aged 18–65 years with a definite diagnosis of RRMS according to the McDonald criteria, including:1
  - ≥ 1 relapse in the 12 months before study entry, but no relapses within the 28 days before entry.
  - Neurological lesions detectable by MRI consistent with MS.
  - An Expanded Disability Status Scale (EDSS) score of 0–5.5.

- Patients were excluded if they had received a disease-modifying drug (DMD) within 3 months before study entry, or treatment with 1 DMD had failed.

- Patients randomised to Cladribine Tablets 3.5 mg/kg in CLARITY who then switched to placebo in CLARITY Extension were retrospectively analysed using two HDA definitions based on relapse history, prior treatment, and MRI characteristics.

- Two overlapping sets of criteria (Figure 2) were applied in the analysis of baseline disease characteristics to subdivide patients into HDA groups based upon:
  1. High relapse activity (HRA), defined as patients with ≥ 2 relapses during the year before study entry, regardless of prior use of DMDs.
  2. HRA plus disease activity on treatment (HRA+DAT), defined as patients with ≥ 2 relapses in the year before study entry, regardless of prior use of DMDs, plus patients with ≥ 1 relapse in the year before study entry AND ≥ 1 T1 gadolinium (Gd+) or ≥ 2 T2 lesions while on DMD therapy.

RESULTS

- A total of 98 patients received Cladribine Tablets 3.5 mg/kg in CLARITY and placebo in CLARITY Extension.

- Baseline demographics and disease characteristics at baseline of the CLARITY study are shown in Table 1.

- Of these 98 patients, 29 were retrospectively classified as HRA and 31 as HRA+DAT.

- Both HDA subgroups (HRA and HRA+DAT) had a lower mean age and a higher proportion of females compared with the corresponding non-HDA subgroups and the overall subgroup.

- There was a higher proportion of patients with prior MD use in both HDA subgroups compared with the corresponding non-HDA subgroups.

Table 1. Patient Demographics and Disease Characteristics by HDA Definitions for Patients Who Received Cladribine Tablets 3.5 mg/kg in CLARITY and Placebo in CLARITY Extension

<table>
<thead>
<tr>
<th>HDA Subgroup</th>
<th>Overall</th>
<th>HRA</th>
<th>HRA+DAT</th>
</tr>
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<tbody>
<tr>
<td>Age, years; mean (SD)</td>
<td>45.1 (12.4)</td>
<td>46.0 (12.7)</td>
<td>42.4 (12.7)</td>
</tr>
<tr>
<td>Female, N (%)</td>
<td>51 (48.0)</td>
<td>32 (100.0)</td>
<td>19 (61.3)</td>
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<tr>
<td>Prior use of DMDs (N)</td>
<td>60 (56.8)</td>
<td>36 (100.0)</td>
<td>24 (77.4)</td>
</tr>
<tr>
<td>Relapses prior to entry, N (%)</td>
<td>1 (8.3)</td>
<td>1 (8.3)</td>
<td>1 (3.1)</td>
</tr>
<tr>
<td>EDSS score, mean (SD)</td>
<td>3.2 (1.6)</td>
<td>3.2 (1.6)</td>
<td>3.2 (1.6)</td>
</tr>
<tr>
<td>% with Gd+ lesions</td>
<td>26 (24.7)</td>
<td>15 (47.0)</td>
<td>11 (35.5)</td>
</tr>
<tr>
<td>% with T2 lesions</td>
<td>85 (80.0)</td>
<td>58 (173.0)</td>
<td>37 (118.0)</td>
</tr>
</tbody>
</table>

EDSS Progression

- At the end of CLARITY Extension, numerically fewer patients in the HRA (13.8%) and HRA+DAT (12.9%) subgroups had confirmed 3-month EDSS progression from baseline compared with those treated with Cladribine Tablets 3.5 mg/kg in CLARITY (20.3%), non-HRA+DAT (20.9%) and overall groups (18.4%) (Table 2 and 3).

- The proportions of patients with confirmed 6-month EDSS progression were similar in the HRA (13.8%), HRA+DAT (12.9%), non-HRA (13.0%), non-HRA+DAT (13.4%) and overall groups (13.3%) (Table 2 and 3).

CONCLUSIONS

- At the end of CLARITY Extension, sustained clinical efficacy was observed both in the overall population and in HDA patients treated with Cladribine Tablets 3.5 mg/kg in CLARITY and placebo in CLARITY Extension.

- Fewer patients with HDA who had 3-month confirmed EDSS progression throughout CLARITY and CLARITY Extension than patients without HDA at baseline.

- It should be noted, however, that the subgroups used in this analysis represent a small number of patients and therefore these results should be viewed with caution.

REFERENCES


ACKNOWLEDGEMENTS

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DISCLOSURES

- P.V. has received honoraria for participation in two congresses from Biogen, Sanofi-Genzyme, Bayer, Novartis, Merck, Celgene, Roche and Almirall; and research support from Biogen, Sanofi-Genzyme, Bayer.

- G.S.-S. has served as a consultant to Merck, Sanofi-Genzyme, Bayer, and Novartis; has received speaker honoraria from Biogen, Sanofi-Genzyme, Bayer, and Merck; and has received research grants from Biogen, Sanofi-Genzyme, Bayer, and Merck.

- B.K. has served as a consultant and independent data monitoring board member for Biogen, Sanofi-Genzyme, and Merck; has served as a steering committee member for Merck, Sanofi-Genzyme, and Genzyme; and has received speaker honoraria from Biogen, Sanofi-Genzyme, and Merck.

- H.S. has served as a consultant to Biogen, Sanofi-Genzyme, Merck, and Genzyme; has served as an independent data monitoring board member for Biogen, Sanofi-Genzyme, and Merck; and has received speaker honoraria from Biogen, Sanofi-Genzyme, and Merck.

- N.S. has served as a consultant to Biogen, Novartis, Genentech, and Genzyme; has served as an independent data monitoring board member for Biogen, Sanofi-Genzyme, Merck, and Genzyme; and has received speaker honoraria from Biogen, Sanofi-Genzyme, Merck, and Genzyme.

- S.K. has served as a consultant to Biogen, Sanofi-Genzyme, Merck, and Genzyme; and has received speaker honoraria from Biogen, Sanofi-Genzyme, Merck, and Genzyme.

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The CLARITY Extension study: NCT01461957

Cladribine Tablets are approved by the Guttmann Commission for the treatment of adult patients with highly active relapsing multiple sclerosis (RRMS) as defined by clinical or magnetic features.