INTRODUCTION

- In patients with relapsing multiple sclerosis (RMS), treatment with two short annual courses of cladribine tablets 3.5 mg/kg produced significant improvements in clinical and MRI measures of disease activity.

- Cladribine is an adenosine analogues drug which produces selective effects on lymphocytes as a result of intracellular accumulation of deoxyribonucleotides leading to failure of DNA synthesis and repair in these cells.

- Short-duration treatment courses with cladribine tablets produce lymphocyte reductions that are transient relative to the sustained clinical efficacy characteristic of selective immune reconstitution therapy:
  - Outcomes from the CLARITY, CLARITY Extension, and ORACLE-MS studies and the post hoc analysis of patients given 2 years of short-term duration treatment courses produce significant benefits in a spectrum of patients with multiple sclerosis (MS), including RMS and clinically isolated syndrome (CIS).

- Consistent with its pharmacologic mechanism of action, studies in rodents indicate that treatment with cladribine is associated with teratogenic risk at concentrations many times higher than the exposure from the recommended dose in RMS.

- Consequently, the protocols of clinical trials involving treatment with cladribine specified the use of contraception in study participants.

- Despite the precautions specified during clinical trials, some study participants did become pregnant, and is of interest to review the outcomes of these pregnancies.

- The Summary of Product Characteristics states the following:

  - Before starting treatment with cladribine tablets, women of childbearing potential and males potentially capable of fathering a child should be counselled about potential risks to the foetus and the need for effective contraception during cladribine treatment and for at least 6 months after the last dose; pregnancy should be excluded in women of childbearing potential before initiating cladribine treatment.

  - Women using systemic hormonal contraceptives should add a barrier contraceptive method during cladribine treatment and for at least 4 weeks after the last dose in each treatment year.

  - Male patients should take precautions to prevent partner pregnancies during cladribine treatment and for at least 6 months after the last dose.

  - Cladribine tablets are contraindicated in pregnant women.

METHODS

- In addition to CLARITY, CLARITY Extension, and ORACLE-MS, data are available from a Phase II study (OMAND), which assessed the effects of treatment with cladribine tablets plus interferon in patients with RMS.

- Earlier clinical studies assessed the effects of parenteral cladribine in the treatment of RMS patients with MS, and safety data from 5 Phase II or III studies are also available.

- The PREMIRE registry is following patients from these studies to provide insights into the medium-to-long-term safety of treatment with cladribine in patients with RMS or early MS.

- Integration of safety data from all of these studies greatly increases the size of the patient cohort available for assessment of the safety profile of cladribine in patients with RMS or early MS.

- The outcomes of pregnancies were recorded from the integrated analysis of safety of the all exposed cohort (Table 2).

- The clinical studies included in the integrated analysis recorded pregnancy as an adverse event, and used parenteral cladribine or cladribine tablets.

RESULTS

Pregnancies

- In total, 64 pregnancies occurred among 57 women in the all exposed cohort (Table 2).

  - 41% of the pregnancies in women treated with cladribine resulted in live births.

  - In women who had received placebo, there were 20 pregnancies in 19 women.

  - 45% of the pregnancies in placebo recipients resulted in live births.

Table 2. Demographics of Patients Included in the All Exposed Cohort

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 82)</th>
<th>Cladribine (n = 1976)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female (%)</td>
<td>55.6 (46)</td>
<td>53.9 (1044)</td>
</tr>
<tr>
<td>Male (%)</td>
<td>44.4 (36)</td>
<td>46.1 (932)</td>
</tr>
<tr>
<td>Age (years), mean (SD)</td>
<td>37.4 (9.6)</td>
<td>37.7 (9.1)</td>
</tr>
<tr>
<td>Max.</td>
<td>75</td>
<td>75.5</td>
</tr>
<tr>
<td>Age ≤ 40 years, n (%)</td>
<td>68.4 (9)</td>
<td>109.4 (8)</td>
</tr>
<tr>
<td>Age &gt; 40 years, n (%)</td>
<td>31.6 (33)</td>
<td>31.5 (55)</td>
</tr>
<tr>
<td>Time since diagnosis, mean (SD)</td>
<td>5.03 (4.7)</td>
<td>5.4 (4.1)</td>
</tr>
<tr>
<td>Patients with live births, n (%)</td>
<td>32 (39)</td>
<td>1047 (53)</td>
</tr>
</tbody>
</table>

Table 3. Pregnancy Outcomes in the All Exposed Cohort

<table>
<thead>
<tr>
<th></th>
<th>No. of Pregnancies</th>
<th>Placebo (n = 82)</th>
<th>Cladribine (n = 1976)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Live birth, n (%)</td>
<td>22 (26.8)</td>
<td>16 (16)</td>
<td></td>
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<tr>
<td>Spontaneous abortion, n (%)</td>
<td>5 (6.1)</td>
<td>14 (7.1)</td>
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<tr>
<td>Induced abortion, n (%)</td>
<td>1 (1.2)</td>
<td>1 (0.1)</td>
<td></td>
</tr>
<tr>
<td>Unknown, n (%)</td>
<td>2 (2.4)</td>
<td>1 (0.1)</td>
<td></td>
</tr>
</tbody>
</table>

- Among women who became pregnant, 32% of pregnancies in those treated with cladribine and 35% of pregnancies among those treated with placebo were terminated by an induced abortion as per the decision of the individual patient.

- Spontaneous abortions occurred in 20% of pregnancies in women treated with cladribine, with a total exposure time of 8650 patient-years and in women treated with placebo, with a total exposure time of 10450 patient-years.

- These rates of spontaneous abortions are consistent with epidemiological studies.

- Furthermore, for ethical reasons, some trials used a switch design so that patients who did not placate did not spend prolonged periods without active treatment.

- A conservative approach used in the analysis of all the exposed cohort also contributed to the imbalance between the patient numbers in the cladribine and placebo groups:

  - In patients initially treated with placebo and subsequently with cladribine, the first 2 years of their data were analysed as part of the placebo group and (when they switched to cladribine, all of their subsequent data was attributed to cladribine.

- If a patient received cladribine followed by placebo, all of their data were analysed as part of the cladribine group and never as part of the placebo group.

- In total, 12 pregnancies occurred among 11 female partners of male trial participants.

- There were 10 pregnancies among the female partners of 9 cladribine-treated males.

- 9 of these 10 pregnancies resulted in the birth of healthy newborn infants (there were 1 that resulted in an abortion).

- There were 2 pregnancies among the female partners of 2 placebo-treated males with unknown outcome.

Pregnancies Which Occurred Within 6 Months of Cladribine Treatment in Women Whose Partners Were Study Participants

- During the period of active treatment with cladribine or within 6 months after the last recorded dose of cladribine, 16 pregnancies occurred among female partners who were 3 pregnant women who were participating in clinical trials.

- Each of these 3 pregnancies resulted in the birth of a healthy newborn infant.

CONCLUSIONS

- In this limited population of pregnancies with potential exposure to cladribine, no congenital malformations were identified.

- Further monitoring of pregnancy outcomes will occur following the approval of cladribine tablets in the European Union.

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DISCLOSURES

All is an employee of Merck. Autobiography, Switzerland, a division of Merck KGaA, Darmstadt, Germany. AR is an employee of Merck KGaA, Darmstadt, Germany. SC has received honoraria for lecture/consultancies from Merck, Bayer Healthcare, Sanofi-Aventis, Neurology Review, Biogen Idec, Takeda Pharmaceuticals, and Achillion Biosciences. SC has served on advisory boards for Bayer Healthcare, Merck, Autobiograph, the Takeda Pharmaceuticals, and Biogen Idec and received grant support from Bayer Healthcare. LC has received honoraria for lecture or research grants from Merck-Kauto, Bayer, Biogen, Daichi, EMD Serono, Novartis, ONG, Pfizer, Takeda Neuroscience. JU has received honoraria for lecture, research or research grants from Merck, Bayer-Schering, Takeda Pharmaceutical Industries Ltd., Sanofi-Aventis, Merck, Biogen Idec, Merck, Roche, Genentech-Roche, and Bayer Schering. BW has served on advisory boards for Daiichi Sankyo, Takeda Pharmaceutical Industries Ltd. and received research grants from Daiichi Sankyo. FB is an employee of Merck, the Takeda Pharmaceutical Industries Ltd., Sanofi-Aventis, Merck, Biogen Idec, Genentech-Roche, and Bayer Schering. JM has received honoraria and travel expenses for scientific presentations. AR has served on advisory board and executive committee of clinical trials for Bayer Schering Pharma, Biogen, EMD Serono, Genentech, Roche, Novartis, Sanofi-Aventis, Takeda Pharmaceuticals, and Amgen. OR is an employee of Merck, Darmstadt, Germany. PD is an employee of EMD Serono, Inc., a business of Merck KGaA, Darmstadt, Germany. Presented at European Charcot Foundation (ECF) 2017; 30 November - 2 December; Baveno, Italy.