Pregnancy Outcomes During the Clinical Development of Cladribine in Multiple Sclerosis: An Integrated Analysis of Safety for All Exposed Patients

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- **A. Galazka:** is an employee of Merck, Aubonne, Switzerland, a division of Merck KGaA, Darmstadt, Germany
- **A. Nolting:** is an employee of Merck KGaA, Darmstadt, Germany
- **S. Cook:** has received honoraria for lectures/consultations from Merck, Bayer HealthCare, Sanofi-Aventis, Neurology Reviews, Biogen Idec, Teva Pharmaceuticals, and Actinobac Biomed Inc.; has served on advisory boards for Bayer HealthCare, Merck, Actinobac Biomed, Teva Pharmaceuticals, and Biogen Idec; and received grant support from Bayer HealthCare
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- **C. Hicking:** is an employee of Merck KGaA, Darmstadt, Germany
- **F. Dangond:** is an employee of EMD Serono, Inc., a business of Merck KGaA, Darmstadt, Germany
Introduction and Objective

- In CLARITY, CLARITY Extension and ORACLE-MS, Cladribine Tablets significantly improved outcomes in patients with RRMS and clinically isolated syndrome\textsuperscript{1-3}
- Studies in rodents have suggested that cladribine is associated with teratogenic risk with exposure at concentrations many times higher than the exposure from the recommended dose in RMS
- Consequently, clinical trial protocols involving treatment with cladribine specified the use of contraception in study participants
- Despite these precautions, some study participants did become pregnant, and the outcomes of these pregnancies are of interest
- Cladribine Tablets are contraindicated in pregnant women

**OBJECTIVE**

To report pregnancy outcomes from an integrated analysis of safety for patients exposed to cladribine during the clinical development programme in MS


\textit{MS}, multiple sclerosis; \textit{RMS}, relapsing multiple sclerosis; \textit{RRMS}, relapsing-remitting multiple sclerosis
Methods

• Integration of safety data from a number of Phase II and III studies greatly increased the size of the patient cohort available for assessment

• Clinical studies of both parenteral cladribine and Cladribine Tablets were included

• The outcomes of pregnancies were recorded from the integrated analysis of safety of the all exposed patients

• The all exposed cohort contained 1976 patients who had been treated with cladribine and 802 patients who had received placebo

Summary of Clinical Studies Using Cladribine Tablets or Parenteral Cladribine Used in Analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Formulation</th>
<th>Phase</th>
<th>Number*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLARITY R, DB</td>
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<td>CT</td>
<td>III</td>
<td>1326</td>
</tr>
<tr>
<td>CLARITY Extension R, DB</td>
<td>R, DB</td>
<td>CT</td>
<td>IIIb</td>
<td>806</td>
</tr>
<tr>
<td>ORACLE-MS R, DB</td>
<td>R, DB</td>
<td>CT</td>
<td>III</td>
<td>617</td>
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<tr>
<td>ONWARD R, DB</td>
<td>R, DB</td>
<td>CT</td>
<td>IIb</td>
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<td>PREMIERE N/A N/A N/A N/A</td>
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<tr>
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<td>11</td>
</tr>
<tr>
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</tr>
<tr>
<td>MS-Scripps R, DB iv II</td>
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<td>iv</td>
<td>II</td>
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</tr>
<tr>
<td>MS-001 R, DB sc III</td>
<td>R, DB</td>
<td>sc</td>
<td>III</td>
<td>159</td>
</tr>
</tbody>
</table>

* number of patients randomised to double-blind treatment or enrolled into study.

CT, Cladribine Tablets; DB, double-blind; iv, intravenous; N/A, not applicable; OL, open-label; R, randomised; sc, subcutaneous.
Pregnancies in Study Participants

- In women who had been exposed to cladribine, 44 pregnancies occurred in 38 women
- In women who had received placebo, there were 20 pregnancies in 19 women
- Spontaneous abortions occurred in 20% of pregnancies in women treated with cladribine, and 25% among those treated with placebo
  - Rates of spontaneous abortions are consistent with epidemiological data on pregnancy outcomes

### Pregnancy Outcomes in the All Exposed Cohort

<table>
<thead>
<tr>
<th>Number of Pregnancies</th>
<th>Placebo (n = 20)</th>
<th>Cladribine (n = 44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Live birth, n (%)</td>
<td>9 (45)</td>
<td>18 (41)</td>
</tr>
<tr>
<td>Induced abortion(^a), n (%)</td>
<td>4 (20)</td>
<td>14 (32)</td>
</tr>
<tr>
<td>Spontaneous abortion, n (%)</td>
<td>5 (25)</td>
<td>9 (20)</td>
</tr>
<tr>
<td>Medically indicated abortion, n (%)</td>
<td>1 (5)</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Unknown, n (%)</td>
<td>1 (5)</td>
<td>0</td>
</tr>
</tbody>
</table>

\(^a\)Patient’s decision
Pregnancies During the Potential At-Risk Period

• Based on theoretical considerations, the time from the first dose of active treatment with cladribine to within 6 months after the last dose is considered to be the potential period during which patients may be exposed to any teratogenic effects of treatment.

• A total of 16 pregnancies occurred in women exposed to cladribine within the 6 month period prior to becoming pregnant:
  - 3 of these pregnancies resulted in live births (a healthy male infant in each case)
  - 10 pregnancies were terminated at the patient’s decision by induced abortions
  - 2 patients experienced spontaneous abortions
  - There was 1 medically indicated abortion, for an ectopic pregnancy.
Pregnancies in Women Whose Partners Were Study Participants

• In total, 12 pregnancies occurred among 11 female partners of male trial participants:
  – There were 10 pregnancies among female partners of 9 cladribine-treated males
  – 9 of these 10 pregnancies resulted in the birth of healthy infants
    (1 unknown outcome)
• There were 2 pregnancies among the female partners of 2 placebo-treated males with unknown outcome
• During the period of active treatment with cladribine or within 6 months after the most recent dose, 3 pregnancies occurred among females who were partners of 3 males who were participating in clinical trials
  – Each of these 3 pregnancies resulted in the birth of a healthy infant
Conclusions

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

• Monitoring of pregnancy outcomes is on-going, following the approval of Cladribine Tablets in the European Union