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

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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 neurological measures of disease activity.[1]
- Cladribine is an adenosine analogue prodrug 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.[5]
- Short-duration annual 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 show that cladribine tablets given annually for 2 years in short-duration treatment courses produce significant benefits in a spectrum of patients with multiple sclerosis (MS), including RMS and clinically isolated syndrome (early MS).[1–3]

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 it 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 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.

OBJECTIVE

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

METHODS

- In addition to CLARITY, CLARITY Extension, and ORACLE-MS, data are available from a Phase II study (ONWARD), which assessed the effects of treatment with cladribine tablets plus interferon in patients with RMS.[4]
- Earlier clinical studies assessed the effects of parenteral cladribine in the treatment of patients with MS, and safety data from 5 Phase II or III studies are also available.
- The PREMIERE registry is following patients from these studies to provide insights into the medium-to-longer 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 (**Table 1**).
- The outcomes of pregnancies were recorded from the integrated analysis of safety of the all exposed patients.
- The clinical studies included in the integrated analysis recorded pregnancy as an adverse event, and used parenteral cladribine or cladribine tablets.

Table 1. Summary of Clinical Studies Using Cladribine Tablets or Parenteral Cladribine Used in Analysis

Study	Design	Formulation	Phase	Number*
CLARITY	R, DB	CT	III	1326
CLARITY Extension	R, DB	CT	IIIb	806
ORACLE-MS	R, DB	CT	III	617
ONWARD	R, DB	CT	IIb	172
PREMIERE	N/A	N/A	N/A	1133
Scripps-A	OL	iv	II	7
Scripps-B	R, DB	sc	II	11
Scripps-C	R, DB	sc	II	52
MS-Scripps	R, DB	iv	II	49
MS-001	R, DB	sc	III	159

* number of patients randomized to double-blind treatment or enrolled into study.
CT, cladribine tablets; **DB**, double-blind; **iv**, intravenous; **N/A**, not applicable; **OL**, open-label; **R**, randomized; **sc**, subcutaneous.

RESULTS

Patients

- The all exposed cohort contained 1976 patients (**Table 2**) who had been treated with cladribine, with a total exposure time of 8650 patient-years and 802 patients who had received placebo (2361 patient-years of exposure).
  - Exposure to cladribine in the all exposed cohort, especially with regard to duration of follow-up, was higher than exposure to placebo because the majority of clinical studies involved randomization of patients to treatment in a 2:1 ratio (active treatment: placebo).
  - Furthermore, for ethical reasons, some trials used a switch design so that patients initially randomized to placebo did not spend prolonged periods without active treatment.
- A conservative approach used in the analysis of the all 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 analyzed as part of the placebo group and if/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 analyzed as part of the cladribine group and never as part of the placebo group.

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

	Placebo (n = 802)	Cladribine (n = 1976)
Female, n (%)	535 (66.7)	1306 (66.1)
Male, n (%)	267 (33.3)	670 (33.9)
Patient-years	2361	8650
Time on study in weeks, mean (SD)	153.62 (103.10)	228.42 (124.17)
Age (years), mean (SD) Median Min; Max	37.6 (9.8) 37.0 18; 64	37.7 (10.1) 38.0 18; 65
Age ≤ 40 years, n (%)	485 (60.5)	1162 (58.8)
Age > 40 years, n (%)	317 (39.5)	814 (41.2)
Prior treatment with DMD, n (%)	188 (23.4)	505 (25.6)
Disease duration in years, mean (SD)	9.50 (7.44)	8.91 (7.21)
Patients with time on study cumulative interval of at least 2 years, n (%)	559 (69.7)	1630 (82.5)

DMD, disease modifying drug; **SD**, standard deviation.

Pregnancies in Study Participants

- In total, 64 pregnancies occurred among 57 women in the all exposed cohort (**Table 3**).
- In women who had been exposed to cladribine, 44 pregnancies occurred in 38 women.
  - 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 3. Pregnancy Outcomes in the All Exposed Cohort

Number of Pregnancies	Placebo (n = 20)	Cladribine (n = 44)
Live birth, n (%)	9 (45)	18 (41)
Induced abortion[a], n (%)	4 (20)	14 (32)
Spontaneous abortion, n (%)	5 (25)	9 (20)
Medically indicated abortion, n (%)	1 (5)	3 (7)
Unknown, n (%)	1 (5)	0

[a] Patient's decision.

- Among women who became pregnant, 32% of pregnancies in those treated with cladribine and 20% 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, and 25% of pregnancies among those treated with placebo.
  - These rates of spontaneous abortions are consistent with epidemiological data on pregnancy outcomes.
- Three medically indicated abortions were carried out in 2 women who had received cladribine treatment;
  - 2 of these abortions were for ectopic pregnancies (occurring twice in the same patient), and 1 was for choriocarcinoma.
- One medically indicated abortion was carried out in a placebo recipient after ultrasound scanning revealed a Dandy-Walker congenital malformation and progressive placental abruption.

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.

All Pregnancies Among Women Whose Partners Were Study Participants

- 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 was 1 unknown outcome).
- 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 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 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

AG is an employee of Merck, Aubonne, Switzerland, a division of Merck KGaA, Darmstadt, Germany. **AN** is an employee of Merck KGaA, Darmstadt, Germany. **SC** 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. **TL** has received consultancy fees or clinical research grants from Acorda, Bayer, Biogen, Daiichi, EMD Serono, Novartis, ONO, Pfizer, Teva Neuroscience. **GC** has received consulting fees from Novartis, Teva Pharmaceutical Industries Ltd., Sanofi-Aventis, Merck, Receptos, Biogen Idec, Genentech-Roche, andBayer Schering; lecture fees from Novartis, Teva Pharmaceutical Ind. Ltd., Sanofi-Aventis, Merck, Biogen Dompè, Bayer Schering, and Serono Symposia International Foundation; and trial grant support from Novartis, Teva Pharmaceutical Ind. Ltd., Sanofi-Aventis, Receptos, Biogen Idec, Genentech-Roche, Merck, Biogen Dompè, and Bayer Schering. **XM** has received speaker honoraria and travel expenses for scientific meetings, steering committee member, and advisory board member of clinical trials for Bayer Schering Pharma, Biogen Idec, EMD Serono, Genentech, Genzyme, Novartis, Roche, Sanofi-Aventis, Teva Pharmaceuticals, and Almirall. **CH** is an employee of Merck KGaA, Darmstadt, Germany. **FD** is an employee of EMD Serono, Inc., a business of Merck KGaA, Darmstadt, Germany.

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