For reactive Medical use only.

February 2024

# Pregnancy and Infant Outcomes From an Ongoing Worldwide Enhanced Pharmacovigilance Program of Cladribine Tablets: 6-year Results From MAPLE-MS

Kerstin Hellwig[1], Hugh H. Tilson[2], Joerg Seebeck[3], Muriel Danten[4], Tahani Boumenna[5]

[1]Department of Neurology, St. Joseph and St. Elisabeth Hospital, Ruhr University, Bochum, Germany; [2]UNC Gillings School of Global Public Health US, Chapel Hill, NC, USA; [3]Global Patient Safety, the healthcare business of Merck KGaA, Darmstadt, Germany; [4]Global Biostatistics, Merck Santé S.A.S., Lyon, France, an affiliate of Merck KGaA, Darmstadt, Germany; [5]Global Epidemiology, EMD Serono, Billerica, MA, USA



## CONCLUSIONS

**There was one major congenital anomaly in 59 live births in the maternal exposure cohort reported to the sponsor's global patient safety database**

**The interpretation of the results is limited due to the small number of reported pregnancies with known outcomes and loss to follow-up in both cohorts**

## INTRODUCTION

- Cladribine tablets are contraindicated during pregnancy. As a result, pregnancy outcomes on exposure to cladribine tablets before or during pregnancy are expected to be scarce
- In this context, a worldwide pregnancy surveillance program (MAPLE-MS) was setup to assess the effect of cladribine tablets exposure on pregnancy and infant outcomes

## OBJECTIVES

**To present cumulative pregnancy exposure data and prevalence of pregnancy and infant outcomes in:**

- **Women with multiple sclerosis (MS) exposed to cladribine tablets during pregnancy or within 6 months before pregnancy (maternal cohort); and**
- **Pregnancies fathered by men with MS exposed to cladribine tablets within 6 months before pregnancy (paternal cohort)**

## METHODS

- Maternal and paternal exposure to cladribine tablets during pregnancy or within 6 months before pregnancy, was captured in the sponsor's safety database between August 22, 2017 (approval of cladribine tablets) and April 1, 2023 (cut-off date)
- The primary outcome assessed the number of cases of major congenital anomalies (MCA) [excluding genetic anomalies] in the offspring
- Secondary outcomes assessed were live birth (LB, including pre-term delivery and small for gestational age), elective termination and reasons, spontaneous abortion, ectopic pregnancy, and stillbirths among pregnancies
- The prevalence of each outcome, including 95% confidence interval (CI), was calculated; cases were reported prospectively and retrospectively

## RESULTS

- In the maternal cohort, 247 pregnancies were reported
  - Mother's median age 31 (quartile [Q]1,Q3: 27, 35) years at last menstrual period (LMP)
- In the paternal cohort, 35 pregnancies were reported
  - Mother's median age 34 (32, 36) years at LMP
- Pregnancy outcomes are shown in **Table 1**

### Table 1. Case Disposition by Cohort

| Pregnancy outcome | Maternal cohort (N=247), n (%) | Paternal cohort (N=35), n (%) |
|---|---|---|
| Known | 110 (44.5) | 13 (37.1) |
| Unknown/lost to follow-up[a] | 73 (29.6) | 14 (40.0) |
| Pending[b] | 64 (25.9) | 8 (22.9) |

[a]Cases were defined as "lost to follow-up" if all three follow-up attempts with reporter were made without success
[b]No occurrence of birth or pregnancy outcome at time of data lock

- Timing of exposure to cladribine tablets in relation to known pregnancy outcomes is shown in **Table 2**

### Table 2. Timing of Exposure to Cladribine Tablets

| Timing | Maternal exposure, outcome known (N=110), n (%) | Paternal exposure, outcome known (N=13), n (%) |
|---|---|---|
| Before pregnancy[a] | 61 (55.5) | 10 (76.9) |
| First trimester | 28 (25.5) | NA |
| Only after first trimester | 0 | NA |
| Unknown | 21 (19.1) | 3 (23.1) |

[a]Within 6 months before date of LMP
**NA**, not applicable

### Primary outcome: MCA

- In the maternal cohort, there was one case of MCA (an atrial septal defect) in LB, excluding genetic anomalies, n/N (%) [95% CI]=1/59 (1.7%) [0.0, 9.9]
  - For perspective, number of cases of congenital birth defects in patients exposed to interferon beta-1b during pregnancy,[1] n/N (%) [95% CI]=14/981 (1.4%) [0.78, 2.38]
- In the paternal cohort, no MCAs were reported

### Secondary outcomes

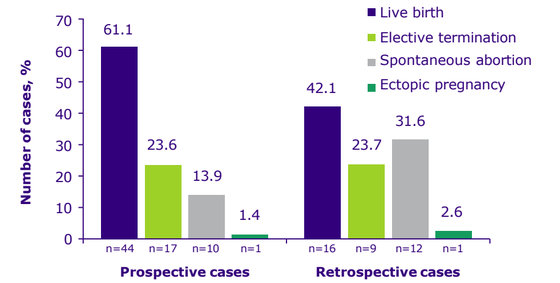
- Known pregnancy outcomes for the maternal cohort (N=110) are shown in **Table 3** and by case reporting type in **Figure 1**
- Known pregnancy outcomes for the paternal cohort (N=13) are shown in **Table 3**
  - Nine partner pregnancies (all LB) were observed during the clinical development program[2]

### Table 3. Known Pregnancy Outcomes by Cohort

| Known pregnancy outcome | Maternal exposure, (N=110), n (%) [95% CI] | Paternal exposure, (N=13), n (%) [95% CI] |
|---|---|---|
| Live birth[a] | 60 (54.5) [45.2, 63.5] | 11 (84.6) [56.5, 96.9] |
| Pre-term delivery | 6 (10.0[b]) [4.3, 20.5] | 1 (9.1[b]) [0.0, 39.9] |
| SGA | 1 (1.7[b]) [0.0, 9.7] | 0 |
| Elective termination | 26 (23.6) [16.6, 32.4] | 0 |
| Patient decision/wish | 17 (65.4[c]) | NA |
| Other[d] | 9 (34.6[c]) | NA |
| Spontaneous abortion | 22 (20.0) [13.5, 28.5] | 2 (15.4) [3.1, 43.5] |
| Ectopic pregnancy | 2 (1.8) [0.1, 6.8] | 0 |
| Stillbirth | 0 | 0 |

[a]In case of multifetal gestation, all associated fetuses/babies were counted separately. [b]The denominator is the number of live births in the given cohort. [c]The denominator is the number of elective terminations in the given cohort. [d]Other included Unknown, n=4 (15.4%); No consent, n=3 (11.5%); Others, n=1 (3.8%); TOPFA, n=1 (3.8%).
**CI**, confidence interval; **NA**, not applicable; **SGA**, small for gestational age; **TOPFA**, termination of pregnancy due to fetal anomaly

### Figure 1. Known Pregnancy Outcomes (Maternal Cohort) by Case Reporting Type (Prospective and Retrospective)




**REFERENCES**
1. Hellwig K, et al. *Ther Adv Neurol Disord.* 2020;13:1–11; 2. Giovannoni G, et al. *Drug Saf.* 2020;43(7):635–643.

Cladribine tablets 10 mg (3.5 mg/kg cumulative dose over 2 years) are indicated for the treatment of patients with MS in the United States (relapsing forms of MS, including relapsing-remitting disease and active secondary progressive disease, in adults).

**Disclosures: KH** has received honoraria and research support from Bayer, Biogen, Novartis, Sanofi, Teva, and the healthcare business of Merck KGaA, Darmstadt, Germany. **HHT** provides services as an epidemiologist on multiple pregnancy and drug-exposure registries, for which he receives honoraria. **JS** is an employee of the healthcare business of Merck KGaA, Darmstadt, Germany. **MD** is an employee of Merck Santé S.A.S., Lyon, France, an affiliate of Merck KGaA, Darmstadt, Germany. **TB** was an employee of EMD Serono, Billerica, MA, USA at the time of this study.

Medical writing assistance was provided by Claire Snaith of inScience Communications, Springer Healthcare Ltd, UK, and was funded by the healthcare business of Merck KGaA, Darmstadt, Germany.

**Presented at ACTRIMS 2024 Forum | February 29–March 2 | West Palm Beach, FL, USA**

**Data collection and analysis was sponsored by the healthcare business of Merck KGaA, Darmstadt, Germany (CrossRef Funder ID: 10.13039/100009945)**