Cladribine tablets in the treatment of patients with multiple sclerosis: an integrated analysis of the safety from the multiple sclerosis clinical development program

S Cook, T Leist, G Comi, X Montalban, E Sylvester, C Hicking, F Dangond

1. Rutgers, The State University of New Jersey, New Jersey Medical School, Newark, NJ, USA; 2. Division of Clinical Neuroimmunology, Thomas Jefferson University, Jefferson Medical College, Philadelphia, PA, USA; 3. Department of Neurology and Institute of Experimental Neurobiology, Università Vita-Salute San Raffaele, Ospedale San Raffaele, Milan, Italy; 4. Department of Neurology - Neuroimmunology, Hospital Universitari Vall d’Hebron, Barcelona, Spain; 5. Merck KGaA, Darmstadt, Germany; 6. EMD Serono, Inc., Billerica, MA, USA

INTRODUCTION
- Treatment with cladribine tablets in the CLARITY, CLARITY Extension, and ORACLE-MS studies demonstrated efficacy versus placebo across a spectrum of both early and relapsing remitting multiple sclerosis (RRMS).
- The adverse event (AE) profiles from these individual studies have been presented elsewhere. Pooling safety data for integrated analyses provides comprehensive characterization of the safety profile of a therapy.

OBJECTIVE
- To report the emergent overall AE profile from an integrated pool of safety data collected in trials which evaluated cladribine tablets as monotherapy, in patients with early MS or RRMS.

METHODS
- The monotherapy oral cohort (patients who received either placebo or cladribine tablets only) was derived from CLARITY, CLARITY Extension, and ORACLE-MS, and the PREMIERE registry, and included:
  - 303 patients who received cladribine tablets as a cumulative dose of 3.5 mg/kg (3433 patient-years follow-up)
  - 641 patients who received placebo (2026 patient-years follow-up)
  - 303 patients who received cladribine tablets as a cumulative dose of 5.25 mg/kg (2137 patient-years follow-up; data not shown)
- Adjusted AE incidences per 100 patient-years (Adj-AE per 100PY) were calculated for all AEs. Adj-AE per 100PY is the time-adjusted AE incidence rate which can be interpreted as the number of events occurring in 100 patient-years.
- Adj-AE per 100PY = 100(Number of patients with at least 1 AE)/(sum of time on study/365.25).

RESULTS
Baseline demographics
- Patients exposed to cladribine tablets were more numerous and were followed over a longer period of time compared with placebo. (Table 1).

Overview of AEs
- The reported number of AEs per 100PY was somewhat higher in the cladribine tablets 3.5 mg/kg dose group compared with placebo (103.29 vs 94.24 AEs per 100PY) (Table 2).
- The overall number of AEs that led to treatment discontinuation was low, with a higher incidence rate among the patients treated with cladribine tablets 3.5 mg/kg compared with the patients on placebo.
- There was a higher rate of drug-related treatment-emergent AEs on cladribine tablets 3.5 mg/kg compared with placebo (33.76 vs 25.03 AEs per 100PY).
- The incidence of serious AEs and AEs leading to death were low and similar for patients treated with cladribine tablets 3.5 mg/kg and placebo.

Adverse events of interest/relevance
- As part of its mechanism of action, cladribine selectively reduces lymphocyte counts which may lead to transient lymphopenia.
- Reduced lymphocyte counts could potentially lead to clinical complications. Therefore the adverse events of lymphocyte, infection, and malignancy were examined in more detail.

CONCLUSIONS
- The AE profile for cladribine tablets 3.5 mg/kg as a monotherapy has been well-characterized in a pooled population of patients from early to more advanced relapsing–remitting MS.
- Lymphopenia was expected from the mode of action of cladribine tablets.
- Herpes zoster was reported more frequently in patients experiencing Grade 3 or 4 lymphopenia.
- There was no clustering of malignancies with a common aetiology, and no hematological malignancies commonly associated with immunosuppression were observed.

REFERENCES

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DISCLOSURES
* SG has received honoraria for lecture/consultations from Merck, Bayer HealthCare, Sanofi-Aventis, Biogen Idec, Genzyme, and GSK. She is a consultant for Biogen Idec, Aventis Pharma, and Actinobac Biomedical Inc., has not had any advisory board for Bayer HealthCare, Merck, Acorda Biomed, TEVA Pharmaceuticals, and Biogen, Rieh; and received grant support from Bayer HealthCare, NL, in consultancy to EMD Serono, TEC Neurosciences, Biogen, and Pfizer, and is involved in clinical trials sponsored by EMD Serono, TecNeurosciences, Biogen, NV, Novartis, Dativ, and Almirall. SG has received consulting fees from Genzyme, the Novartis Pharmaceutical Inc Ltd, Sanofi-Aventis, Merck, Biogen, and Bayer Schering. BMD has worked as a medical writer to support the medicinal information section of one of the studies. BMD has received honoraria for accommodation and travel expenses for scientific meetings, in a steering committee member for, and is an advisory board member of various Clinical trials for Bayer Schering Pharma, Biogen Idec, EMD Serono, Genzyme, Genzyme, Biogen, Rieh, Sanofi-Aventis, Teva Pharmaceuticals, and Almirall. BB and EM are employees of Merck KGaA, Darmstadt, Germany. FB is an employee of EMD Serono, Inc.* BILERICA, MA USA.

Cladribine tablets are currently under clinical investigation and has not yet been approved by any regulatory agency. Status: May 2017.

S Table 1. Incidence rates of lymphopenia AEs (overall, serious AEs, AEs leading to treatment discontinuation and by severity) were higher in the patients treated with cladribine tablets 3.5 mg/kg in those who received placebo (Table 3).

S Table 3. Lymphopenia from AE reporting

Table 1. Incidences of AEs presented in the analysis

Table 2. Adjusted incidences of TAEs

Table 3. Lymphopenia from AE reporting

Figure 3. Lymphopenia was expected from the mode of action of cladribine tablets...