Poster No. DX69

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

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INTRODUCTION

- Treatment with cladribine tablets in the CLARITY, CLARITY Extension, and ORACLE-MS studies demonstrated efficacy versus placebo across a spectrum of patients with both early and relapsing multiple sclerosis (RMS).[1-3]
- The adverse event (AE) profiles from these individual studies have been presented elsewhere. Pooling safety data for integrated analyses allows 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 RMS.

METHODS

- The monotherapy oral cohort (patients who received either placebo or cladribine tablets only) was derived from CLARITY, CLARITY Extension, ORACLE-MS, and the PREMIERE registry, and included:
  - 923 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)
  - 632 patients who received cladribine tablets as a cumulative dose of 5.25 mg/kg (2317 patient-years follow-up; data not shown).
- Adjusted AE incidences per 100 patient-years (Adj-AE per 100PY) were calculated for the integrated analyses. 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 = 100x(number of patients with at least 1 AE)/(sum of observation time in days among patients at risk for initial occurrence of an AE or 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 94.26 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 trend for 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 lymphopenia, infection, and malignancy were examined in more detail.

Table 1. Demographics of patients included in the analysis

	Placebo (n=641)	Cladribine tablets 3.5 mg/kg (n=923)
Patient-years	2026	3433
Time on study in weeks, mean (SD)	164.92 (105.97)	194.05 (110.50)
Time on study cumulative interval at least 2 years, n (%)	486 (75.8)	772 (83.6)
Time on study cumulative interval at least 4 years, n (%)	181 (28.2)	395 (42.8)
Age (years), mean (SD) Median Min; max	36.6 (9.8) 36.0 18; 64	36.5 (10.3) 36.0 18; 65
Age ≤40 years, n (%)	415 (64.7)	592 (64.1)
Age >40 years, n (%)	226 (35.3)	331 (35.9)
Male, n (%)	217 (33.9)	311 (33.7)
Female, n (%)	424 (66.1)	612 (66.3)
Prior treatment with DMD, n (%)	131 (20.4)	184 (19.9)

Disease characteristics were balanced in both groups.
DMD, disease-modifying drug; **SD**, standard deviation.

Table 2. Adjusted incidence of TEAEs

	Placebo (n=641)			Cladribine tablets 3.5 mg/kg (n=923)		
	n	T	Adj-AE per 100PY	n	T	Adj-AE per 100PY
Number of patients with TEAEs	515	546.3	94.26	773	748.4	103.29
Number of patients with TEAEs related to study drug	291	1162.8	25.03	542	1605.5	33.76
Number of patients with TEAEs leading to treatment discontinuation	21	1993.7	1.05	67	3229.0	2.07
Number of patients with serious[a] TEAEs	67	1876.3	3.57	124	3096.8	4.00
Number of patients with TEAEs leading to death	5	2024.7	0.25	9	3431.0	0.26

n is the number of patients with events; T is the total patient's time on study in years. If a patient has multiple events, the time to first event is considered. For a patient with no event the time is censored at the last follow-up time for that patient.
Adj-AE per 100PY, adjusted adverse event incidences per 100 patient-years; **TEAE**, treatment-emergent adverse event.
[a]Serious was defined as resultant in death, life-threatening, requiring inpatient hospitalization, congenital anomaly or birth defect, or was otherwise considered as medically important.

Lymphopenia

- The 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 than in patients who received placebo (**Table 3**).
- The AE of special interest (AESI) lymphopenia was dose-related; the incidences in the cladribine tablets 3.5-mg/kg group were lower than those observed with the higher dose of 5.25 mg/kg (data not shown).
- The main assessment of lymphopenia was based on laboratory data from individual studies. Results from CLARITY and CLARITY Extension showed that when lymphocyte counts were Grade 0 at baseline of Year 1, and Grade 0 or 1 at baseline in Year 2, recovery to Grade 0 to 1 at the end of each treatment year occurred in approximately 86% of patients. In ORACLE-MS, all patients for whom data were available returned to Grade 0 or 1 by 13 weeks after the end of Year 2 (see poster DX71 at this meeting).

Table 3. Lymphopenia from AE reporting

	Placebo (n=641)	Cladribine tablets 3.5 mg/kg (n=923)
AESI: lymphopenia from AE		
Adj-AE per 100PY	1.16036	8.88445
95% CI	0.7711; 1.7462	7.8203; 10.0934
AESI: serious lymphopenia from AE		
Adj-AE per 100PY	0	0.11691
95% CI	0.0000; 0.0018	0.0439; 0.3115
AESI: lymphopenia from AE leading to treatment discontinuation		
Adj-AE per 100PY	0.04936	0.89926
95% CI	0.0070; 0.3504	0.6287; 1.2861
AESI in worst severity[a]		
Mild Adj-AE per 100PY	0.75167	3.58857
Moderate Adj-AE per 100PY	0.39690	3.18466
Severe Adj-AE per 100PY	0	0.71709

Adj-AE per 100PY, adjusted adverse event incidences per 100 patient-years; **AE**, adverse event; **AESI**, adverse event of special interest; **CI**, confidence interval; **CTCAE**, Common Terminology Criteria for Adverse Events; **MedDRA**, Medical Dictionary of Regulatory Activities.
[a]The investigator graded the severity of each AE using either clinical judgement according to the following definitions or the CTCAE criteria, as most appropriate:
Mild: the patient was aware of the event or symptom but the event or symptom was easily tolerated.
Moderate: the patient experienced sufficient discomfort to interfere with or reduce his or her usual level of activity.
Severe: significant impairment of functioning: unable to carry out usual activities and/or life threatening.
AESI = Lymphopenia from AE is a custom query generated as a subset from MedDRA.
SMQ = Hematopoietic leukopenia by using all preferred terms which describe drop of lymphocytes.

Infection

- For the system organ class of infections and infestations, the AE rate for cladribine tablets 3.5 mg/kg was 24.93 per 100PY and for placebo 27.05 per 100PY.
  - The rate classed as severe was 0.26 per 100PY for cladribine tablets 3.5 mg/kg and 0.40 for placebo.
- For the system organ class infections and infestations, the AE rates of the preferred term herpes zoster for cladribine tablets 3.5 mg/kg was 0.83 per 100PY and for placebo 0.20 per 100PY.
- For the AESI severe infection, the AE rates of severe or serious herpes zoster for cladribine tablets 3.5 mg/kg was 0.09 per 100PY and for placebo 0.05 per 100PY.
  - Two cases were assessed as serious; neither led to treatment discontinuation and both resolved.
- The incidence of herpes zoster (reported as an AESI) was higher in the period of treatment with cladribine tablets 3.5 mg/kg in which Common Terminology Criteria for Adverse Events Grade 3 or 4 lymphopenia occurred, compared with the time when the patients were not experiencing Grade 3 or 4 lymphopenia (see poster DX68 at this meeting). The rate per 100PY was 2.16 during the period with Grade 3/4 lymphopenia, compared with 0.75 per 100PY without lymphopenia.

Neoplasms

- Adj-AEs per 100PY for the system organ class of neoplasms, benign, malignant, and unspecified were 1.14 and 1.01, for cladribine tablets 3.5 mg/kg and placebo, respectively.

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

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Cladribine tablets is currently under clinical investigation and has not yet been approved by any regulatory authority. Status: March 2017.

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