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Cladribine in the treatment of patients with multiple sclerosis: an integrated analysis of infections in association with severe lymphopenia

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INTRODUCTION

- The results from CLARITY, CLARITY Extension, ORACLE-MS, and ONWARD show that cladribine tablets given annually for 2 years in short-duration courses are efficacious across a broad spectrum of patients.[1-4]
- Safety data are available from studies with cladribine tablets and with subcutaneous or intravenous cladribine.
- Lymphopenia, a dose-related expected event related to the mechanism of action of cladribine, has been well-characterized and consistently reported across studies with oral cladribine monotherapy.

OBJECTIVES

- To assess the nature of infections observed in patients treated with cladribine, and to explore the association between severe lymphopenia and infections.

METHODS

- Integrated safety data were used to assess infection in association with cladribine treatment.
- The cohorts were: monotherapy oral (MO; 1555 patients exposed to cladribine tablets with 923 receiving cladribine tablets 3.5 mg/kg), placebo-controlled double-blind (PDB; 1458 patients exposed to cladribine) and all exposed (All-E; 1976 patients exposed to cladribine).
- Adjusted adverse events incidences per 100 patient years (Adj-AE per 100PY) were calculated for the integrated analyses.
  - Adj-AE per 100PY = 100X(number of subjects with at least 1 AE)/(sum of observation time in days among subjects at risk for initial occurrence of an AE or time on study/365.25).

RESULTS

- The All-E cohort of 1976 patients treated with cladribine gave a total follow-up time of 8650 patient-years (PY) and 802 patients received placebo for a total follow-up time of 2361 PY.
- The incidence rates of infections overall and severe infections were similar for cladribine-exposed groups and placebo, except for herpes zoster. Most common infections are presented in **Table 1** and severe infections are presented in **Table 2**.
  - Patients who received cladribine tablets 3.5 mg/kg in both CLARITY and CLARITY Extension had Adj-AE of 24.93 and 21.52 (infections and infestations system organ class [SOC]) respectively during each trial. Respective values for AE special interest severe infection were 0.84 and 0.66.
- In All-E, herpes zoster was a rare event (101 patients, in 1593 patients with overall infection and infestation) but was more frequent in patients (n=95) treated with cladribine than placebo (n=6).
  - Of note 90% (86/95 patients) of these herpes zoster events were non-severe.
  - Severe herpes zoster occurred more frequently in the cladribine group than in the placebo group in the All-E cohort (**Table 2**), and in the PDB cohort (cladribine 0.21 vs placebo 0 Adj-AE per 100PY).
    - Patients who received cladribine tablets 3.5 mg/kg in both CLARITY and CLARITY Extension had Adj-AE special interest herpes zoster of 0.83 and 0.93, respectively, during each trial.

Table 1. Most frequent[a] TEAEs for infections and infestations SOC: all-exposed cohort

	Placebo (N=802)			Cladribine-exposed (all doses) (N=1976)		
Patient years	2361.13			8650.16		
	n	T	Adj-AE per 100PY	n	T	Adj-AE per 100PY
Overall infections and infestations SOC	415	1320.2	31.44	1178	4344.4	27.12
Preferred term						
Nasopharyngitis	118	2077.3	5.68	361	7351.1	4.91
Upper respiratory tract infection	92	2152.0	4.28	308	7584.0	4.06
Influenza	72	2195.8	3.28	222	7901.1	2.81
Urinary tract infection	76	2190.5	3.47	214	7943.3	2.69
Bronchitis	26	2288.0	1.14	126	8175.4	1.54
Herpes zoster	6	2354.0	0.25	95	8365.5	1.14
Sinusitis	26	2313.8	1.12	92	8385.5	1.10
Cystitis	24	2293.5	1.05	78	8412.8	0.93
Pharyngitis	31	2296.6	1.35	69	8407.2	0.82

Preferred terms are presented by descending order of incidence in the cladribine group. n=number of patients with events; T is the total patient time on study in years. If a patient has multiple events, it is the time to first event. For a patient with no event it is censored at the last follow-up time for that patient.
Adj-AE per 100PY, adjusted adverse events incidences per 100 patient years; **PY**, patient years; **SOC**, system organ class; **TEAE**, treatment-emergent adverse event.
[a]Treatment-emergent adverse events in the cladribine or placebo group with an Adj-AE per 100PY ⩾1.0.

Table 2. Most frequent[a] AESI – severe infections: all-exposed cohort

	Placebo (N=802)			Cladribine (N=1976)		
Patient years	2361.13			8650.16		
	n	T	Adj-AE per 100PY	n	T	Adj-AE per 100PY
AESI severe infection	25	2309.3	1.08	104	8343.2	1.25
Pneumonia	3	2354.9	0.13	16	8595.9	0.19
Urinary tract infection	2	2358.6	0.08	13	8617.6	0.15
Herpes zoster	1	2359.6	0.04	9	8626.6	0.10
Upper respiratory tract infection	1	2360.9	0.04	6	8637.3	0.07
Pyelonephritis	0	0	0	5	8630.4	0.06
Sinusitis	0	0	0	4	8644.1	0.05
Appendicitis	2	2358.7	0.08	2	8644.0	0.02

AESI: severe infection is a custom grouping defined by any serious or severe event belonging to the MedDRA infections and infestations SOC. n=number of patients with events; T is the total patient time on study in years. If a patient has multiple events, it is the time to first event. For a patient with no event it is censored at the last follow-up time for that patient.
Adj-AE per 100PY, adjusted adverse events incidences per 100 patient years; **AESI**, adverse event of special interest; **MedDRA**, Medical Dictionary of Regulatory Activities; **PY**, patient years; **SOC**, system organ class; **TEAE**, treatment-emergent adverse event.
[a]Most frequent AESI TEAEs (severe infections) in the cladribine or placebo group with an Adj-AE per 100PY ⩾0.05. Preferred terms are presented by descending order of incidence in the cladribine group.

- Across the clinical program in MS, there were no cases of systemic, serious, disseminated herpes zoster; 3 cases, coded as disseminated, involved the skin only and were reported as non-serious and non-severe.

Herpes zoster in patients with lymphopenia

- Overall, in patients exposed to cladribine in each cohort, the incidence of herpes zoster (reported as an adverse event of special interest) was higher in the period of treatment in which Common Terminology Criteria for Adverse Events Grade 3 or 4 lymphopenia occurred until recovery to Grade 1, compared with the time when the patients were not experiencing Grade 3 or 4 lymphopenia.
  - For example, the MO 3.5 mg/kg dose had Adj-AE incidence per 100PY (95%CI) 2.16 (0.90–5.19) during the period with Grade 3/4 lymphopenia, compared with 0.75 (0.50–1.12) without lymphopenia (**Table 3**).
- In the MO 3.5-mg/kg cohort, 25.4% of patients had at least one Grade 3 lymphopenia at any time and 0.7% had at least one Grade 4 lymphopenia at any time.

Table 3. Adjusted incidence rates of herpes zoster in each cohort during and outside of lymphopenia Grade 3 or 4 episode

Cohort all exposed	Placebo (N=802)	Cladribine (N=1976)
During Grade 3/4 episode and recovery to Grade 1		
Time at risk[a] (years)	9.91	1118.69
Adjusted-AESI per 100PY (95% CI)	0 (0.00–0.37)	2.32 (1.58–3.41)
Outside Grade 3/4 episode		
Adjusted-AESI per 100PY (95% CI)	0.30 (0.14–0.63)	1.01 (0.81–1.26)
Cohort placebo controlled double blind	**Placebo (N=745)**	**Cladribine (N=1458)**
During Grade 3/4 episode and recovery to Grade 1		
Time at risk[a] (years)	1.79	399.90
Adjusted-AESI per 100PY (95% CI)	0 (0.00–2.06)	3.75 (2.26–6.22)
Outside Grade 3/4 episode		
Adjusted-AESI per 100PY (95% CI)	0.18 (0.04–0.71)	0.95 (0.61–1.49)
Cohort monotherapy oral	**Placebo (N=641)**	**Cladribine tablets 3.5 mg/kg (N=923)**
During Grade 3/4 episode and recovery to Grade 1		
Time at risk[a] (years)	7.24	231.50
Adjusted-AESI per 100PY (95% CI)	0 (0.00–0.51)	2.16 (0.90–5.19)
Outside Grade 3/4 episode		
Adjusted-AESI per 100PY (95% CI)	0.20 (0.07–0.53)	0.75 (0.50–1.12)

Confidence intervals computed with the Wald method for the number of subjects with events using a Poisson regression model with fixed effect for treatment group and with log of time at risk as an offset.
AESI, adverse event of special interest; **CI**, confidence interval; **PY**, patient years.
[a]The period at risk of infections is the time during lymphopenia Grade 3/4 (up to recovery to Grade 1). The period not at risk of infections is the time outside of lymphopenia Grade 3 or 4 episode.

CONCLUSIONS

- **Cladribine did not increase the general risk of infections versus placebo; there was a small increase in the risk of severe infections with cladribine, which was mostly associated with herpes zoster.**
- **There were no cases of systemic, serious disseminated herpes zoster across the program.**
- **Herpes zoster was reported more frequently in patients while they were experiencing Grade 3 or 4 lymphopenia.**

REFERENCES

1. Giovannoni G, *et al. N Engl J Med* 2010;362:416–26.
2. Giovannoni G, *et al. Neurology* 2013;80:P07-119 [Abstract].
3. Leist T, *et al. Lancet Neurol* 2014;13:257–67.
4. Montalban X, *et al. Neurology*. 2013;80:P07-099 [Abstract].

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DISCLOSURES

SC: has received honoraria for lectures/consultations from Merck, Bayer HealthCare, Sanofi-Aventis, Neurology Reviews, Biogen Idec, TEVA, 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:** is a consultant to EMD Serono, Teva Neuroscience, Biogen, Bayer, Pfizer; and is involved in clinical trials sponsored by EMD Serono, Teva Neuroscience, Bayer, ONO, Novartis, Daiichi, and Acorda. **GC:** has received consulting fees from Novartis, Teva Pharmaceutical Industries Ltd., Sanofi-Aventis, Merck, and Bayer Schering; lecture fees from Novartis, Teva Pharmaceutical Ind. Ltd., Sanofi-Aventis, Merck Serono, Biogen Dompè, Bayer Schering, and Serono Symposia International Foundation; and trial grant support from Novartis, Teva Pharmaceutical Ind. Ltd., Sanofi-Aventis, 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. **ES** and **CH:** employees of Merck KGaA, Darmstadt, Germany. **FD:** employee of EMD Serono, Inc.,* Billerica, MA, USA.

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

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