Infections and Grade 3 or 4 Lymphopenia in Patients Taking Cladribine Tablets 3.5 mg/kg: Data from an Integrated Safety Analysis

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INTRODUCTION

- Results from CLARITY, CLARITY Extension, ORACLE-MS, and ONWARD show that cladribine tablets given annually for 2 years in short-duration courses are efficacious in a spectrum of patients with relapsing multiple sclerosis.[1-4]
- The most common adverse event (AE) was lymphopenia, reflecting the mode of action of cladribine.[1]
- An integrated analysis of safety showed that the incidence of infections overall was not higher in patients receiving cladribine tablets 3.5 mg/kg than in patients receiving placebo, except for a small increased risk of herpes zoster.[5]

OBJECTIVE

- This *post hoc* analysis examined the infectious AEs occurring during exact periods of Grade 3 or 4 lymphopenia in patients treated with cladribine tablets 3.5 mg/kg.
  - Previous analyses used recovery to Grade 1 lymphopenia or better to define periods of severe lymphopenia.[5]

METHODS

- A monotherapy oral cohort was derived from CLARITY, CLARITY Extension, ORACLE-MS, and the PREMIERE registry, with 923 patients receiving cladribine tablets 3.5 mg/kg and 641 receiving placebo.
- The AE profile for cladribine tablets 3.5 mg/kg during the exact periods of Grade 3 or 4 lymphopenia was analyzed.
  - Periods of Grade 3 or 4 lymphopenia were defined as the onset of the Grade 3 or 4 lymphopenia to first Grade 2 or lower plus 2 weeks.
  - Periods of Grade 4 lymphopenia were defined as the onset of the Grade 4 lymphopenia to first Grade 3 or lower plus 2 weeks.
- Adjusted AE incidences per 100 patient-years (Adj-AE per 100PY) were calculated.

RESULTS

Incidence of Infections Overall (Monotherapy Oral Cohort)

- In the entire monotherapy oral cohort, the incidence rate for infections overall, severe infections, infections leading to discontinuation, or opportunistic infections was not higher for patients receiving cladribine tablets compared with patients receiving placebo (**Table 1**).

Table 1. Overview of Infections in Patients Receiving Placebo or Cladribine Tablets 3.5 mg/kg (Monotherapy Oral Cohort)

Number of Patients (Adj-AE per 100 PY)	Placebo (n = 641)	Cladribine Tablets (n = 923)
Infections and infestations SOC	314 (27.1)	478 (24.9)
Infections and infestations SOC leading to treatment discontinuation	3 (0.2)	4 (0.1)
AESI severe infections	17 (0.9)	28 (0.8)
AESI opportunistic infections	23 (1.2)	36 (1.1)
AESI herpetic infections	19 (1.0)	60 (1.8)
AESI herpes zoster	4 (0.2)	29 (0.9)

Adj-AE per 100PY, adjusted AE incidences per 100 patient-years; **AE**, adverse event; **AESI**, adverse event of special interest; **SOC**, system organ class.

- More than half of the opportunistic infections were of mucocutaneous and cutaneous fungal nature, resolved, and did not include any infections that were "difficult to treat" (such as cryptococcosis, toxoplasmosis, pneumocystis jirovecii pneumonia, or cytomegalovirus infection).

Infections Associated with Severe Lymphopenia in Patients Receiving Cladribine Tablets 3.5 mg/kg (Monotherapy Oral Cohort)

- Adj-AE per 100PY for any infections and infestations during periods of Grade 3 or 4 lymphopenia and outside these periods (without G3/4) were 57.53 and 24.50, respectively (**Table 2 and Table 3**).
- Types of infectious AEs during periods of Grade 3 or 4 lymphopenia were similar to outside these periods and did not show any specific pattern.
- More than half of cases occurring during periods of Grade 3 or 4 lymphopenia were easily-treatable infections of the upper respiratory tract (Adj-AE per 100PY: nasopharyngitis, 13.48 vs 5.24 without G3/4; upper respiratory tract infection, 9.67 vs 3.41 without G3/4; pharyngitis, 4.51 vs 0.73 without G3/4).
- Herpes zoster was reported in 4 patients during periods of Grade 3 or 4 lymphopenia (Adj AE per 100PY 4.50 vs 0.73 without G3/4).
  - Cases were dermatomal and mild to moderate in severity.
- Single occurrences were reported for most infectious AEs during periods of Grade 3 or 4 lymphopenia.
- Opportunistic infections during periods of Grade 3 or 4 lymphopenia were single occurrences of 'urinary tract infection fungal' and 'fungal infection' (preferred terms) and neither was severe or serious.
  - There were no opportunistic infections that were "difficult to treat" during periods of Grade 3 or 4 lymphopenia.
- During the exact period of Grade 4 lymphopenia, sinusitis and urinary tract infection were the only infections reported (each occurred in single patients only).
- Analysis of severe or serious infectious AEs revealed 1 patient with severe, non-serious streptococcal tonsillitis and 1 patient with serious tuberculosis during the period of Grade 3 or 4 lymphopenia, and no events during Grade 4 lymphopenia.

Table 2. Adverse Events of the SOC Infections and Infestations by Preferred Term Occurring During the Exact Periods of Grade 3 or 4 Lymphopenia in Patients Receiving Cladribine Tablets 3.5 mg/kg

Preferred Term	Cladribine Tablets (n = 923)		
	n	T	Adj-AE per 100PY
Any infections and infestations	**40**	**69.5**	**57.53**
Nasopharyngitis	11	81.6	13.48
Upper respiratory tract infection	8	82.7	9.67
Pharyngitis	4	88.6	4.51
Herpes zoster	4	88.9	4.50
Influenza	3	89.6	3.35
Urinary tract infection	3	89.2	3.36
Bronchitis	2	89.7	2.23
Viral upper respiratory tract infection	2	89.6	2.23
Urinary tract infection fungal	1	88.6	1.13
Bacteriuria	1	89.5	1.12
Cystitis	1	87.6	1.14
Diverticulitis	1	89.2	1.12
Ear infection	1	90.1	1.11
Erythema infectiosum	1	89.7	1.11
Eye infection	1	90.0	1.11
Fungal infection	1	89.9	1.11
Gastroenteritis	1	87.0	1.15
Gastroenteritis viral	1	89.5	1.12
Genital herpes	1	90.0	1.11
Herpes simplex	1	89.9	1.11
Lower respiratory tract infection	1	89.2	1.12
Oral herpes	1	90.0	1.11
Respiratory tract infection bacterial	1	90.0	1.11
Sinusitis	1	89.8	1.11
Tonsillitis	1	90.0	1.11
Tracheitis	1	86.5	1.16
Tonsillitis streptococcal	1	90.0	1.11
Tuberculosis	1	90.1	1.11

n is the number of patients with events. T is the total patients time at risk in years (cumulative periods).
Adj-AE per 100PY, adjusted AE incidences per 100 patient-years; **AE**, adverse event; **SOC**, system organ class.

Table 3. Adverse Events of the SOC Infections and Infestations by Preferred Term Occurring Outside the Exact Periods of Grade 3 or 4 Lymphopenia Occurring in > 2 Patients Receiving Cladribine Tablets 3.5 mg/kg

Preferred Term	Cladribine Tablets (n = 923)		
	n	T	Adj-AE per 100PY
Any infections and infestations	**468**	**1910.5**	**24.50**
Nasopharyngitis	152	2899.7	5.24
Upper respiratory tract infection	104	3045.8	3.41
Influenza	85	3096.4	2.75
Bronchitis	54	3148.4	1.72
Urinary tract infection	54	3170.9	1.70
Sinusitis	31	3263.5	0.95
Respiratory tract infection viral	26	3268.7	0.80
Cystitis	26	3276.0	0.79
Gastroenteritis	24	3260.7	0.74
Rhinitis	24	3264.3	0.74
Herpes zoster	24	3280.4	0.73
Pharyngitis	24	3269.1	0.73
Viral upper respiratory tract infection	21	3259.7	0.64
Oral herpes	20	3292.9	0.61
Vaginal infection	14	3285.9	0.43
Respiratory tract infection	13	3311.6	0.39
Viral infection	13	3304.3	0.39
Gastroenteritis viral	12	3297.2	0.36
Conjunctivitis	11	3319.3	0.33
Pneumonia	11	3304.4	0.33

n is the number of patients with events. T is the total patients time at risk in years (cumulative periods).
Adj-AE per 100PY, adjusted AE incidences per 100 patient-years; **AE**, adverse event; **SOC**, system organ class.

Table 3 (cont'd). Adverse Events of the SOC Infections and Infestations by Preferred Term Occurring Outside the Exact Periods of Grade 3 or 4 Lymphopenia Occurring in > 2 Patients Receiving Cladribine Tablets 3.5 mg/kg

Preferred Term	Cladribine Tablets (n = 923)		
	n	T	Adj-AE per 100PY
Ear infection	10	3315.8	0.30
Acute tonsillitis	9	3319.5	0.27
Periodontitis	9	3309.1	0.27
Tonsillitis	9	3325.0	0.27
Vulvovaginal mycotic infection	9	3312.3	0.27
Fungal infection	8	3309.0	0.24
Tooth abscess	8	3329.1	0.24
Otitis media	7	3326.6	0.21
Vulvovaginal candidiasis	7	3327.7	0.21
Gingivitis	6	3328.9	0.18
Laryngitis	6	3322.3	0.18
Tooth infection	6	3319.9	0.18
Acute sinusitis	5	3314.3	0.15
Furuncle	5	3323.2	0.15
Herpes simplex	5	3326.8	0.15
Salpingo-oophoritis	5	3333.8	0.15
Gastrointestinal infection	4	3329.7	0.12
Herpes virus infection	4	3326.8	0.12
Hordeolum	4	3333.1	0.12
Onychomycosis	4	3329.2	0.12
Tracheitis	4	3328.6	0.12
Fungal skin infection	3	3340.7	0.09
Tinea pedis	3	3337.1	0.09
Ureaplasma infection	3	3330.9	0.09
Varicella	3	3332.8	0.09
Wound infection	3	3335.8	0.09

n is the number of patients with events. T is the total patients time at risk in years (cumulative periods).
Adj-AE per 100PY, adjusted AE incidences per 100 patient-years; **AE**, adverse event; **SOC**, system organ class.

CONCLUSIONS

- **Severe lymphopenia resulted in an increased frequency of infections but did not have any differential effect on the type of infectious AEs in patients treated with cladribine tablets 3.5 mg/kg monotherapy.**
- **The profile of herpes zoster was uncomplicated, consistent with the findings of previous safety analyses.[5]**
- **In general, patients with Grade 4 lymphopenia are more susceptible to infections. If lymphocyte counts drop below 200 cells/mm^3 during treatment with cladribine tablets 3.5 mg/kg, anti-herpes prophylaxis according to local standard practice should be considered during the time of Grade 4 lymphopenia.**

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