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Updated Safety of Cladribine Tablets in the Treatment of Patients with Multiple Sclerosis: Integrated Safety Analysis and Post-approval Data

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CONCLUSIONS

The updated safety profile from this analysis, containing final data from the PREMIERE registry cumulative to January 2020, was generally consistent with that from previously published analyses (cumulative to February 2015 and cumulative to May 2017)[4,5]

Respiratory viral infections were seen at similar rates in patients treated with cladribine tablets compared with placebo

No new safety signals were identified in the real-world post-approval data, cumulative to January 2020

INTRODUCTION

- The safety of treatment with cladribine tablets was assessed in the clinical trial program,[1-3] including the CLARITY[1] and CLARITY EXT[2] studies in patients with RMS
- Integrated safety data (cumulative to February 2015 and cumulative to May 2017) for cladribine tablets have previously been published[4,5]
- There have been additional safety data obtained from use in clinical practice since the approval of cladribine tablets 10 mg (3.5 mg/kg cumulative dose over 2 years; referred to as cladribine tablets 3.5 mg/kg) in many countries around the world
  - In light of COVID-19, we present more detail of other respiratory viral infections in the clinical program and post-approval setting
- This analysis represents the final analysis of data from the clinical development of cladribine tablets and moving forward there will be only post-approval updates

OBJECTIVES

- To report post-approval safety data from worldwide sources, cumulative to January 2020
- To analyze rates of respiratory viral infections in patients treated with cladribine tablets compared with placebo

METHODS

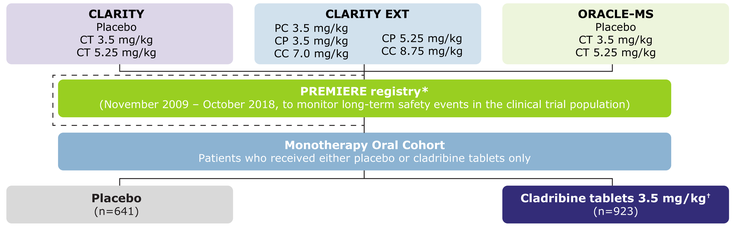
Post-approval Data

- The sum total of serious AEs, as well as individual numbers of serious and non-serious AEs from post-approval sources are reported

Monotherapy Oral Cohort Data

- The Monotherapy Oral cohort comprised patients from the CLARITY, CLARITY EXT, and ORACLE-MS trials, and the PREMIERE registry (**Figure 1**):
  - 923 patients received cladribine tablets 3.5 mg/kg
  - 641 patients received placebo

Figure 1. Summary of Data Included in the Monotherapy Oral Cohort from the Clinical Program



*Patients with prior enrollment into selected clinical trials with cladribine tablets were eligible to enter PREMIERE once participation in the clinical trial had ended.
†The Monotherapy Oral cohort also contained a cladribine tablets (CT) 5.25 mg/kg treatment group; data not shown. All safety analyses were performed using the "as treated principle". For the Monotherapy Oral Cohort, if patients received only placebo or were in the observational follow-up period without having switched to CT (i.e. in CLARITY EXT), then their data became part of the placebo group. Patients who switched treatment from placebo to CT in subsequent studies/periods had their time on placebo censored at the time of the switch. Patients who switched treatment from placebo to CT 3.5 mg/kg had their time on CT 3.5 mg/kg initiated at the time of switching. Patients who were treated with CT 3.5 mg/kg in CLARITY and were then re-exposed to CT 3.5 mg/kg in a subsequent study/period (i.e. in CLARITY Ext) had their time on CT 3.5 mg/kg censored at the time of re-exposure.

RESULTS

Additional Content Supplementary Table 1

Table 1. Characteristics of Patients Included in the Monotherapy Oral Cohort from the Clinical Program

Patient characteristic	Placebo (n=641)	Cladribine tablets 3.5 mg/kg (n=923)
Patient-years*	2422	3937
Time on study, years*, mean (SD)	3.78 (2.66)	4.27 (2.53)
Time on study, ≥96 weeks [~2 years], n (%)	493 (76.9)	784 (84.9)
Time on study, ≥192 weeks [~4 years], n (%)	204 (31.8)	431 (46.7)
Time on study, ≥432 weeks [~9 years], n (%)	18 (2.8)	26 (2.8)
Age, years†; mean (SD)	37.15 (9.83)	37.84 (10.48)
Median	36.53	37.62
Min; max	18.1; 64.2	18.2; 66.1
Age ≤40 years, n (%)	396 (61.8)	540 (58.5)
Age >40 years, n (%)	245 (38.2)	383 (41.5)
Female, n (%)	424 (66.1)	612 (66.3)
Prior treatment with DMD, n (%)	131 (20.4)	184 (19.9)

*Cumulative to October 2018; †As reported at first dosing date.

Monotherapy Oral Cohort Data

- Patient characteristics were generally balanced among groups (**Table 1**)
- The reported number of serious TEAEs was higher in the cladribine tablets 3.5 mg/kg group versus the placebo group (**Table 2; Additional Content Supplementary Table 1**)
- In the cladribine tablets 3.5 mg/kg group, the Adj-AE for serious lymphopenia was 0.10 per 100PY (**Table 2**)
  - Lymphopenia is an expected pharmacological effect of cladribine tablets due to its mechanism of action
  - The incidence of herpes zoster was higher in the cladribine-treated group than in the placebo group, but serious respiratory infections occurred at a similar frequency

Post-approval Data

- A total of 2570 AEs were reported in the first 14,813 patients who received cladribine tablets post-approval
- In total, 303 (12%) of the 2570 AEs were classified as serious during the reporting period, and none represented a new safety signal
- The pattern of AEs of special interest was consistent with the clinical safety profile for cladribine tablets (**Table 3**)

RESULTS (cont.)

Viral Infections Including COVID-19

- Viral infections (all patients) are summarized in **Table 4**
- As of 29 June 2020, 47 suspected cases of COVID-19 occurring in patients treated with cladribine tablets have been reported to the Merck KGaA, Darmstadt, Germany safety database
- As of 29 June 2020, 18 COVID-19 cases have been confirmed in patients treated with cladribine tablets (seven males, nine females, and 2 unknown; age range: 25-67 years)
- Four of the confirmed cases were classified as serious, 3 due to hospitalization and 1 due to medical significance as reported by the physician. No patients were reported to require mechanical ventilation

Table 2. Serious* TEAEs of Special Interest in the Monotherapy Oral Cohort from the Clinical Program

	Placebo (n=641)			Cladribine tablets 3.5 mg/kg (n=923)		
	n	Total PY	Adj-AE per 100PY	n	Total PY	Adj-AE per 100PY
At least 1 serious TEAE	68	2226.2	3.05	133	3498.1	3.80
Lymphopenia	0	2421.5	0	4	3925.4	0.10
Herpes zoster	0	2421.5	0	2	3929.7	0.05
Pneumonia	3	2415.2	0.12	6	3907.4	0.15
Pulmonary tuberculosis	0	2421.5	0	1	3933.6	0.03
Tuberculosis	0	2421.5	0	1	3936.7	0.03
Urinary tract infection	1	2419.9	0.04	4	3923.4	0.10
Malignancies	3	2414.8	0.12	10	3918.9	0.26
Rash generalized	0	2421.5	0	1	3936.6	0.03

*Serious was defined as resultant in death, life-threatening, required inpatient hospitalization, congenital anomaly or birth defect, or was otherwise considered as medically important.

Table 3. Adverse Events of Special Interest* (Serious and Non-serious) in the Monotherapy Oral Cohort from the Clinical Program and the Analysis of Post-approval Data (Until 7 January 2020)**

	Monotherapy Oral Cohort cladribine tablets 3.5 mg/kg (n=923)		Post-approval Cohort cladribine tablets 3.5 mg/kg (n=14,813)	
	n	Crude AE incidence rate, %	n	Crude AE incidence rate, %
Severe lymphopenia	24	2.6	27[‡]	0.2
Herpes zoster	28	3.0	117	0.8
Tuberculosis	2[†]	0.2	6	0.04
Severe infections	29	3.1	138[‡]	0.9
PML	0	0	0	0
Opportunistic infections*	10	1.1	19	0.1
Malignancies	10	1.1	22	0.15
Teratogenicity	0**	0	0[§]	0

The Monotherapy Oral Cohort comprises patients from the CLARITY, CLARITY EXT, and ORACLE-MS trials, and the PREMIERE registry; AE rates are based on the numbers of patients with at least one AE. Post-approval Cohort comprises the first 14,813 patients treated with cladribine tablets using post-approval sources from 22 August 2017 to 7 January 2020 (N.B. patients in this cohort were not systematically followed); AE rates are based on the overall number of AEs.
*Majority of the opportunistic infections were mucocutaneous and cutaneous fungal infections, which resolved on standard treatments. Opportunistic infections that could be life-threatening were not observed.
**No cases of teratogenicity in pregnancies occurred during cladribine treatment or within 6 months after the last dose.
†Both cases of tuberculosis in the Monotherapy Oral Cohort were serious (one coded as tuberculosis, one coded as pulmonary tuberculosis).
‡In the Post-approval Cohort, all serious events were counted towards severe lymphopenia and severe infections.
§In one case of maternal exposure during pregnancy reported by a Health Authority (#E2B_90073559), an elective termination was performed due to a congenital anomaly of the fetus (not further specified). Exposure to cladribine tablets occurred in the first trimester. The patient was on concomitant medication with terbutaline and ferrous sulfate which could adversely impact fetal development.

Table 4. Respiratory Viral Infections in the Monotherapy Oral Cohort from the Clinical Program and the Analysis of Post-approval Data (until 7 January 2020)

	Monotherapy Oral Cohort placebo (n=641)		Monotherapy Oral Cohort cladribine tablets 3.5 mg/kg (n=923)		Post-approval Cohort cladribine tablets 3.5 mg/kg	
	n	Crude AE incidence rate, %	n	Crude AE incidence rate, %	n	Crude AE incidence rate, %
H1N1 influenza	-	-	1	0.1	0	0
Influenza	51	8.0	88	9.5	73	0.5
Laryngitis viral	-	-	1	0.1	0	0
Respiratory tract infection viral	13	2.0	26	2.8	0	0
Viral infection	12	1.9	13	1.4	34	0.2
Viral pharyngitis	1	0.2	1	0.1	0	0
Viral upper respiratory tract infection	96	15.0	158	17.1	6	0.04

Abbreviations: Adj-AE per 100PY, adjusted adverse events incidences per 100 PY; **AE,** adverse event; **CC 7 mg/kg:** CT 3.5 mg/kg in CLARITY followed by CT 3.5 mg/kg in CLARITY EXT; **CC 8.75 mg/kg:** CT 5.25 mg/kg in CLARITY followed by CT 3.5 mg/kg in CLARITY EXT; **CP 3.5 mg/kg:** CT 3.5 mg/kg in CLARITY followed by placebo in CLARITY EXT; **CP 5.25 mg/kg**: CT 5.25 mg/kg in CLARITY followed by placebo in CLARITY EXT; **DMD,** disease-modifying drug; **EXT,** Extension; **n,** number of events; **PC 3.5 mg/kg:** placebo in CLARITY followed by CT 3.5 mg/kg in CLARITY EXT; **PML,** progressive multifocal leukoencephalopathy; **PY,** patient-years; **RMS,** relapsing multiple sclerosis; **SD,** standard deviation; **TEAE,** treatment-emergent adverse event

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