Abstract no. 41

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

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INTRODUCTION

- The safety of treatment with cladribine tablets was assessed in the clinical trial program,[1-3] including the CLARITY[1] and CLARITY Extension[2] studies in patients with relapsing multiple sclerosis (RMS).
- Integrated safety data (cumulative to February 2015 and cumulative to May 2017) for cladribine tablets have previously been published.[4,5]
  - Integrated analysis of pooled clinical safety data is an established method facilitating the comprehensive characterisation of the safety profile of a therapy.
- 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 addition to clinical data, we present the sum total of serious adverse events (AEs) from the reporting of post-approval data.

OBJECTIVES

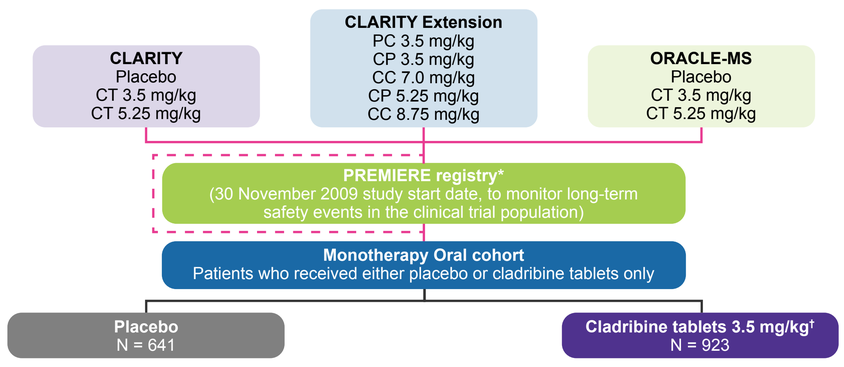
- Provide an update to the previously reported cumulative serious treatment emergent AEs (TEAE) profile of cladribine tablets 3.5 mg/kg from the clinical trial program following integration of final data from the PREMIERE Registry, completed in October 2018.
- To report post-approval safety data from worldwide sources.

METHODS

Monotherapy Oral Cohort: Data from the Clinical Program

- The Monotherapy Oral cohort comprised patients from the CLARITY, CLARITY Extension, and ORACLE-MS trials, and the PREMIERE registry (**Figure 1**).
  - 923 patients received cladribine tablets 3.5 mg/kg.
  - 641 patients received placebo.
- Adjusted adverse event incidences per 100 patient-years (Adj-AE per 100PY) were calculated, using a data cut-off of October 2018 (end of the PREMIERE registry).

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 Extension [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. 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; 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; PC 3.5 mg/kg: placebo in CLARITY followed by CT 3.5 mg/kg in CLARITY Ext.

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.
  - Post-approval sources included spontaneous individual case safety reports (i.e. health care professionals, consumers, competent authorities [worldwide], and scientific literature), non-interventional post-marketing studies, and reports from other solicited sources.

RESULTS

Monotherapy Oral Cohort: Patient Characteristics

- Patient characteristics were generally balanced among groups (**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) Median Min; max	37.15 (9.83) 36.53 18.1; 64.2	37.84 (10.48) 37.62 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. **DMD**, disease modifying drug; **SD**, standard deviation.

- The reported number of serious TEAEs was higher in the cladribine tablets 3.5 mg/kg group versus the placebo group (**Table 2; Supplementary Table 1**).
- Cumulative to 2018, there were:
  - Cladribine tablets 3.5 mg/kg: 3.80 AEs per 100PY; 133/923 patients with serious TEAEs;
  - Placebo: 3.05 AEs per 100PY; 68/641 patients with serious TEAEs.
- There were no cases of progressive multifocal leukoencephalopathy with cladribine tablets 3.5 mg/kg.

Monotherapy Oral Cohort: Lymphopenia

- In the cladribine tablets 3.5 mg/kg group, Adj-AE per 100PY for serious lymphopenia (preferred term) was 0.10 (**Table 2**):
  - Lymphopenia is an expected pharmacological effect of cladribine tablets due to its mechanism of action.
  - In the placebo group, there were no serious lymphopenia events.

Monotherapy Oral Cohort: Infections

- Serious infections and infestations (system organ class; **Table 2**):
  - Cladribine tablets 3.5 mg/kg: 0.60 Adj-AE per 100PY
  - Placebo: 0.42 Adj-AE per 100PY.
- Serious herpes zoster (preferred term):
  - Cladribine tablets 3.5 mg/kg group: 0.05 Adj-AE per 100PY; the probability of occurrence is higher during severe lymphopenia.
  - In the placebo group, there were no serious herpes zoster events.

Monotherapy Oral Cohort: Malignancy

- Malignant tumours (adverse event of special interest) (**Table 2**):
  - Cladribine tablets 3.5 mg/kg: 0.26 Adj-AE per 100PY
  - Placebo: 0.12 Adj-AE per 100PY
  - These incidence rates are similar to those in the previously published analysis (0.29 and 0.15 Adj-AE per 100PY, respectively, cut-off date February 2015).[4]

Supplementary Appendix 1: Additional Safety Details

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

System organ class Preferred term	Placebo (N = 641) n	Placebo (N = 641) Total PY	Placebo (N = 641) Adj-AE per 100 PY	Cladribine tablets 3.5 mg/kg (N = 923) n	Cladribine tablets 3.5 mg/kg (N = 923) Total PY	Cladribine tablets 3.5 mg/kg (N = 923) Adj-AE per 100 PY
At least 1 serious TEAE	68	2226.2	3.05	133	3498.1	3.80
Blood and lymphatic system disorders	**0**	**2421.5**	**0**	**10**	**3912.7**	**0.26**
Lymphopenia	0	2421.5	0	4	3925.4	0.10
Infections and infestations	**10**	**2395.8**	**0.42**	**23**	**3857.2**	**0.60**
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
Neoplasms benign, malignant and unspecified†	**8**	**2398.7**	**0.33**	**26**	**3865.7**	**0.67**
AESI malignant tumours	3	2414.8	0.12	10	3918.9	0.26
Uterine leiomyoma	2	2413.1	0.08	6	3905.7	0.15
Skin and subcutaneous tissue disorders	**1**	**2420.5**	**0.04**	**3**	**3934.5**	**0.08**
Rash generalised	0	2421.5	0	1	3936.6	0.03

The Medical Dictionary for Regulatory Activities (MedDRA) v20.0 was used for adverse event coding. System Organ Classes are groupings by aetiology, manifestation site or purpose; Preferred Term is a distinct descriptor (single medical concept) for a symptom, sign, disease diagnosis, therapeutic indication, investigation, surgical or medical procedure, and medical social or family history characteristic.
*Serious was defined as resultant in death, life-threatening, required inpatient hospitalisation, congenital anomaly or birth defect, or was otherwise considered as medically important; †Including cysts and polyps.
Adj-AE per 100PY, adjusted adverse events incidences per 100 patient-years; **AESI**, adverse event of special interest; **PY**, patient-years; **TEAE**, treatment emergent adverse events.

Supplementary Table 1: Most Frequently Reported Serious TEAEs with an Adj-AE per 100PY ≥ 0.10

Post-approval Data

- A total of 1622 AEs were reported in the first 8419 patients who have received the product, cladribine tablets, post-approval.
- In total, 275 (17%) of the 1622 AEs were classified as serious during the reporting period, none of which represented a new safety signal.
  - Overall, the pattern of serious and non-serious AEs observed was consistent with the clinical safety profile for cladribine tablets.
  - In the post-approval data, there were three serious cases of herpes zoster, and one serious case of ophthalmic herpes zoster reported for cladribine tablets.

Adverse Events of Special Interest

- AEs of special interest (including serious and non-serious AEs) with cladribine tablets 3.5 mg/kg in both the monotherapy oral cohort and from post-approval sources (in the first 8419 patients treated with cladribine tablets) are presented as crude incidences in **Table 3**.
  - There were no cases of teratogenicity or progressive multifocal leukoencephalopathy with cladribine tablets 3.5 mg/kg.

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

	Monotherapy Oral Cohort Cladribine tablets 3.5 mg/kg (N = 923) n	Monotherapy Oral Cohort Cladribine tablets 3.5 mg/kg (N = 923) AE rate (crude incidence)	Post-approval Cladribine tablets (N = 8419)‡ n	Post-approval Cladribine tablets (N = 8419)‡ AE rate (crude incidence)
Severe lymphopenia	24	0.03	9§	0.001
Herpes zoster	28	0.03	71	0.008
Tuberculosis	2†	0.002	1	0.0001
Severe infections	29	0.03	61§	0.007
PML	0	0	0	0
Opportunistic infections*	10	0.01	7	0.0008
Malignancies	10	0.01	13	0.002
Teratogenicity	0	0	0	0

The Monotherapy Oral cohort comprises patients from the CLARITY, CLARITY Extension, 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 8419 patients treated with cladribine tablets using post-approval sources (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; †Both cases of tuberculosis in the monotherapy oral cohort were serious (one coded as tuberculosis, one coded as pulmonary tuberculosis); ‡Includes patients who had received the first course of treatment and patients who had completed both treatment courses. §In the post-approval setting, all serious events were counted towards severe lymphopenia and severe infections.
AE, adverse event; **n**, number of events; **PML**, progressive multifocal leukoencephalopathy.

CONCLUSION

- **No new major safety findings were identified in this finalised integrated safety dataset from the clinical program involving 923 patients who received cladribine tablets 3.5 mg/kg.**
  - **The updated safety profile from this analysis, containing final data from the PREMIERE registry cumulative to October 2018, was generally consistent with that from previously published analyses (cumulative to February 2015 and cumulative to May 2017).[4,5]**
- **Similarly, no new safety signals were identified in the real-world post-approval data from the first 8419 patients to receive cladribine tablets.**

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DISCLOSURES

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The CLARITY study, NCT00213135;
The CLARITY Extension study, NCT00641537;
The ORACLE-MS study, NCT00725985;
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