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Updated Safety Analysis of Cladribine Tablets in the Treatment of Patients with Multiple Sclerosis

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INTRODUCTION

- Efficacy of Cladribine Tablets was demonstrated in the CLARITY,[1] CLARITY Extension[2] and ORACLE-MS[3] studies in patients with both early and relapsing multiple sclerosis (RMS).
- Integrated analysis by pooling of safety data is an established methodology for the comprehensive characterisation of the safety profile of a therapy.
  - The safety profile of Cladribine Tablets based on the integrated analysis of safety data has been presented previously.[4]
- With the recent approvals of Cladribine Tablets 10 mg (3.5 mg/kg cumulative dose over 2 years; referred to as Cladribine Tablets 3.5 mg/kg) for patients with highly active RMS, the integrated safety profile from clinical trials represent the best source of safety data until comprehensive real-world post-approval safety data are accumulated.
  - Although post-approval experience is limited, we report the sum total of serious adverse drug reactions (ADR) from post-approval data sources, in addition to clinical data.

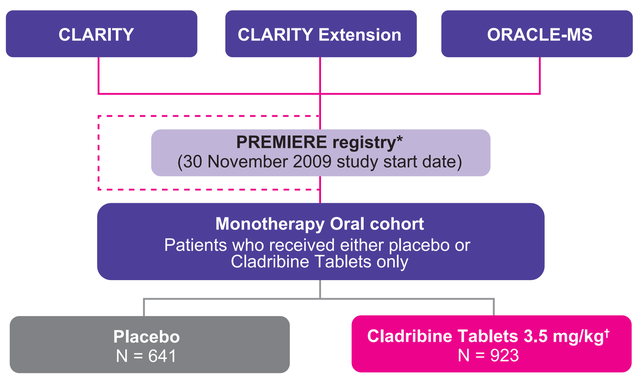
OBJECTIVES

- To provide integrated safety data for Cladribine Tablets 3.5 mg/kg, cumulative to May 2017: an update to the previously reported serious treatment emergent adverse event (TEAE) profile.
- To report initial (1-year) post-approval safety data from Europe.

METHODS

- The Monotherapy Oral cohort was derived from the CLARITY, CLARITY Extension, and ORACLE-MS trials, and the PREMIERE registry (30 November 2009 study start date) (**Figure 1**).
  - 923 patients received Cladribine Tablets 3.5 mg/kg.
  - 641 patients received placebo.

Figure 1. Summary of Data Included for Integrated Safety Analysis



*Patients with prior enrolment into selected oral cladribine clinical trials are eligible to enter PREMIERE once participation in the clinical trial has ended.

†The Monotherapy Oral cohort also contained a Cladribine Tablets 5.25 mg/kg treatment group; data not shown.

- Adjusted adverse events incidences per 100 patient-years (Adj-AE per 100PY) were calculated, with a data cut-off of May 2017.
- The sum total of serious ADRs from post-approval sources (August 2017 – July 2018) are also reported.
  - Post-approval sources included non-interventional post-marketing studies, reports from other solicited sources and spontaneous individual case safety reports (i.e., health care professionals, consumers, competent authorities [worldwide], and scientific literature).

Table 1. Characteristics of Patients Included in the Analysis

Patient characteristic	Placebo (n = 641)	Cladribine Tablets 3.5 mg/kg (n = 923)
Patient-years*	2275	3754
Time on Study, weeks*; mean (SD)	185.21 (122.33)	212.22 (119.98)
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)	430 (46.6)
Time on study, ≥ 432 weeks (~9 years), n (%)	18 (2.8)	23 (2.5)
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 (58.4)
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 May 2017. †As reported at first dosing date.
DMD, disease modifying drug; **SD**, standard deviation.

Table 2. Most Frequently Reported Serious* TEAEs (Adj-AE per 100 PY of ≥ 0.10)

	Placebo (N = 641)			Cladribine Tablets 3.5 mg/kg (N = 923)		
	n	Total PY	Adj-AE per 100 PY	n	Total PY	Adj-AE per 100 PY
At least 1 serious TEAE	68	2099.7	3.24	130	3354.8	3.88
Blood and lymphatic system disorders	0	2275.3	0	10	3730.0	0.27
Lymphopenia	0	2275.3	0	4	3742.8	0.11
Cardiac disorders	6	2264.2	0.26	7	3736.2	0.19
Endocrine disorders	4	2266.6	0.18	3	3746.7	0.08
Thyroid mass	3	2267.6	0.13	1	3751.9	0.03
Eye disorders	2	2272.6	0.09	3	3745.2	0.08
Gastrointestinal disorders	3	2258.5	0.13	11	3713.3	0.30
General disorders and administration site conditions	3	2267.9	0.13	6	3747.8	0.16
Hepatobiliary disorders	3	2266.8	0.13	6	3747.5	0.16
Infections and infestations†	10	2250.7	0.44	23	3676.8	0.63
Appendicitis	2	2272.8	0.09	1	3748.1	0.03
Pneumonia	3	2269.0	0.13	6	3724.8	0.16
Urinary tract infection	1	2273.6	0.04	4	3740.8	0.11
Injury, poisoning and procedural complications	5	2252.2	0.22	17	3705.2	0.46
Road traffic accident	2	2267.3	0.09	0	3754.0	0
Investigations	6	2258.5	0.27	14	3704.5	0.38
Blood creatine phosphokinase increased	4	2271.8	0.18	7	3727.7	0.19
Musculoskeletal and connective tissue disorders	3	2269.4	0.13	6	3738.1	0.16
Neoplasms benign, malignant and unspecified‡	8	2258.4	0.35	24	3691.5	0.65
Uterine leiomyoma	2	2268.9	0.09	5	3731.0	0.13
Nervous system disorders	6	2265.5	0.26	11	3725.9	0.30
Multiple sclerosis relapse	0	2275.3	0	4	3745.2	0.11
Pregnancy, puerperium and perinatal conditions	7	2262.4	0.31	9	3722.9	0.24
Abortion spontaneous	3	2270.4	0.13	2	3752.4	0.05
Pregnancy	3	2267.2	0.13	1	3748.0	0.03
Psychiatric disorders	5	2265.5	0.22	4	3746.9	0.11
Renal and urinary disorders	3	2267.9	0.13	3	3744.3	0.08
Ureterolithiasis	2	2624.1	0.08	0	3754.0	0
Reproductive system and breast disorders	3	2265.3	0.13	8	3718.9	0.22
Respiratory, thoracic and mediastinal disorders	4	2264.8	0.18	8	3722.9	0.21
Surgical and medical procedures	2	2267.8	0.09	6	3734.0	0.16

The Medical Dictionary for Regulatory Activities (MedDRA) v20.0 was used for adverse event coding.
*Serious was defined as resultant in death; life-threatening; required inpatient hospitalisation; congenital anomaly or birth defect; or was otherwise considered as medically important; †Herpes zoster is an expected event after treatment with Cladribine Tablets, Adj-E per 100PY was < 0.10 therefore data not shown in table; ‡Including cysts and polyps.
Adj-AE per 100PY, adjusted adverse events incidences per 100 patient-years; **PY**, patient-years; **TEAE**, treatment emergent adverse events.

RESULTS

Clinical 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**).
- Cumulative to 2017, there were 3.88 and 3.24 AEs per 100PY in the Cladribine Tablets 3.5 mg/kg and placebo groups, respectively.
  - There were 130/923 patients with serious TEAEs in the Cladribine Tablets 3.5 mg/kg group and 68/641 patients with serious TEAEs in the placebo group.
- Adj-AE per 100PY for serious lymphopenia (preferred term) was 0.11 in the Cladribine Tablets 3.5 mg/kg group (**Table 2**):
  - Lymphopenia is expected due to the mechanism of action of Cladribine Tablets.
  - No serious lymphopenia events were observed in the placebo group.
- Adj-AE per 100PY for serious infection and infestations (system organ class) was 0.63 in the Cladribine Tablets 3.5 mg/kg group and 0.44 in the placebo group (**Table 2**).
- For serious herpes zoster (preferred term), an expected event after treatment with Cladribine Tablets, Adj-AE per 100PY in the Cladribine Tablets 3.5 mg/kg group was 0.05.
  - No serious herpes zoster events were observed in the placebo group.
- Adj-AE per 100PY for serious neoplasms, benign, malignant and unspecified (system organ class) was 0.65 in the Cladribine Tablets 3.5 mg/kg group and 0.35 in the placebo group.

Post-approval data

- A total of 47 serious ADRs were identified from post-approval sources.
  - None of the serious ADRs identified during the reporting period represented a new safety signal.
  - The observed pattern of serious ADRs was consistent with the clinical safety profile for Cladribine Tablets 3.5 mg/kg.

CONCLUSIONS

- **This integrated analysis confirms the low level of serious TEAEs associated with Cladribine Tablets 3.5 mg/kg in patients with early and active RMS.**
- **The safety profile was generally consistent with the previously-published integrated safety analysis profile for Cladribine Tablets 3.5 mg/kg.**
- **No new major safety findings were identified in this latest integrated safety dataset.**
- **Similarly, no new safety signals were identified in the post-approval data. However, with Cladribine Tablets 3.5 mg/kg having only recently been approved, it must be noted that this represents a smaller number of PY compared with the clinical trial follow up.**
- **The benefit-risk balance of Cladribine Tablets for the treatment of highly active RMS is considered positive.**

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DISCLOSURES

SC has received honoraria for lectures/consultations from Merck, Bayer HealthCare, Sanofi-Aventis, Neurology Reviews, Biogen Idec, Teva Pharmaceuticals, 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. **GG** has received speaker honoraria and consulting fees from Abbvie, Actelion, Atara Bio, Almirall, Bayer Schering Pharma, Biogen Idec, FivePrime, GlaxoSmithKline, GW Pharma, Merck, Pfizer Inc, Protein Discovery Laboratories, Teva Pharmaceutical Industries Ltd, Sanofi-Genzyme, UCB, Vertex Pharmaceuticals, Ironwood, and Novartis; and has received research support unrelated to this study from Biogen Idec, Merck, Novartis, and Ironwood. **TL** has received consultancy fees or clinical research grants from Acorda, Bayer, Biogen, Daiichi, EMD Serono, Novartis, ONO, Pfizer, Teva Neuroscience. **SS** and **DD** are employees of EMD Serono Research & Development Institute Inc., Billerica, USA, a business of Merck KGaA, Darmstadt, Germany. **AN** and **RS** are employees of Merck KGaA, Darmstadt, Germany.

The CLARITY study, NCT00213135; The CLARITY Extension study, NCT00641537; The ORACLE-MS study, NCT00725985; The PREMIERE registry, NCT01013350.

Cladribine Tablets are approved by the European Commission for the treatment of adult patients with highly active relapsing multiple sclerosis (MS) as defined by clinical or imaging features.

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