Updated Post-Approval Safety of Cladribine Tablets in the Treatment of Multiple Sclerosis, with Particular Reference to Respiratory Viral Infections

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ACTRIMS-ECTRIMS 2020 Virtual Congress | 11 – 13 September

Disclosures

This study was sponsored by Merck KGaA, Darmstadt, Germany.

- **GG** has received speaker honoraria and consulting fees from AbbVie, Actelion, Atara Bio, Almirall, Bayer Schering Pharma, Biogen, Celgene, FivePrime, GlaxoSmithKline, GW Pharma, Ironwood, Merck & Co., Merck KGaA (Darmstadt, Germany), Novartis, Pfizer Inc., Protein Discovery Laboratories, Roche, Sanofi-Genzyme, Teva Pharmaceutical Industries Ltd, UCB, and Vertex Pharmaceuticals; and has received research support unrelated to this study from Biogen, Ironwood, Merck & Co., Novartis, and Takeda.
- **JB** has received honoraria as a Scientific Advisory Board member for Inhibikase and Novartis; has received consultancy fees from Amgen, Celgene, Dr. Reddy's Laboratories, EMD Serono, Encycle, Excision Bio, Genzyme, Merck KGaA (Darmstadt, Germany), MAPI, Millennium/Takeda, Morphic, and Shire; and has received honoraria and institutional grants for consultancy from Biogen and Roche/Genentech.
- **TL** has received consultancy fees or clinical research grants from Alkermes, Biogen, Chugai, Genentech, Merck KGaA (Darmstadt, Germany), and Novartis.
- **DJ** and **AN** are employees of Merck KGaA, Darmstadt, Germany.
- **AG** is an employee of Merck, Aubonne, Switzerland, a division of Merck KGaA, Darmstadt, Germany.
- **DD** is an employee of EMD Serono Research & Development Institute, Inc., Billerica, MA, USA, a business of Merck KGaA, Darmstadt, Germany.

Medical writing assistance was provided by Steve Winter of inScience Communications, Springer Healthcare Ltd, UK, and was funded by Merck KGaA, Darmstadt, Germany.

The CLARITY study: NCT00213135; the CLARITY Extension study: NCT00641537; the ORACLE study: NCT00725985; the PREMIERE registry: NCT01013350

INTRODUCTION

- The safety of treatment with cladribine tablets was assessed in the clinical trial program, including the CLARITY,[1] CLARITY Extension,[2] and ORACLE-MS[3] studies.
- Integrated safety data for cladribine tablets, including findings for the PREMIERE registry, 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) in many countries around the world.[6]
  - In light of the COVID-19 pandemic, we present more detail on respiratory viral infections in the clinical trial program and post-approval setting.

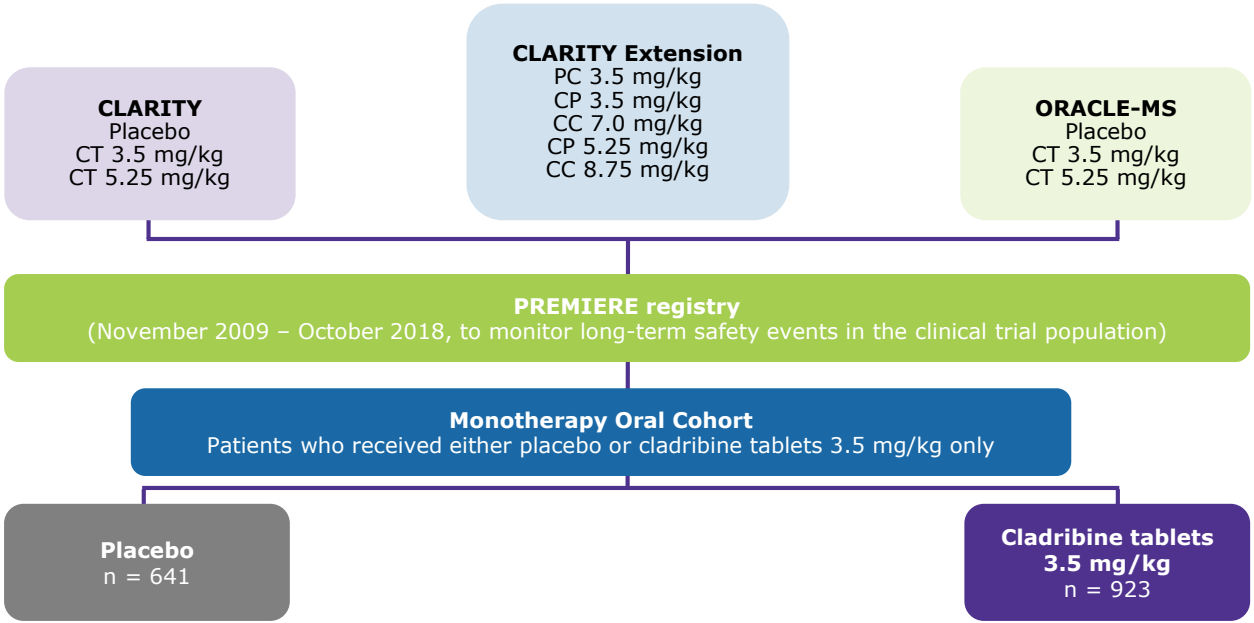
1. Giovannoni G, et al. *N Engl J Med*. 2010;362:416–426. 2. Giovannoni G, et al. *Mult Scler*. 2018;24:1594–1604. 3. Leist T, et al. *Lancet Neurol*. 2014;13:257–267. 4. Cook S, et al. *Mult Scler Relat Disord*. 2019;29:157–167. 5. Cook S, et al. *Mult Scler*. 2018;24(S2):465–466; 6. Periodic Benefit-Risk Evaluation Report (PBRER 6) (data on file, Merck KGaA, Darmstadt, Germany).

OBJECTIVES

To report post-approval safety data from worldwide sources, cumulative to July 2020, and to analyze rates of respiratory viral infections (including COVID-19) in patients treated with cladribine tablets.

METHODS

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



CP 3.5 mg/kg, cladribine tablets 3.5 mg/kg in CLARITY followed by placebo in CLARITY Extension; **CP 5.25 mg/kg**, cladribine tablets 5.25 mg/kg in CLARITY followed by placebo in CLARITY Extension; **CC 7.0 mg/kg**, cladribine tablets 3.5 mg/kg in CLARITY followed by cladribine tablets 3.5 mg/kg in CLARITY Extension; **CC 8.75 mg/kg**, cladribine tablets 5.25 mg/kg in CLARITY followed by cladribine tablets 3.5 mg/kg in CLARITY Extension; **PC 3.5 mg/kg**, placebo in CLARITY followed by cladribine 3.5 mg/kg in CLARITY Extension

METHODS

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

Monotherapy Oral Cohort Data

- The Monotherapy Oral Cohort comprised patients from the CLARITY, CLARITY Extension, and ORACLE-MS trials, and the PREMIERE registry.
  - 923 patients received cladribine tablets 3.5 mg/kg.
  - 641 patients received placebo.

Post-approval Data

- Adverse event reports (serious and non-serious) from post-approval worldwide sources are presented, cumulative to July 2020.

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RESULTS

Baseline Characteristics of the Monotherapy Oral Cohort from the Clinical Program

	Placebo (n = 641)	Cladribine tablets 3.5 mg/kg (n = 923)
Patient-years	2422	3937
Mean time on study, years (SD)	3.78 (2.66)	4.27 (2.53)
Time on study, ≥96–480 weeks [~2–9 years], n (%)	493 (76.9)	784 (84.9)
Time on study, ≥192–480 weeks [~4–9 years], n (%)	204 (31.8)	431 (46.7)
Median age, years[a] (range)	36.5 (18.1, 64.2)	37.6 (18.2, 66.1)
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)

[a] As reported at first dosing date.
DMD, disease-modifying drug; **SD**, standard deviation

RESULTS

Adverse Events of Special Interest in the Clinical Program and Post-approval

	Monotherapy Oral Cohort cladribine tablets 3.5 mg/kg (n = 923)		Post-approval Cohort cladribine tablets 3.5 mg/kg (n = 18,463)	
	n	AE rate (crude incidence, %)	n	AE rate (crude incidence, %)
Severe lymphopenia	24	2.60	39	0.21
Herpes zoster	28	3.03	197	1.07
Tuberculosis	2[b]	0.22	10	0.05
Severe infection	29	3.14	227	1.23
PML	0	0	0	0
Opportunistic infection[a]	10	1.08	7	0.04
Malignancy	10	1.08	42	0.23
Congenital anomaly	0[c]	0	0[d]	0

Post-approval Cohort comprises the first 18,463 patients treated with cladribine tablets using post-approval sources from August 2017 to July 2020; [a] Majority of opportunistic infections were superficial dermal and mucosal fungal infections that resolved on standard treatments. Opportunistic infections that could be life-threatening were not observed; [b] Both cases of tuberculosis were serious (one coded as tuberculosis, one coded as pulmonary tuberculosis);[c] No cases of congenital anomaly occurred in pregnancies during cladribine treatment or within 6 months after the last dose; [d] 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.

AE, adverse event; **n**, number of events; **PML**, progressive multifocal leukoencephalopathy

RESULTS

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Post-approval Data

- A total of 3357 AEs were reported in the first 18,463 patients who received cladribine tablets post-approval.
- In total, 435 (13%) of the 3357 AEs were classified as serious.
- The pattern of AEs of special interest was largely consistent with the clinical safety profile for cladribine tablets.

AE, adverse event; **n**, number of events; **PML**, progressive multifocal leukoencephalopathy

RESULTS

Respiratory Viral Infections in the Clinical Program and Post-approval

	Monotherapy Oral Cohort				Post-approval Cohort cladribine tablets 3.5 mg/kg (n = 18,463)	
	Placebo (n = 641)		Cladribine tablets 3.5 mg/kg (n = 923)			
	n	AE rate (crude incidence, %)	n	AE rate (crude incidence, %)	n	AE rate (crude incidence, %)
H1N1 influenza	0	0	1	0.11	2	0.01
Influenza	51	7.96	88	9.53	126	0.68
Laryngitis viral	0	0	1	0.11	0	0
Respiratory tract infection viral	13	2.03	26	2.82	1	0
Viral infection	12	1.87	13	1.41	49	0.27
Viral pharyngitis	1	0.16	1	0.11	0	0
Viral upper respiratory tract infection	96	14.98	158	17.12	7	0.04

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Respiratory Viral Infections in the Clinical Program and Post-approval

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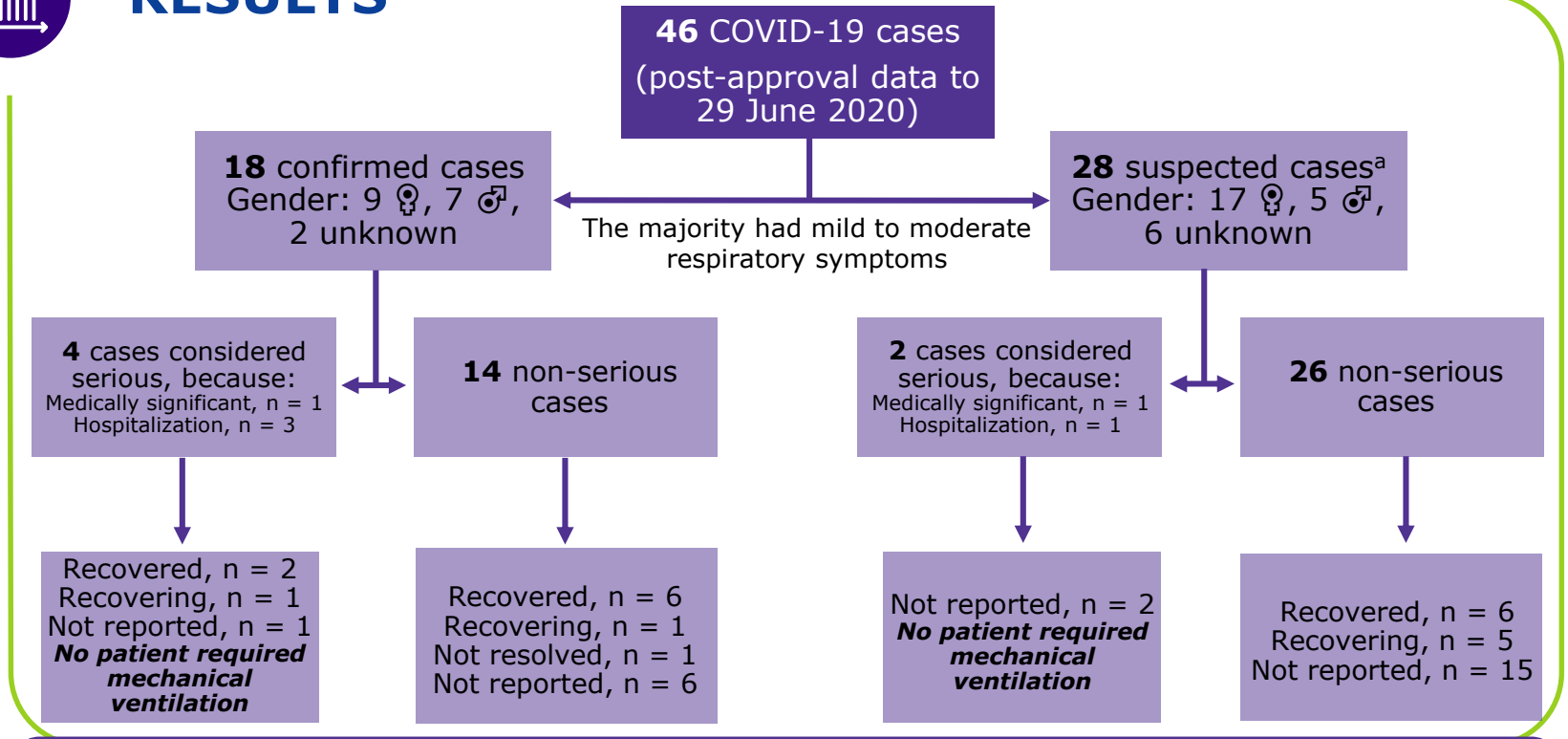
- Respiratory viral infections were seen at similar rates in patients treated with cladribine tablets compared with placebo.
- The pattern of respiratory viral infections was also consistent in the real-world (post-approval) setting.

AE, adverse eve

RESULTS



- The time to onset of COVID-19 from last dose of cladribine tablets was available for 21/46 patients; median of 180 days (i.e. approximately 6 months after the last dose).

CONCLUSIONS

The pattern of AEs of special interest in the real-world (post-approval) safety data, cumulative to July 2020, was largely consistent with the clinical safety profile for cladribine tablets.

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

Regarding COVID-19, the majority of patients had mild to moderate respiratory symptoms; none received mechanical ventilation and there were no deaths.