Treatment-emergent Adverse Events Occurring Early in the Treatment Course of Cladribine Tablets in Two Phase 3 Trials in Multiple Sclerosis

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SUMMARY

The objective of this *post hoc* analysis was to identify TEAEs early in the course of treatment with cladribine tablets 3.5 mg/kg among patients enrolled in the Phase 3 CLARITY and ORACLE-MS studies

By Week 12, more patients receiving cladribine tablets experienced a drug-related TEAE compared to placebo: cladribine tablets 34.7% vs. placebo 23.2%

By Week 12, a similar proportion of patients experienced a TEAE across treatment groups: cladribine tablets 61.3% vs. placebo 55.2%, with low incidences of serious TEAEs

Cladribine tablets 3.5 mg/kg were well-tolerated during the first 12 weeks as evidenced by a low incidence of TEAEs leading to treatment discontinuation

Abbreviations: AE, adverse event; DMD, disease-modifying drugs; MS, multiple sclerosis; RMS, relapsing forms of MS; TEAE, treatment emergent adverse events

References: 1. Mavenclad [package insert]. Rockland MES, Inc.; 2019. **2.** Giovannoni G, et al. *N Engl J Med*. 2010;362:416–26. **3.** Leist T, et al. *Lancet Neurol*. 2014;13:257–67. **4.** Higuera L et al. *J Manag Care Spec Pharm*. 2016;22(12):1394-1401.

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BACKGROUND INFORMATION

- Early intervention with DMDs has been shown to improve outcomes for people with MS
- Cladribine tablets 10 mg (3.5 mg/kg cumulative dose over 2 years) are approved in >75 countries worldwide for various indications related to RMS
  - Patients receive cladribine tablets over 2 treatment weeks (4–5 consecutive treatment days per week) per treatment year[1]
- The safety profile of cladribine tablets were reported in the 96-week, Phase 3, placebo-controlled CLARITY and ORACLE-MS studies of patients with relapsing-remitting MS and a first clinical demyelinating event, respectively[2,3]
  - The most frequent TEAEs reported in ≥10% of patients were headache, nasopharyngitis, lymphopenia, nausea, and upper respiratory tract infection
  - Overall frequency of treatment discontinuation due to TEAEs was low and similar between cladribine tablets 3.5 mg/kg and placebo (CLARITY: 3.5% vs. 2.1%; ORACLE-MS: 5% vs. 2%, respectively)
- Tolerability and adherence to DMDs can be influenced by TEAEs, some of which may start shortly after treatment initiation[4]
  - It is not yet known if any tolerability challenges occur early in patients receiving cladribine tablets for MS and thus may pose adherence issues during the first treatment year

Abbreviations: AE, adverse event; DMD, disease-modifying drugs; MS, multiple sclerosis; RMS, relapsing forms of MS; TEAE, treatment emergent adverse events

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OBJECTIVE

To identify TEAEs that begin early in the course of treatment with cladribine tablets 3.5 mg/kg in patients enrolled in the Phase 3 CLARITY and ORACLE-MS clinical trials

METHODS

- This was a *post hoc* analysis of the combined safety populations in CLARITY and ORACLE-MS studies[2,3]
  - **CLARITY**: N=430 cladribine tablets 3.5 mg/kg; N=435 placebo[2]
  - **ORACLE-MS**: N=206 cladribine tablets 3.5 mg/kg; N=206 placebo[3]
- The incidence of early TEAEs, serious TEAEs, drug-related TEAEs, and TEAEs leading to discontinuation were summarized based on incidence within 2, 6, and 12 weeks after commencement of therapy
  - The 12-week time epoch encompasses the full cladribine tablets dosing period in the first treatment year. The TEAE evaluation time points at Week 2 and 6 correspond to the completion of active treatment in Weeks 1 and 5, respectively
  - All AEs were coded according to the MedDRA dictionary Version 11.0 as per the CLARITY and ORACLE-MS study protocols
  - TEAE evaluation time points show the cumulative TEAEs at each time point
  - All analyses were performed using SAS® software version 9.4 or higher

Abbreviations: AE, adverse event; DMD, disease-modifying drugs; MS, multiple sclerosis; RMS, relapsing forms of MS; TEAE, treatment emergent adverse events

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RESULTS

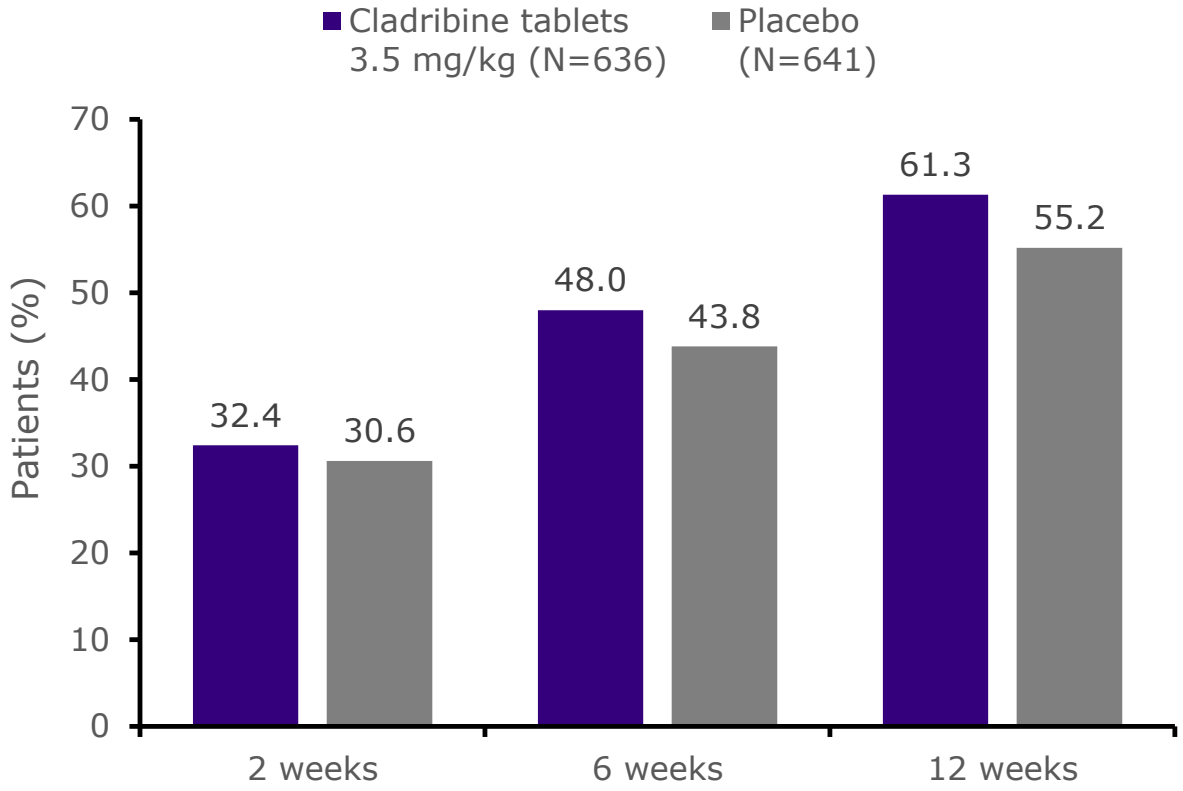
Patient disposition

- >85% of patients across treatment groups remained on study for ≥12 weeks:
  - **CLARITY** (cladribine tablets 3.5 mg/kg: 425 [98.8%]; placebo: 428 [98.4%])
  - **ORACLE-MS** (cladribine tablets 3.5 mg/kg: 191 [92.7%]; placebo: 177 [85.9%])

Severity of TEAEs

- TEAEs reported in the combined CLARITY and ORACLE-MS safety populations (cladribine tablets: N=636; placebo: N=641) were mostly mild in severity:
  - First 2 weeks (68.0% vs. 68.4%), 6 weeks (58.4% vs. 61.2%), and 12 weeks (54.4% vs. 53.8%) of all TEAEs were mild for cladribine tablets vs. placebo, respectively

Incidence of TEAEs in the first 2[a], 6[b] or 12 weeks after commencement of cladribine tablets 3.5 mg/kg



[a]One week after completing the first treatment week of cladribine tablets. [b]One week after completing the second and final treatment week of cladribine tablets in the first treatment year

Abbreviations: AE, adverse event; DMD, disease-modifying drugs; MS, multiple sclerosis; RMS, relapsing forms of MS; TEAE, treatment emergent adverse events

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RESULTS

TEAEs were similar within the first 12 weeks in cladribine tablets- vs. placebo-treated patients

Most common TEAEs, n (%)	Cladribine tablets 3.5 mg/kg (N=636)	Placebo (N=641)
First 2 weeks: Patients with any TEAE*	**206 (32.4)**	**196 (30.6)**
Headache	57 (9.0)	53 (8.3)
Nausea	31 (4.9)	21 (3.3)
First 6 weeks: Patients with any TEAE*	**305 (48.0)**	**281 (43.8)**
Headache	94 (14.8)	76 (11.9)
Nausea	41 (6.4)	24 (3.7)
Nasopharyngitis	21 (3.3)	22 (3.4)
Diarrhea	19 (3.0)	19 (3.0)
Influenza-like illness	18 (2.8)	7 (1.1)
Fatigue	16 (2.5)	20 (3.1)

Most common TEAEs, n (%)	Cladribine tablets 3.5 mg/kg (N=636)	Placebo (N=641)
First 12 weeks: Patients with any TEAE*	**390 (61.3)**	**354 (55.2)**
Headache	117 (18.4)	97 (15.1)
Nausea	51 (8.0)	29 (4.5)
Lymphopenia	43 (6.8)	3 (0.5)
Nasopharyngitis	35 (5.5)	41 (6.4)
Upper respiratory tract infection	29 (4.6)	27 (4.2)
Diarrhea	26 (4.1)	24 (3.7)
Abdominal pain upper	21 (3.3)	11 (1.7)
Influenza-like illness	21 (3.3)	14 (2.2)
Fatigue	20 (3.1)	28 (4.4)

Lymphopenia (all mild to moderate in severity) occurred more frequently with cladribine tablets (0.3%, 2.5%, and 6.8% of patients) vs. placebo (0%, 0%, and 0.5% of patients), at Weeks 2, 6, and 12, respectively

*Reported in ≥3% of patients in any treatment group; TEAEs pertain to first treatment year only; ordered by most common in cladribine tablets 3.5 mg/kg group; combined CLARITY and ORACLE-MS

Abbreviations: AE, adverse event; DMD, disease-modifying drugs; MS, multiple sclerosis; RMS, relapsing forms of MS; TEAE, treatment emergent adverse events

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RESULTS

Incidence of drug-related TEAEs with cladribine tablets was low and were mostly mild in severity

- In the first 12 weeks, more patients receiving cladribine tablets had drug-related TEAEs compared to placebo (cladribine tablets: 34.7% vs. placebo: 23.2%)
  - However, most drug-related TEAEs were mild in severity (cladribine tablets: 54.8% vs. placebo: 59.1%)
- In the first 12 weeks, lymphopenia occurred more frequently with cladribine tablets compared to placebo (cladribine tablets: 6.8% vs. placebo: 0.5%)
  - All cases of lymphopenia were mild to moderate in severity

Most common drug-related TEAEs, n (%)	Cladribine tablets 3.5 mg/kg (N=636)	Placebo (N=641)
First 2 weeks: Patients with any drug-related TEAE*	**100 (15.7)**	**78 (12.1)**
Nausea	26 (4.1)	14 (2.2)
Headache	25 (3.9)	16 (2.5)
First 6 weeks: Patients with any drug-related TEAE*	**169 (26.6)**	**109 (17.0)**
Headache	39 (6.1)	22 (3.4)
Nausea	32 (5.0)	15 (2.3)
First 12 weeks: Patients with any drug-related TEAE*	**221 (34.7)**	**149 (23.2)**
Headache	46 (7.2)	32 (5.0)
Lymphopenia	43 (6.8)	3 (0.5)
Nausea	38 (6.0)	18 (2.8)

*Reported in ≥3% of patients in any treatment group; TEAEs pertain to first treatment year only; ordered by most common in cladribine tablets 3.5 mg/kg group; combined CLARITY and ORACLE-MS

Abbreviations: AE, adverse event; DMD, disease-modifying drugs; MS, multiple sclerosis; RMS, relapsing forms of MS; TEAE, treatment emergent adverse events

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RESULTS

Incidence of serious TEAEs and TEAEs leading to discontinuation with cladribine tablets was low

Serious TEAEs

- Incidence of serious TEAEs was low and similar across treatment groups (≤2.2%) within the first 12 weeks and the reported events were unique to each treatment group

TEAEs leading to discontinuation

- The proportion of patients experiencing TEAEs leading to discontinuation was low during the first 12 weeks and similar between groups (<2% in both groups)
  - Lymphopenia was the most common TEAE leading to treatment discontinuation with cladribine tablets and was reported in 3 (0.5%) patients

n (%)	Cladribine tablets 3.5 mg/kg (N=636)	Placebo (N=641)
Any serious TEAE* (up to 12 weeks of study)		
Occurring in the first 2 weeks	2 (0.3)	2 (0.3)
Occurring in the first 6 weeks	7 (1.1)	7 (1.1)
Occurring in the first 12 weeks	14 (2.2)	11 (1.7)
Any TEAE leading to discontinuation* (up to 12 weeks of study)		
Occurring in the first 2 weeks	2 (0.3)	3 (0.5)
Occurring in the first 6 weeks	6 (0.9)	5 (0.8)
Occurring in the first 12 weeks	10 (1.6)	8 (1.2)

*TEAEs pertain to first treatment year only; combined CLARITY and ORACLE-MS

Abbreviations: AE, adverse event; DMD, disease-modifying drugs; MS, multiple sclerosis; RMS, relapsing forms of MS; TEAE, treatment emergent adverse events

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CONCLUSIONS

- **Cladribine tablets 3.5 mg/kg were well tolerated during the first 12 weeks after treatment initiation, as evidenced by a low incidence of TEAEs leading to treatment discontinuation**
- **In the first 12 weeks, a similar proportion of patients experienced a TEAE across treatment groups, most of which were mild in intensity**
- **In the first 12 weeks, the incidence of drug-related TEAEs with cladribine tablets 3.5 mg/kg was low and were mostly mild in severity**
  - **Lymphopenia was seen more frequently in cladribine tablets-treated patients**
- **Incidence of serious TEAEs was low and similar across treatment groups (≤2.2%) within the first 12 weeks**
- **The low incidence of TEAEs and drug-related TEAEs in the first 12 weeks of treatment initiation may improve adherence and support the use of cladribine tablets 3.5 mg/kg in people with MS**

Abbreviations: AE, adverse event; DMD, disease-modifying drugs; MS, multiple sclerosis; RMS, relapsing forms of MS; TEAE, treatment emergent adverse events

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