Poster No. DX34

Cladribine tablets in the ORACLE-MS study open-label maintenance period: analysis of efficacy in patients after conversion to clinically definite multiple sclerosis (CDMS)

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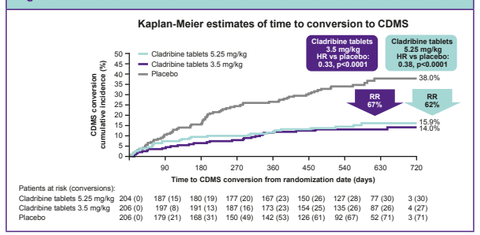
INTRODUCTION

- The ORACLE-MS study was designed to investigate the effect of cladribine tablets 3.5 mg/kg of bodyweight or 5.25 mg/kg on conversion to clinically definite multiple sclerosis according to Poser criteria (CDMS) in patients with a first clinical demyelinating event (FCDE).[1]
- Cladribine tablets were found to significantly reduce the risk of conversion to CDMS in the double-blind treatment period (**Figure 1**).[1]

Figure 1. Cladribine tablets reduced risk of conversion to CDMS in ORACLE-MS



CDMS, clinically definite MS according to Poser criteria; **HR**, hazard ratio; **RR**, risk ratio

- Patients who did convert to CDMS were entered into an open-label maintenance period and treated with subcutaneous (sc) interferon (IFN) β-1a 44 µg, three times per week (tiw).

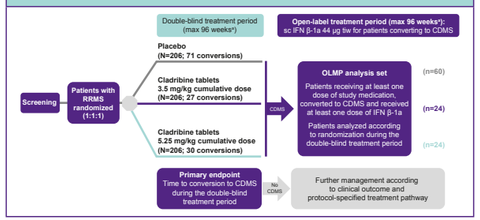
OBJECTIVE

- To assess relapse rate and magnetic resonance imaging (MRI) activity during the open-label maintenance period of ORACLE-MS.

METHODS

- In ORACLE-MS, patients aged 18 to 55 years, with a first event within 75 days of screening, at least 2 clinically silent T2 lesions on MRI, and Expanded Disability Status Scale of ⩽5 were randomized to cladribine tablets at cumulative doses of 5.25 mg/kg or 3.5 mg/kg or to placebo.
- The primary endpoint was time to conversion to CDMS according to the Poser criteria.
- In the event of conversion to CDMS, patients were entered into the open-label maintenance and treated with sc IFN β-1a 44 µg tiw (**Figure 2**).
- The time in the double-blind and open-label periods varied by patient and depended on the time to conversion to CDMS.
- Analysis of relapse rates and MRI activity was performed according the treatment group that patients were randomized to in the double-blind treatment period.
- Efficacy objectives reported are exploratory and all determinations of significance are nominal.

Figure 2. The ORACLE-MS study



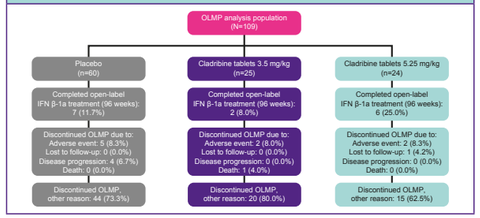
[a]Time in the double-blind treatment and open-label treatment periods was variable and depends on the time to CDMS conversion for each patient.
CDMS, clinically definite MS according to Poser criteria; **FCDE**, first clinical demyelinating event; **IFN**, interferon; **OLMP**, open-label maintenance period; **RRMS**, relapsing–remitting multiple sclerosis; **sc**, subcutaneous; **tiw**, three times per week.

RESULTS

Patients

- The open-label maintenance period analysis set includes 109 patients in ORACLE-MS who converted to CDMS in the double-blind treatment period and received at least one dose of sc IFN β-1a (**Figure 3**).

Figure 3. Patient disposition in the open-label period



The most frequent other reason was "Sponsor decision to terminate the study".
IFN, interferon; **OLMP**, open-label maintenance period

- Demographics and disease characteristics of patients converting to CDMS and entering the open-label period are shown in **Table 1**. Patient characteristics were similar to the intent-to-treat population at the study baseline (data not shown).

Table 1. Demographics and disease characteristics of patients at baseline of the open-label period

	Randomization group during double-blind treatment period			
	Placebo (n=60)	Cladribine tablets 3.5 mg/kg (n=25)	Cladribine tablets 3.5 mg/kg (n=24)	All patients (N=109)
Time from FCDE to randomization, mean (SD), days	80.9 (18.5)	74.3 (16.7)	79.7 (17.2)	79.1 (17.9)
Age at study entry, mean (SD), years	31.2 (7.3)	33.3 (9.8)	28.5 (7.8)	31.1 (8.2)
Female, n (%)	39 (65.0)	17 (68.0)	14 (58.3)	70 (64.2)
White, n (%)	58 (96.7)	22 (88.0)	22 (91.7)	102 (93.6)
Number of T1 Gd+ lesions, mean (SD)	1.4 (2.8)	0.9 (1.8)	1.4 (5.5)	1.3 (3.4)
Patients with T1 Gd+ lesions, n (%)	23 (38.3)	8 (32.0)	4 (16.7)	35 (32.1)

FCDE, first clinical demyelinating event; **Gd+**, gadolinium-enhancing; **SD**, standard deviation.

Time in the open-label period

- Patients who received placebo during the double-blind period had a longer median time in the open-label period than patients treated with either dose of cladribine tablets (**Table 2**).

Table 2. Open-label sc IFN β-1a: time in study and on treatment

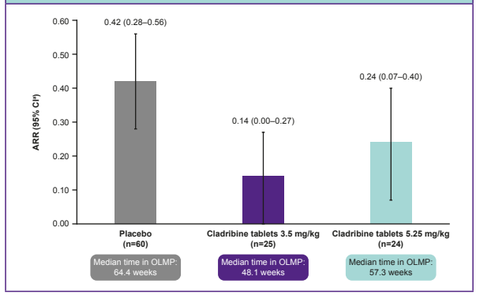
	Randomization group during double-blind treatment period			
	Placebo (n=60)	Cladribine tablets 3.5 mg/kg (n=25)	Cladribine tablets 3.5 mg/kg (n=24)	All patients (N=109)
Time in OLMP, weeks				
Mean (SD)	61.8 (28.5)	52.3 (27.5)	66.9 (24.6)	60.7 (27.7)
Median	64.4	48.1	57.3	58.3
Min; max	3.9; 102.1	1.0; 103.0	17.1; 112.1	1.0; 112.1
Time on open-label IFN β-1a treatment, weeks				
Mean (SD)	57.9 (28.0)	48.2 (26.0)	60.2 (29.0)	56.2 (27.9)
Median	57.4	44.1	56.9	56.0
Min; max	0.1; 102.0	0.4; 98.6	10.0; 97.3	0.1; 102

IFN, interferon; **OLMP**, open-label maintenance period; **sc**, subcutaneous; **SD**, standard deviation.

ARR and number of relapses

- Estimated annualized relapse rates (ARRs) in the open-label period were 0.14 for patients originally treated with cladribine tablets 3.5 mg/kg, 0.24 for patients originally treated with cladribine tablets 5.25 mg/kg, and 0.42 for patients who originally received placebo.
  - The 95% confidence intervals do not overlap for placebo and cladribine tablets 3.5 mg/kg, indicating a difference in the respective ARRs (**Figure 4**).

Figure 4. ARR by treatment group during the open-label period



Data for ARR are normalized to account for differences in time in the open-label period.
*The figure presents point estimates and associated 95% CIs.
ARR, annualized relapse rate; **CI**, confidence interval; **OLMP**, open-label maintenance period.

- The majority of subjects in each treatment group had no relapses during the open-label period.
  - The mean number of relapses among patients originally treated with cladribine tablets in the double-blind treatment period was lower when compared with patients treated with placebo in the double-blind treatment period (**Table 3**).

Table 3. Number of relapses during the open-label period

	Randomization group during double-blind treatment period			
	Placebo (n=60)	Cladribine tablets 3.5 mg/kg (n=25)	Cladribine tablets 3.5 mg/kg (n=24)	All patients (N=109)
Number of relapses, mean (SD)	0.55 (1.00)	0.16 (0.37)	0.33 (0.64)	0.41 (0.83)
Number of relapses, n (%)				
0	42 (70.0)	21 (84.0)	18 (75.0)	81 (74.3)
1	9 (15.0)	4 (16.0)	4 (16.7)	17 (15.6)
2	4 (6.7)	0	2 (8.3)	6 (5.5)
3	4 (6.7)	0	0	4 (3.7)
4	1 (1.7)	0	0	1 (0.9)

Data are not normalized to account for differences in time in the open-label period.
SD, standard deviation.

Mean numbers of new or persisting T1 Gd+ lesions

- There was a consistent decrease in the mean number of new or persisting T1 gadolinium-enhancing (Gd+) lesions in all treatment groups as patients were treated with sc IFN β-1a during the open-label period.
- The mean number of new or persisting T1 Gd+ lesions at baseline of the open-label period was lower in patients originally treated with cladribine tablets 3.5 mg/kg than either of the other two groups (**Table 4**).
  - MRI scans were scheduled at baseline of the open-label period and Weeks 24, 48, 72, and 96 (end of treatment) for all patients
  - Median time in the open-label period for all patients was 58.3 weeks; after Week 48 a limited number of patients had scans available (data not shown).

Table 4. New or persisting T1 Gd+ lesions

	Randomization group during double-blind treatment period			
	Placebo (n=60)	Cladribine tablets 3.5 mg/kg (n=25)	Cladribine tablets 3.5 mg/kg (n=24)	All patients (N=109)
OLMP baseline				
N (missing)	59 (1)	24 (1)	24 (0)	107 (2)
Mean (SD)	1.3 (2.6)	0.9 (1.8)	1.4 (5.5)	1.2 (3.3)
OLMP Week 24				
N (missing)	57 (3)	22 (3)	24 (0)	103 (6)
Mean (SD)	0.1 (0.6)	0.1 (0.2)	0.2 (0.5)	0.1 (0.5)
OLMP Week 48				
N (missing)	46 (14)	15 (10)	19 (5)	80 (29)
Mean (SD)	0.2 (0.5)	0.0 (0.0)	0.1 (0.2)	0.1 (0.4)

Gd+, gadolinium-enhancing; **OLMP**, open-label maintenance period; **SD**, standard deviation

Safety and discontinuations due to adverse events

- During open-label treatment with IFN β-1a, lymphopenia was reported as an adverse event (AE) in:
  - 2/24 (8.3%) patients previously exposed to cladribine tablets 5.25 mg/kg
  - 1/25 (4.0%) patients previously exposed to cladribine tablets 3.5 mg/kg
  - 2/60 (3.3%) patients previously exposed to placebo.
- Overall, rates of discontinuations due to AEs were low across all groups during the open-label period (**Table 5**).
- One patient who had originally received cladribine tablets 3.5 mg/kg died of cardio-respiratory arrest 4 days after initiating IFN β-1a treatment in the open-label period. This was judged to be unrelated to study medication.

Table 5. Discontinuations due to AEs

	Randomization group during double-blind treatment period			
	Placebo (n=60)	Cladribine tablets 3.5 mg/kg (n=25)	Cladribine tablets 3.5 mg/kg (n=24)	All patients (N=109)
Patients with any AE leading to discontinuation of open-label IFN β-1a				
Patients with any AE leading to discontinuation, n (%)	4 (6.7)	2 (8.0)	2 (8.3)	8 (7.3)
Influenza-like illness	1 (1.7)	1 (4.0)	0	2 (1.8)
Injection site reaction	0	0	1 (4.2)	1 (0.9)
Blood amylase increased	0	0	1 (4.2)	1 (0.9)
Neutralizing antibodies	1 (1.7)	0	0	1 (0.9)
Transaminases increased	0	0	1 (4.2)	1 (0.9)
Headache	0	1 (4.0)	0	1 (0.9)
Pregnancy	2 (3.3)	0	0	2 (1.8)
Deaths during OLMP				
Death, n (%)	0	1 (4.0)	0	1 (0.9)

AE, adverse event; **IFN**, interferon; **OLMP**, open-label maintenance period.

CONCLUSIONS

- **In these exploratory analyses for the open-label maintenance period of ORACLE-MS, treatment effects of cladribine tablets were observed in patients who converted to CDMS and subsequently received sc IFN β-1a.**
- **The point estimate of ARR in the open-label period was lower in patients originally randomized to cladribine tablets 3.5 mg/kg, compared with placebo.**
- **There were no observed differences in MRI activity during the open-label period, presumably due to the established effect of sc IFN β-1a treatment.**
- **The incidence of lymphopenia during the open-label period following conversion to CDMS was low, even if sc IFN β-1a was administered within 10 months of the last dose of cladribine tablets.**

REFERENCES

1. Leist T, et al. *Lancet Neurol* 2014;13:257–67.

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DISCLOSURES

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Cladribine tablets is currently under clinical investigation and has not yet been approved by any regulatory authority.

Status: March 2017.

The ORACLE-MS study: NCT00725985.

*A business of Merck KGaA, Darmstadt, Germany.

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