Primary Results from 8–11 Years of Follow-up in the CLASSIC-MS Study Show Long-Term Efficacy for Patients Who Received Cladribine Tablets in ORACLE MS

Thomas Leist, Gavin Giovannoni, Aida Aydemir, Elisabetta Verdun Di Cantogno, on behalf of the CLASSIC-MS Steering Committee

ACKNOWLEDGMENTS
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DISCLOSURES
TL has received consultancy fees or clinical research grants from Acorda, Bayer, Biogen, Daiichi, EMD Serono, Novartis, ONO, Pfizer, and Teva Neuroscience.
GG has received speaker honoraria and consulting fees from AbbVie, Actelion (Janssen/J&J), Almirall, Atara Bio, Bayer, Biogen, Celgene (BMS), FivePrime, GlaxoSmithKline, GW Pharma, Ironwood, Merck & Co., Novartis, the healthcare business of Merck KGaA (Darmstadt, Germany), Pfizer Inc., Protein Discovery Laboratories, Roche, Sanofi, 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.
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[1]Division of Clinical Neuroimmunology, Jefferson University, Philadelphia, PA, USA; [2]Blizard Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, UK; [3]EMD Serono Research & Development Institute, Inc., Billerica, MA, USA

CONCLUSIONS

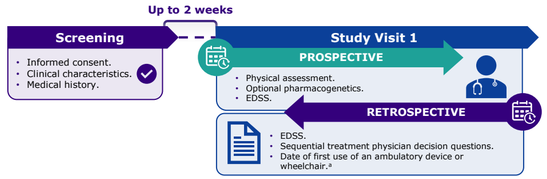
With a median of 9.5 years' follow-up since last dose, findings suggest that patients with a FCDE exposed to cladribine tablets experienced:

- **Delayed conversion to CDMS, with more patients remaining relapse-free than never exposed patients.**
- **Sustained efficacy (long-term mobility/disability).**

INTRODUCTION

- CLASSIC-MS (NCT03961204) was an exploratory, ambispective Phase IV study designed to evaluate the long-term efficacy of cladribine tablets in the real-world setting in patients who were previously enrolled in the Phase III (parent) trials CLARITY,[1] CLARITY Extension,[2] and ORACLE-MS.[3]

Figure 1. CLASSIC-MS Study Design



[a]Was determined through retrospective chart review and/or at Study Visit 1, e.g. if conversion or disability progression occurred between last regular clinical visit and Study Visit 1.
EDSS, Expanded Disability Status Scale

OBJECTIVE

To report on long-term efficacy findings for patients who participated in ORACLE MS, in terms of:

Conversion to clinically definite multiple sclerosis (CDMS) and relapse rates

Mobility
(no wheelchair use in the previous 3 months and not bedridden at any time prior to first visit in CLASSIC-MS; i.e. Expanded Disability Status Scale [EDSS] score <7)

Disability status
(no use of an ambulatory device at any time since last parent study dose [LPSD]; i.e. EDSS score <6)

METHODS

- CLASSIC-MS patients who participated in ORACLE MS,[3] having experienced a first clinical demyelinating event (FCDE), were evaluated.
- All patients must have received ≥1 course of cladribine tablets or placebo during the parent study, in which patients were assigned 1:1:1 to either cladribine tablets 3.5 mg/kg, cladribine tablets 5.25 mg/kg, or placebo.
- A total of 227 patients were included in the analysis, with 156 (68.7%) having been exposed to cladribine tablets during the ORACLE MS parent trial. The remaining 71 patients (31.3%) were never exposed to cladribine tablets.
- **Median time since LPSD** in this cohort of the CLASSIC-MS study was **9.5** (range 8.2, 11.2) **years**.
- Conversion to CDMS was determined according to the McDonald 2017 criteria.

RESULTS

Table 1. Patient Demographics and Disease Characteristics at Parent Study Baseline and Study Visit 1 of CLASSIC-MS

	Never exposed to cladribine tablets (N=71)	Exposed to cladribine tablets (N=156)	Total (N=227)
Age at Study Visit 1, years (mean ± SD)	42.9 ± 8.37	42.7 ± 8.26	42.7 ± 8.28
Female, n (%)	44 (62.0)	105 (67.3)	149 (65.6)
EDSS score at parent study baseline (mean ± SD)	1.61 ± 0.86	1.73 ± 0.82	1.69 ± 0.83
EDSS score at CLASSIC-MS baseline (mean ± SD)	2.40 ± 1.86	2.04 ± 1.54	2.15 ± 1.65
Time from CDMS conversion (years), mean ± SD	8.58 ± 2.41	7.43 ± 2.78	7.87 ± 2.69
Missing, n (%)	13 (18.3)	63 (40.4)	76 (33.5)
Employment status at Study Visit 1, n (%)			
Employed for wages	46 (64.8)	95 (60.9)	141 (62.1)
Self-employed	5 (7.0)	29 (18.6)	34 (15.0)
Homemaker	4 (5.6)	8 (5.1)	12 (5.3)
Not in active employment[a]	12 (16.9)	14 (9.0)	26 (11.5)
Unknown[b]	4 (5.6)	10 (6.4)	14 (6.2)

55 (77.5%) | 132 (84.6%)

[a]Not in active employment includes retired and out of work/unable to work. [b]Unknown includes those with missing/not reported data or information not collected at study site.
CDMS, clinically definitive multiple sclerosis; **EDSS**, Expanded Disability Status Scale

- Patient characteristics are shown in **Table 1**.
  - Of the patients exposed to cladribine tablets, 84.6% (n=132) were **actively employed** at inclusion in CLASSIC-MS compared with 77.5% (n=55) of the never exposed patients.

Conversion to CDMS and Proportion of Patients Relapse-Free

- The proportion of patients **converting to CDMS** was lower in the exposed cohort, and this cohort also showed a longer time to conversion (**Table 2**).

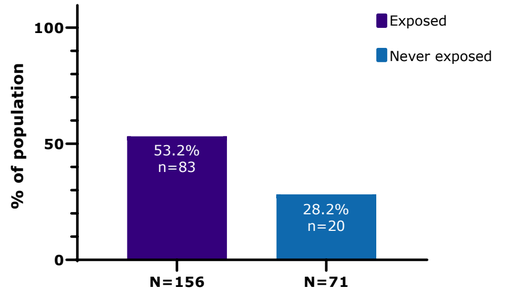
Table 2. Proportion of Patients Converting to CDMS and Time-to Conversion Since Dosing in ORACLE MS

		Never exposed to cladribine tablets (N=71)	Exposed to cladribine tablets (N=156)	Total (N=227)
Since **first** parent study dose	Patients who converted to CDMS[a], n (%)	55 (77.5)	78 (50.0)	133 (58.6)
	Median time to conversion to CDMS, years (min, max)	1.21 (0.0, 10.7)	3.36 (0.0, 11.1)	2.02 (0.0, 11.1)
Since **last** parent study dose	Patients who converted to CDMS[a], n (%)	50 (70.4)	67 (42.9)	117 (51.5)
	Median time to conversion to CDMS, years (min, max)	0.41 (0.0, 9.7)	2.81 (0.0, 9.1)	1.70 (0.0, 9.7)

[a]Conversion to CDMS status was derived using both parent study and CLASSIC-MS data.
CDMS, clinically definite multiple sclerosis.

- Over half of patients (53.2%) exposed to cladribine tablets were relapse-free since LPSD compared with 28.2% in the never exposed cohort (**Figure 2**).

Figure 2. Patients Relapse-free Since LPSD



Long-term Mobility and Disability Status

- For patients exposed to ≥1 dose of cladribine tablets in ORACLE MS (vs never exposed patients):
  - 98.7% vs 94.2% did not use a wheelchair in the previous 3 months and were not bedridden at any time prior to first visit in CLASSIC-MS (odds ratio* 0.40; 95% confidence interval: 0.070, 2.319; p = 0.3079; **Figure 3**).
  - 97.4% vs 94.4% did not use an ambulatory device at any time since LPSD (**Figure 4**).

*Adjusted odds ratio from a logistic regression model with fixed effects for treatment group and disease duration.

Figure 3. Long-term Mobility

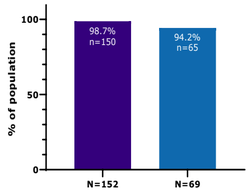
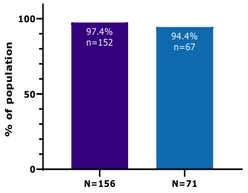


Figure 4. Long-term Disability Status



Missing data were not included in the analysis (n=4 and n=2 for exposed and never exposed cohorts, respectively).

REFERENCES
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.

Cladribine tablets 10 mg (3.5 mg/kg cumulative dose over 2 years) are indicated for the treatment of patients with MS in the United States (relapsing forms of MS, including relapsing-remitting disease and active secondary progressive disease, in adults). The CLASSIC-MS study: NCT03961204.

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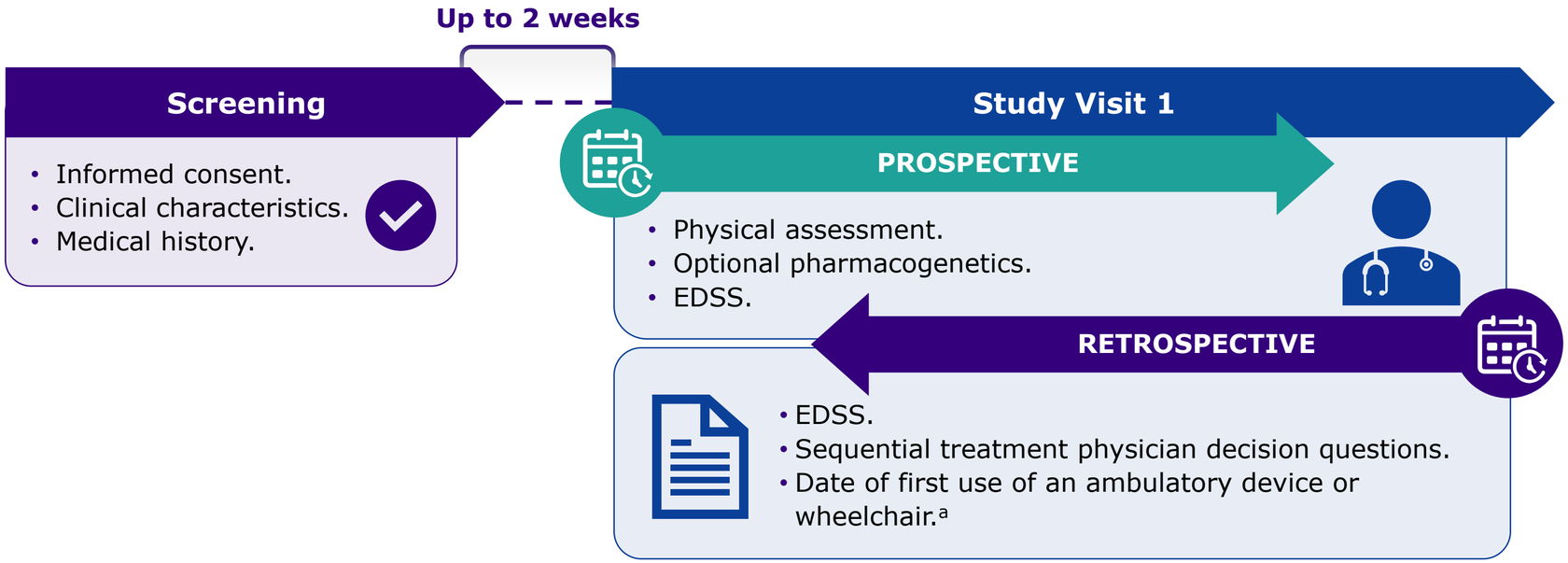

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CDMS, clinically definite multiple sclerosis; **EDSS**, Expanded Disability Status Scale; **FCDE**, first clinical demyelinating event

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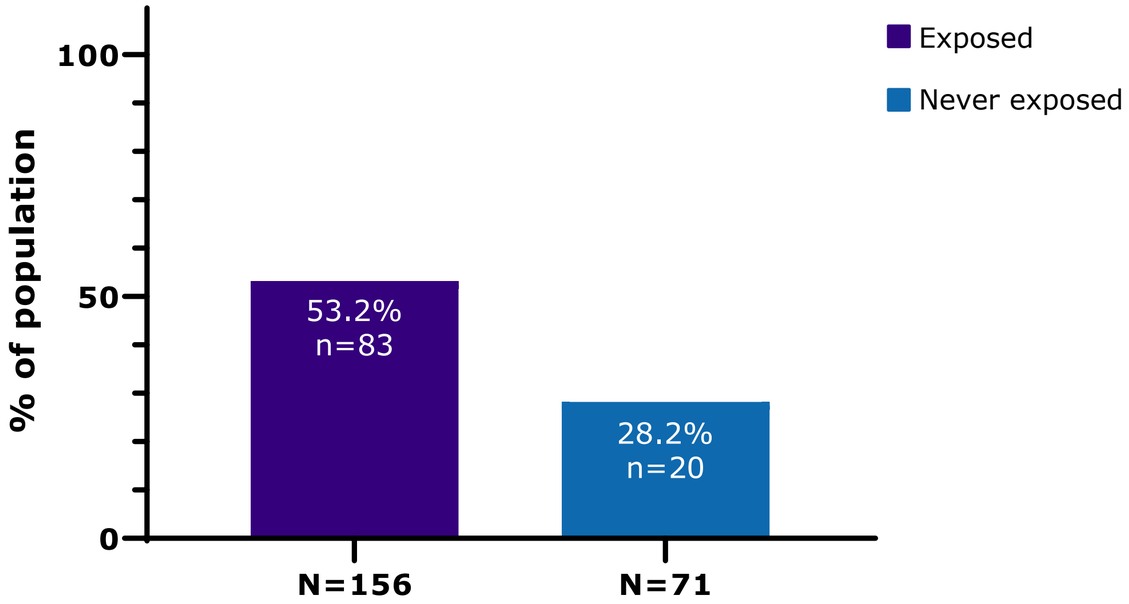
RESULTS

Figure 2. Patients Relapse-free Since Last Parent Study Dose



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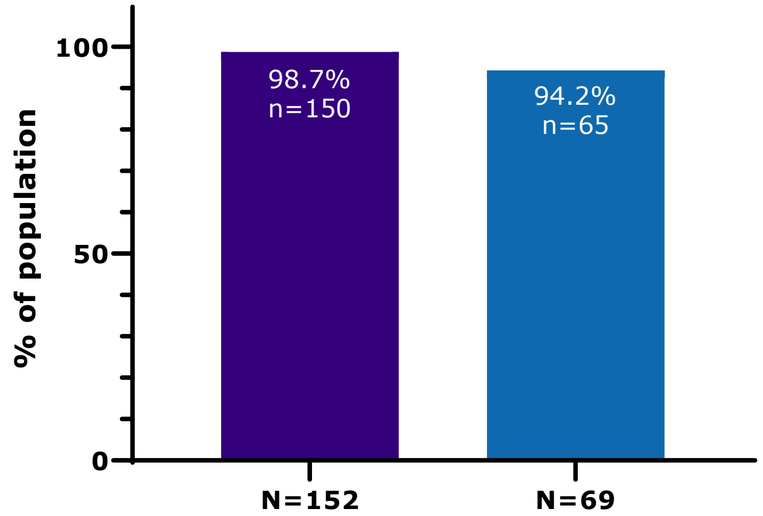

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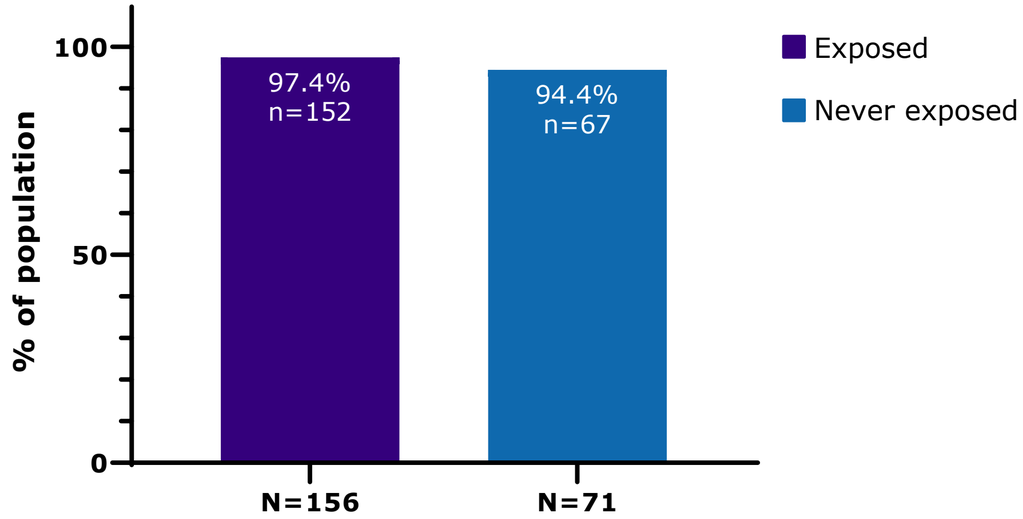

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CI, confidence interval

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