MAVEN 4: Phase IV non-interventional, prospective, Spanish multicenter study to evaluate Cladribine tablets long-term effectiveness in the real-world clinical practice

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CONCLUSIONS

- **This interim analysis is in line with clinical trial findings on the efficacy of cladribine after short oral courses and shows no new safety concerns, in patients with an EDSS of 1.9, a mean of 1.2 relapses in the prior 2 years and mainly naive or from a first switch.**
- **In the first year of follow-up, a high percentage of patients were free from relapses, free of 6-month sustained disability progression and achieved NEDA, and no patients required additional therapy.**
- **The MAVEN 4 study with a 7-year follow-up will provide data on the rate of patients continuing cladribine treatment beyond the fourth year, as well as the long-term efficacy and safety of cladribine tablets in the real world.**

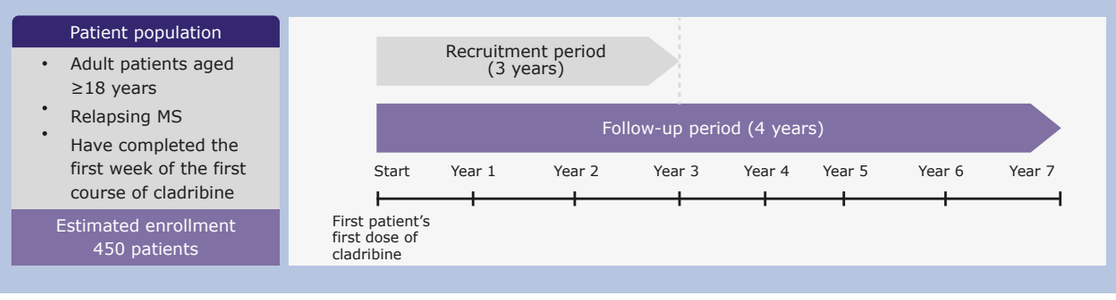
BACKGROUND AND PURPOSE

- Based on results of the pivotal studies of cladribine tablets CLARITY[1] and CLARITY Extension[2], it is expected that clinical efficacy of two annual courses for 2 years is maintained in years 3 and 4. However, the evolution of cladribine-treated patients beyond year 4 needs to be addressed.
- MAVEN 4 study was designed to evaluate the long-term effectiveness and safety of cladribine tablets for the treatment of relapsing multiple sclerosis (MS) under real-world clinical practice in Spain.
- Results from the study will show the number of patients that do not require additional therapy at years 3 and 4. Since patients may be followed for 7 years, this study will allow us to analyze the continuation of treatment with cladribine tablets from year 4 onwards and define the profile of patients candidate to receive cladribine.
- This interim analysis of the ongoing MAVEN 4 study focuses on baseline characteristics and clinical outcomes of patients who completed the first year of follow-up. We present updated data as of August 2022.

METHODS

- MAVEN 4 is a noninterventional, prospective cohort study of patients with relapsing MS who had initiated at least the first course of cladribine tablets per local labelling[3]. Patients were recruited from 39 centers in Spain and the study protocol was approved by the ethics committee of the Hospital Universitario de Bellvitge (Barcelona, Spain).
- During a recruitment period of 3 years, patients were included after completing the first treatment week and before initiating the second course in year two. Patients will be followed for 4 years with regular visits conducted every 6 months as per clinical practice. The study will run for 7 years from the time the first patient received the first dose of cladribine tablets (**Figure 1**).

Figure 1. Study design



Assessments

- Collected data included demographic and clinical characteristics of patients at baseline (start of the observation period), history of previous disease-modifying therapies (DMTs), relapses, Expanded Disability Status Scale (EDSS) score, and Magnetic Resonance Image (MRI). Safety assessment included a review of the occurrence of adverse events during the observation period.

Data analysis

- At database lock, no evidence of disease activity 3 (NEDA-3) defined as no relapses, no confirmed disability (EDSS) progression and no MRI activity during at least 6 months, was assessed. The proportion of patients in whom EDSS scores improved, remained stable or worsened after the first dose of cladribine tablets was also analyzed.
- Quantitative variables are summarized as mean [standard deviation (SD)] while categorical ones are presented as number (percentage). Freedom from relapses, 6-month sustained disability progression, and achievement of NEDA was estimated by the Kaplan Meier method.

RESULTS

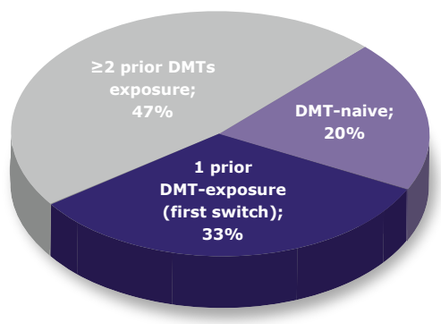
- From June 2019 to February 2022, we enrolled 450 patients. This first interim analysis shows data from 445 patients.
- The mean age at baseline was 39.1±9.9 years and 76.6% were female (**Table 1**). More than half of patients were naive or came from a first switch (**Figure 2**).

Table 1. Baseline demographics and clinical characteristics (N=445)

Characteristic	Value
Age (years), mean±SD[a]	39.2±9.81
Patients aged ≤ 40 years, n (%)	258 (58.2)
Patients aged > 40 years, n (%)	185 (41.8)
Gender, n (%)[b]	
Female	340 (76.6)
Male	104 (23.4)
Disease duration (years), mean±SD[c]	7.1±6.4
Number of relapses in the previous 2 years, mean±SD[d]	1.2±0.9
EDSS score, mean±SD[e]	1.9±1.40
Patients with active gadolinium T1-weighted lesions, n/n tested (%)	121/299 (27.8)
Number of active gadolinium T1-weighted lesions, mean±SD[f]	3.3±5.8
T2-weighted lesions, n/n tested (%)	
<9 lesions	24/121 (19.8)
≥ 9 lesions	97/121 (80.2)

Missing data: [a]n=2; [b]n=1; [c]n=2; [d]n= 1; [e]n=9; [f]n=1. EDSS: Expanded Disability Status Scale; SD: standard deviation.

Figure 2. Prior exposure to DTMs (N=444)



DMTs, disease-modifying treatments.

History of prior DMTs before treatment with cladribine

- **Table 2** shows the immunomodulatory and immunosuppressive therapies used before starting treatment with cladribine, with the injectables IFNβ (1a/1b) and glatiramer acetate or the oral dimethyl-fumarate and teriflunomide as the most frequent treatments used.

Table 2. Previous MS treatments used before cladribine tablets course

Prior MS treatment*	(N=356)
IFNβ 1a or 1b	240
Glatiramer acetate	112
Dimethyl-fumarate	122
Teriflunomide	112
Fingolimod	60
Alemtuzumab	1
Natalizumab	39
Ocrelizumab	1

*Multiple response variable. IFN, interferon; MS, multiple sclerosis.

Effectiveness after 1-year follow-up

- During the first year of treatment no patients required additional therapy.
- At Year 1, 83.6% were free from relapses and 91.3% were free of 6-month sustained disability progression (**Table 3**). The mean EDSS score was 2.0±1.6 and stable from baseline.

Table 3. Key outcomes at 1 Year of follow-up

Outcome	Year 1
ARR, mean±SD	0.16 ±0.43
Relapse-free (%) (95%CI)*	83.6 (79.6-86.9)
Free of 6-month sustained disability progression (%) (95%CI)*	91.3 (88.02-93.7)
NEDA (%) (95% CI)*	71.6 (66.8-75.8)

*Kaplan Meier estimates showing cumulative probability.

ARR, annualized relapse rate; CI, confidence interval; NEDA, no evidence of disease activity.

Safety findings

- Lymphopenia (graded as mild or moderate) was reported in 6.3% of the patients and there were no cases of grades 3-4. Two patients developed herpes zoster infection. Serious pyelonephritis caused by *Escherichia* was reported in 1 patient.

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. SmPC Mavenclad®

Disclosures

A. Saiz reports compensation for consulting services and speaker honoraria from Merck-Serono, Biogen-Idec, Sanofi, Novartis, Roche, Janssen, and Alexion; Y. Aladro reports compensation for consulting services and speaker honoraria Merck, TEVA, Biogen, Novartis, Roche, Sanofi, BMS; L. Costa-Frossard reports compensation for consulting services and speaker honoraria from Biogen, BMS, Janssen, Merck Serono, Novartis, Sanofi, Roche y Teva; I. Sánchez Magro is a MERCK KGaA employee; A. Rodriguez-Antigüedad reports compensation for consulting services and speaker honoraria Merck, Biogen, Novartis, Roche, Sanofi, Janssen and BMS.

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