Cladribine Tablets in Patients With Relapsing-Remitting Multiple Sclerosis or Active Secondary Progressive Multiple Sclerosis After Suboptimal Response to a Disease-Modifying Therapy (CLICK-MS and MASTER-2): Interim Baseline and Safety Review

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DISCLOSURES

AAM: Received research grants from or is a consultant/speaker for EMD Serono, Rockland, MA, USA, Genzyme, Genentech, Novartis, Alexion, Celgene. **JK**: Member of speakers bureau for EMD Serono, Rockland, MA, USA, Sanofi-Genzyme, Biogen, Genentech and Novartis. **DR**: Has received consultancy fees from Alexion, Biogen, Bristol Myers Squibb, EMD Serono, Rockland, MA, USA, Genentech, Greenwich Biosciences, Horizon, Janssen, Novartis, Sanofi Genzyme. He has received honoraria or speaker fees from Alexion, Biogen, Bristol Myers Squibb, EMD Serono, Rockland, MA, USA, Genentech, Janssen, Mallinckrodt, Novartis, Sanofi Genzyme, and has received research grant support from Biogen, EMD Serono, Rockland, MA, USA, Genentech, GW Pharmaceuticals, Janssen, Mallinckrodt, MedDay, Novartis, PCORI, Sanofi Genzyme, and TG Therapeutics. **JA**: Employee of EMD Serono, Billerica, MA, USA. **EE, DEH**, and **LAL**: Employees of EMD Serono, Rockland, MA, USA. **JAS**: Has served as a consultant for Biogen, EMD Serono, Rockland, MA, USA, Celgene, Genzyme, Genentech and Teva, and has received grant funding from Biogen, Genzyme and the National MS Society. **ADB**: Member of research, advisory board, and speakers' bureau for Biogen, EMD Serono, Rockland, MA, USA, Mallinckrodt, Novartis, Roche-Genentech, Sanofi-Genzyme, and TG Therapeutics. **EJF**: Has received compensation for research, consulting, speakers bureau, and/or Advisory work from AbbVie, Alexion, Biogen, Bristol Myers Squibb, Chugai, EMD Serono, Rockland, MA, USA, Genentech Roche, MedDay, Novartis, Sanofi Genzyme, and TG Therapeutics.

INTRODUCTION

- DMT switching is common in the management of MS[1,2]
  - Frequently cited reasons for switching DMTs include lack of efficacy and AEs
- Cladribine tablets 3.5 mg/kg (cumulative dose over two years, administered as one treatment course of 1.75 mg/kg per year) are approved for the treatment of RMS, including RRMS and active SPMS[3]
- Real-world data on the effectiveness and safety of cladribine tablets 3.5 mg/kg in patients who switched from another MS DMT are lacking
- CLICK-MS (NCT03933215) and MASTER-2 (NCT03933202) are ongoing single arm, observational, 54-month Phase 4 studies based in the US examining the effectiveness, safety, and PROs of cladribine tablets 3.5 mg/kg in patients with RRMS or active SPMS with previous suboptimal response to an injectable (CLICK-MS), oral, or infusion (MASTER-2) DMT in the real world[4]

OBJECTIVE

To review interim data on baseline characteristics, safety, and adherence from patients enrolled in the Phase 4 CLICK-MS and MASTER-2 trials

Abbreviations: AE, adverse event; ALC, absolute lymphocyte count; ARR, annualized relapse rate; BDI-FS, Beck-Depression Inventory – Fast Screen; CBC, complete blood count; DMT, disease-modifying therapy; ePRO, electronic PRO; Gd+, gadolinium enhancing; IFN, interferon; LLN = lower limit of normal; MFIS-5, Modified Fatigue Impact Scale – 5-item version; MRI, magnetic resonance imaging; MS, multiple sclerosis; MS-TAQ, MS Treatment Adherence Questionnaire; PDDS, Patient Determined Disease Steps; PPMS, primary progressive MS; PRO, patient-reported outcome; PY, patient years; RMS, relapsing forms of MS; RRMS, relapsing-remitting MS; SD, standard deviation; SF-36, 36-Item Short Form Health Survey; SPMS, secondary progressive MS; TEAE, treatment emergent AE; TSQM, 14-Item Treatment Satisfaction Questionnaire for Medication; Tx, treatment; USPI, United States Prescribing Information; WPAI-MS, Work Productivity Activity Impairment – MS; yrs, years

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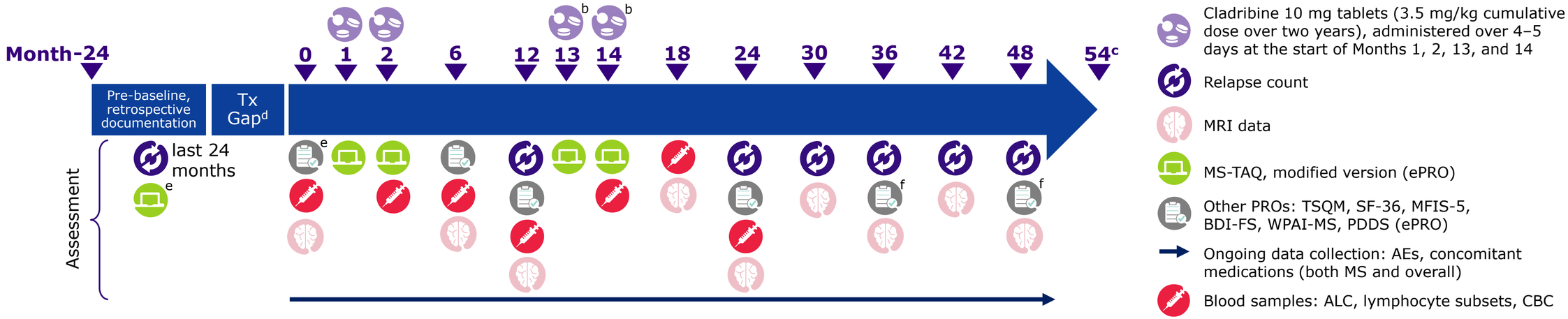
METHODS

- Both studies began in 2019 and are expected to complete in 2025 (CLICK-MS) and 2026 (MASTER-2) (**Figure 1**)
  - CLICK-MS is expected to enroll 100 patients
  - MASTER-2 is expected to enroll 250 patients, including 100 patients who switched to cladribine tablets from ocrelizumab
- Eligible patients are adults diagnosed with RRMS or active SPMS who had suboptimal response to an injectable, oral, or infusion DMT
  - Full inclusion and exclusion criteria have been previously published[4]
- Patients will receive cladribine tablets per the USPI[5]
- Baseline and safety data are from the September 7, 2021 and July 20, 2021 data cuts for CLICK-MS and MASTER-2, respectively

Figure 1. CLICK-MS and MASTER-2 study design[a]



As the study is ongoing, variable patient numbers for certain measures are due to ongoing data collection and cleaning.

[a]Since the publication of the study design,[4] the duration of the study has been extended to 54 months from 30 months to further collect data on safety, relapse, MRI, and PDDS. [b]Treatment in the second year may be delayed for up to six months for some patients, according to ALC. This is accounted for in the study duration. [c]If Year 2 treatment is delayed, follow-up may continue up to 54 months. [d]Duration between stopping previous DMT and start of cladribine tablets was variable and at the discretion of the treating physician. [e]First assessment is for prior DMT. [f]PDDS only.

Primary endpoint: ARR over 24 months

Abbreviations: AE, adverse event; ALC, absolute lymphocyte count; ARR, annualized relapse rate; BDI-FS, Beck-Depression Inventory – Fast Screen; CBC, complete blood count; DMT, disease-modifying therapy; ePRO, electronic PRO; Gd+, gadolinium enhancing; IFN, interferon; LLN = lower limit of normal; MFIS-5, Modified Fatigue Impact Scale – 5-item version; MRI, magnetic resonance imaging; MS, multiple sclerosis; MS-TAQ, MS Treatment Adherence Questionnaire; PDDS, Patient Determined Disease Steps; PPMS, primary progressive MS; PRO, patient-reported outcome; PY, patient years; RMS, relapsing forms of MS; RRMS, relapsing-remitting MS; SD, standard deviation; SF-36, 36-Item Short Form Health Survey; SPMS, secondary progressive MS; TEAE, treatment emergent AE; TSQM, 14-Item Treatment Satisfaction Questionnaire for Medication; Tx, treatment; USPI, United States Prescribing Information; WPAI-MS, Work Productivity Activity Impairment – MS; yrs, years

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RESULTS

Baseline demographics and disease characteristics

- Across the two studies, 68.1–80.4% of the patients were female and the mean age was 47–51 years (**Table 1**)
  - 87.2–92.9% of patients were diagnosed with RRMS (**Table 2**)

Table 1. Baseline demographics

	CLICK-MS	MASTER-2	
	Prior Injectable DMT (n=56)	Prior Oral DMT (n=87)	Prior Infusion DMT (n=47)
Female, n (%)	45 (80.4)	67 (77.0)	32 (68.1)
Age (yrs)			
Mean (SD)	50 (12.5)	51 (11.3)	47 (12.5)
Min, max	22, 68	20, 74	22, 68
Race, n (%)			
White	46 (82.1)	73 (83.9)	39 (83.0)
Black/African American	7 (12.5)	9 (10.3)	4 (8.5)
Other	3 (5.4)	5 (5.7)	4 (8.5)

Table 2. Baseline disease characteristics (diagnosis)

	CLICK-MS	MASTER-2	
	Prior Injectable DMT (n=56)	Prior Oral DMT (n=87)	Prior Infusion DMT (n=47)
Diagnosis, n (%)			
RRMS	52 (92.9)	80 (92.0)	41 (87.2)
Active SPMS	2 (3.6)	6 (6.9)	6 (12.8)
PPMS diagnosis	1 (1.8)[a]	-	-
Missing	1 (1.8)	1 (1.1)	-
Time since diagnosis (yrs), mean (SD)	13.5 (10.52) n=54	11.7 (7.22) n=85	12.9 (9.55) n=46

[a]The patient with PPMS was mistakenly enrolled in the study. The patient received one week of cladribine tablets treatment, then discontinued from the study because of protocol deviation. There were no AEs reported.

Abbreviations: AE, adverse event; ALC, absolute lymphocyte count; ARR, annualized relapse rate; BDI-FS, Beck-Depression Inventory – Fast Screen; CBC, complete blood count; DMT, disease-modifying therapy; ePRO, electronic PRO; Gd+, gadolinium enhancing; IFN, interferon; LLN = lower limit of normal; MFIS-5, Modified Fatigue Impact Scale – 5-item version; MRI, magnetic resonance imaging; MS, multiple sclerosis; MS-TAQ, MS Treatment Adherence Questionnaire; PDDS, Patient Determined Disease Steps; PPMS, primary progressive MS; PRO, patient-reported outcome; PY, patient years; RMS, relapsing forms of MS; RRMS, relapsing-remitting MS; SD, standard deviation; SF-36, 36-Item Short Form Health Survey; SPMS, secondary progressive MS; TEAE, treatment emergent AE; TSQM, 14-Item Treatment Satisfaction Questionnaire for Medication; Tx, treatment; USPI, United States Prescribing Information; WPAI-MS, Work Productivity Activity Impairment – MS; yrs, years

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RESULTS

Table 2. Baseline disease characteristics (cont'd; prior DMT, relapse, MRI)[a]

	CLICK-MS	MASTER-2	
	Prior Injectable DMT (n=56)	Prior Oral DMT (n=87)	Prior Infusion DMT (n=47)
ARR for overall population in prior 24 months, mean (SD)	0.24 (0.31)	0.19 (0.30)	0.18 (0.29)
MS diagnosis ≥24 months before study, n (%)[b]	53 (94.6)	85 (97.7)	45 (95.7)
Number of prior DMTs, mean (SD)	1.8 (0.88) n=52	3.0 (1.68) n=85	3.5 (1.76) n=44
ARR in prior 24 months, mean (SD)	0.24 (0.31) n=50	0.19 (0.30) n=78	0.18 (0.29) n=42
Relapse in prior 24 months, n (%)[c]	n=50	n=78	n=42
0	29 (58.0)	52 (66.7)	29 (69.0)
1	18 (36.0)	23 (29.5)	11 (26.2)
2	3 (6.0)	2 (2.6)	2 (4.8)
≥3	-	1 (1.3)	-
MS diagnosis <24 months before study, n (%)[d]	3 (5.4)	2 (2.3)	2 (4.3)
Number of prior DMTs, mean (SD)	1.7 (0.58)	1.0 (0)	1.0 (0)
ARR since MS diagnosis, mean (SD)	0.20 (0.35)	0.79 (1.11)	0.38 (0.54)
Relapse since MS diagnosis, n (%)	n=3	n=2	n=2
0	2 (66.7)	1 (50.0)	1 (50.0)
1	1 (33.3)	-	1 (50.0)
2	-	1 (50.0)	

	CLICK-MS	MASTER-2	
	Prior Injectable DMT (n=56)	Prior Oral DMT (n=87)	Prior Infusion DMT (n=47)
Number of MRI lesions in prior 24 months or since MS diagnosis, if diagnosed within 24 months, mean (SD)			
T1 Gd+ lesions	0.1 (0.30) n=34	0.6 (3.10) n=42	0 (0.10) n=26
New T2 lesions[e]	0.3 (0.74) n=36	0.9 (2.28) n=43	0.9 (3.91) n=26
Combined unique lesions[e,f]	7.8 (13.29) n=18	5.7 (9.61) n=11	13.0 (32.83) n=11

[a]Data in the table were calculated based on the overall population in each group or the population indicated in each section or cell. [b]The data in this section were based on the patient population with MS diagnosis ≥24 months before study, as indicated in each cell/section. [c]The percentages in this section were based on n=50 (Prior Injectable DMT), n=78 (Prior Oral DMT), and n=42 (Prior Infusion DMT). [d]The data in this section were based on the patient population with MS diagnosis <24 months before the study: n=3 (Prior Injectable DMT), n=2 (Prior Oral DMT), and n=2 (Prior Infusion DMT). [e]New/enlarging T2 lesions were compared to the most recent prior MRI. [f]Number of combined, unique lesions at baseline (T1 Gd+, new T2, or enlarging T2 lesions).

Abbreviations: AE, adverse event; ALC, absolute lymphocyte count; ARR, annualized relapse rate; BDI-FS, Beck-Depression Inventory – Fast Screen; CBC, complete blood count; DMT, disease-modifying therapy; ePRO, electronic PRO; Gd+, gadolinium enhancing; IFN, interferon; LLN = lower limit of normal; MFIS-5, Modified Fatigue Impact Scale – 5-item version; MRI, magnetic resonance imaging; MS, multiple sclerosis; MS-TAQ, MS Treatment Adherence Questionnaire; PDDS, Patient Determined Disease Steps; PPMS, primary progressive MS; PRO, patient-reported outcome; PY, patient years; RMS, relapsing forms of MS; RRMS, relapsing-remitting MS; SD, standard deviation; SF-36, 36-Item Short Form Health Survey; SPMS, secondary progressive MS; TEAE, treatment emergent AE; TSQM, 14-Item Treatment Satisfaction Questionnaire for Medication; Tx, treatment; USPI, United States Prescribing Information; WPAI-MS, Work Productivity Activity Impairment – MS; yrs, years

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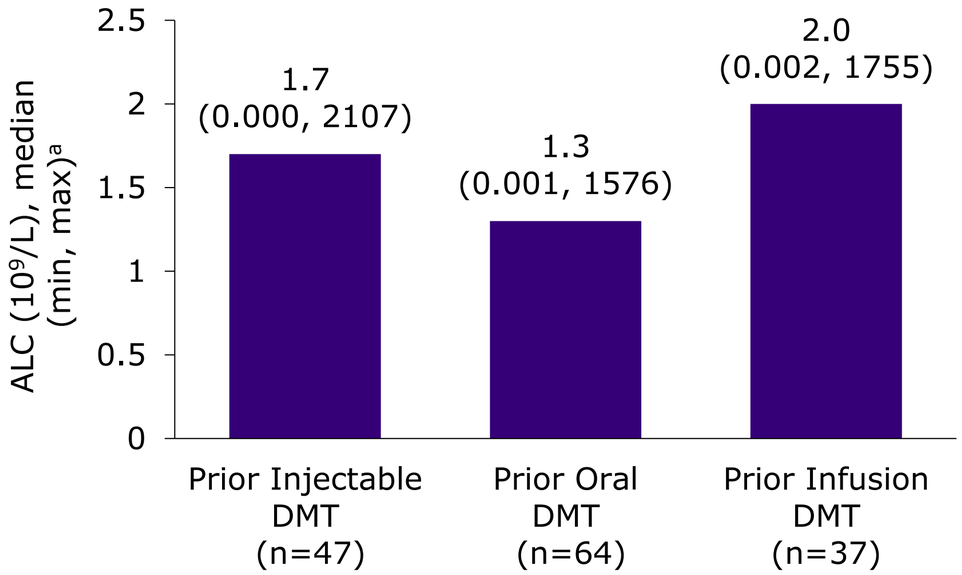
RESULTS

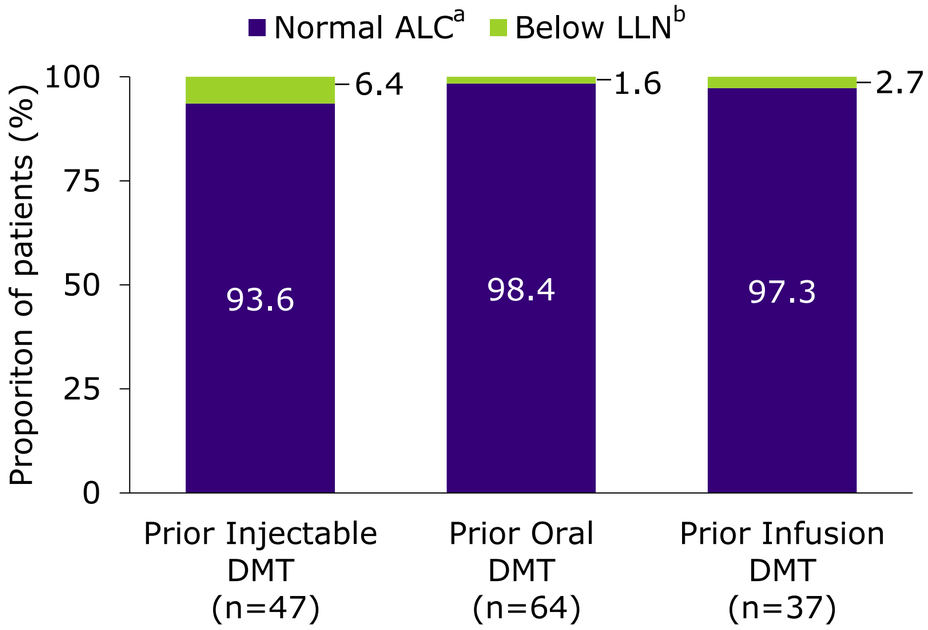
- Patient ALC levels were similar across groups at baseline (**Figure 2**)
  - Most patients (93.6–98.4%) had ALC within or above normal ranges (**Figure 3**)

Figure 2. Baseline ALC



[a]Values and units for min, max, and other outliers have been queried.

Figure 3. Baseline ALC ranges



[a]Includes ALC above normal limit. [b]Defined as <1000 cells/μL.

Abbreviations: AE, adverse event; ALC, absolute lymphocyte count; ARR, annualized relapse rate; BDI-FS, Beck-Depression Inventory – Fast Screen; CBC, complete blood count; DMT, disease-modifying therapy; ePRO, electronic PRO; Gd+, gadolinium enhancing; IFN, interferon; LLN = lower limit of normal; MFIS-5, Modified Fatigue Impact Scale – 5-item version; MRI, magnetic resonance imaging; MS, multiple sclerosis; MS-TAQ, MS Treatment Adherence Questionnaire; PDDS, Patient Determined Disease Steps; PPMS, primary progressive MS; PRO, patient-reported outcome; PY, patient years; RMS, relapsing forms of MS; RRMS, relapsing-remitting MS; SD, standard deviation; SF-36, 36-Item Short Form Health Survey; SPMS, secondary progressive MS; TEAE, treatment emergent AE; TSQM, 14-Item Treatment Satisfaction Questionnaire for Medication; Tx, treatment; USPI, United States Prescribing Information; WPAI-MS, Work Productivity Activity Impairment – MS; yrs, years

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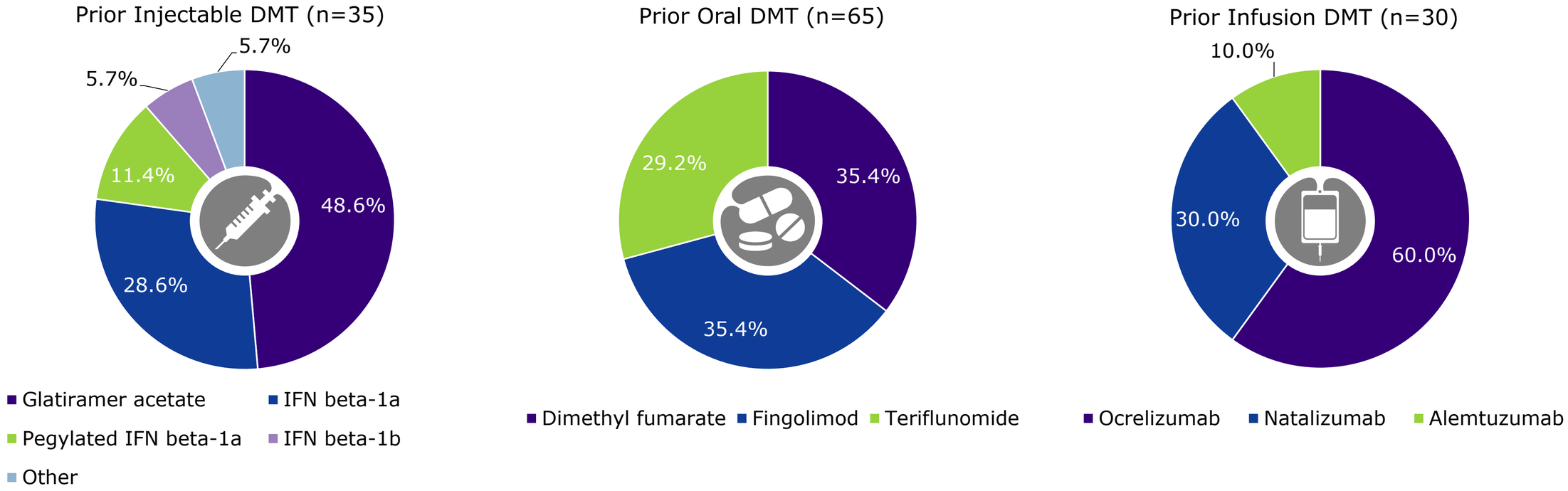
RESULTS

Prior DMTs used before study

- The most commonly used prior DMT was glatiramer acetate in the Prior Injectable DMT group, dimethyl fumarate and fingolimod in the Prior Oral DMT group, and ocrelizumab in the Prior Infusion DMT group (**Figure 4**)

Figure 4. Most recent DMTs used



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RESULTS

Adherence to cladribine tablets[a]

- Of the 190 enrolled patients, 115 and 121 completed MS-TAQ at Months 1 and 2 at data cutoff (CLICK-MS: September 7, 2021; MASTER-2: July 20, 2021), respectively, with **99.1% fully adhering to treatment in Month 1 and 97.5% in Month 2**, representing completion of the full Year 1 treatment course (**Table 3**)

Table 3. MS-TAQ for cladribine tablets[b]

	CLICK-MS		MASTER-2			
	Prior Injectable DMT (n=56)		Prior Oral DMT (n=87)		Prior Infusion DMT (n=47)	
	Month 1 n=25	Month 2 n=33	Month 1 n=58	Month 2 n=57	Month 1 n=32	Month 2 n=31
How many cladribine tablets were you supposed to take during this treatment week? (Mean, SD)	7.5 (1.86)	7.2 (2.14)	7.4 (1.94)	6.9 (2.42)	7.6 (2.0)	7.1 (2.10)
Did you miss or forget to take any cladribine tablets during this treatment week? (n, %) [Patients who responded "Yes"]	0	0	1 (1.7)	2 (3.5)	0	0
Overall, how hard or easy do you feel it is to take cladribine tablets as recommended by your physician during your treatment week? (Mean, SD)[c]	1.2 (0.47)	1.0 (0.18)	1.1 (0.28)	1.1 (0.37)	1.3 (0.57)	1.2 (0.48)
Overall, how satisfied are you with how things have been with your cladribine tablet treatment during your treatment week? (Mean, SD)[d]	4.1 (1.06)	4.2 (1.00)	4.2 (0.75)	4.1 (1.03)	4.0 (0.97)	3.9 (0.85)

[a]Adherence to cladribine tablets is defined as the act of correctly following the treatment regimen recommended in the USPI.[5] [b]Data in this table were based on the patient population in each month. [c]An ordinal scale from 1 to 5 was used: 1 = Extremely easy, 2 = A little hard, 3 = Moderately hard, 4 = Very hard, 5 = Extremely hard. [d]An ordinal scale from 1 to 5 was used: 1 = Not satisfied at all, 2 = A little satisfied, 3 = Moderately satisfied, 4 = Very satisfied, 5 = Completely satisfied

Abbreviations: AE, adverse event; ALC, absolute lymphocyte count; ARR, annualized relapse rate; BDI-FS, Beck-Depression Inventory – Fast Screen; CBC, complete blood count; DMT, disease-modifying therapy; ePRO, electronic PRO; Gd+, gadolinium enhancing; IFN, interferon; LLN = lower limit of normal; MFIS-5, Modified Fatigue Impact Scale – 5-item version; MRI, magnetic resonance imaging; MS, multiple sclerosis; MS-TAQ, MS Treatment Adherence Questionnaire; PDDS, Patient Determined Disease Steps; PPMS, primary progressive MS; PRO, patient-reported outcome; PY, patient years; RMS, relapsing forms of MS; RRMS, relapsing-remitting MS; SD, standard deviation; SF-36, 36-Item Short Form Health Survey; SPMS, secondary progressive MS; TEAE, treatment emergent AE; TSQM, 14-Item Treatment Satisfaction Questionnaire for Medication; Tx, treatment; USPI, United States Prescribing Information; WPAI-MS, Work Productivity Activity Impairment – MS; yrs, years

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RESULTS

Safety of cladribine tablets 3.5 mg/kg

- Of the 190 patients treated with cladribine tablets 3.5 mg/kg, 34.7% experienced a TEAE, with 30.5% being mild or moderate in severity and 4.7% considered serious (**Table 4**)
  - Most common TEAEs as of March 7, 2022 (in ≥6 patients in both studies combined excluding lymphopenia), were fatigue, nausea, headache, diarrhea, and urinary tract infection

Table 4. Overall incidence of TEAEs

	CLICK-MS[a]	MASTER-2[b]	
	Prior Injectable DMT (n=56)	Prior Oral DMT (n=87)	Prior Infusion DMT (n=47)
	n (%)	n (%)	n (%)
Any TEAEs	19 (33.93)	32 (36.78)	15 (31.91)
Mild TEAEs	7 (12.50)	16 (18.39)	6 (12.77)
Moderate TEAEs	11 (19.64)	11 (12.64)	7 (14.89)
Severe TEAEs	1 (1.79)	5 (5.75)	2 (4.26)
Serious TEAEs	1 (1.79)	5 (5.75)	3 (6.38)

Total TEAE rate per PY not calculated.

[a]TEAEs for CLICK-MS as of September 7, 2021. [b]TEAEs for MASTER-2 as of July 20, 2021.

Abbreviations: AE, adverse event; ALC, absolute lymphocyte count; ARR, annualized relapse rate; BDI-FS, Beck-Depression Inventory – Fast Screen; CBC, complete blood count; DMT, disease-modifying therapy; ePRO, electronic PRO; Gd+, gadolinium enhancing; IFN, interferon; LLN = lower limit of normal; MFIS-5, Modified Fatigue Impact Scale – 5-item version; MRI, magnetic resonance imaging; MS, multiple sclerosis; MS-TAQ, MS Treatment Adherence Questionnaire; PDDS, Patient Determined Disease Steps; PPMS, primary progressive MS; PRO, patient-reported outcome; PY, patient years; RMS, relapsing forms of MS; RRMS, relapsing-remitting MS; SD, standard deviation; SF-36, 36-Item Short Form Health Survey; SPMS, secondary progressive MS; TEAE, treatment emergent AE; TSQM, 14-Item Treatment Satisfaction Questionnaire for Medication; Tx, treatment; USPI, United States Prescribing Information; WPAI-MS, Work Productivity Activity Impairment – MS; yrs, years

References: 1. Patti F, et al. Mult Scler Relat Disord. 2020;42:102124. **2.** Hillert J, et al. Front Neurol. 2021;12:647811. **3.** Rammohan K, et al. Drugs 2020;80:1901–28. **4.** Miravalle AA, et al Neurodegener Dis Manag 2021;11:99–111. **5.** Mavenclad [package insert]. Rockland, MA: EMD Serono, Inc.; 2019.

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CONCLUSIONS

- **As of July–September 2021, 56 patients in CLICK-MS and 134 patients in MASTER-2 have initiated treatment with cladribine tablets**
  - **Baseline patient demographics and disease characteristics were broadly similar across the three prior DMT groups**
- **Full adherence to cladribine tablets was reported in ≥97.5% of patients who completed the MS-TAQ**
- **No unexpected safety findings were reported after treatment with cladribine tablets**
- **Results from CLICK-MS and MASTER-2 on treatment switching and adherence will help inform treatment decisions in the real world**

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Abbreviations: AE, adverse event; ALC, absolute lymphocyte count; ARR, annualized relapse rate; BDI-FS, Beck-Depression Inventory – Fast Screen; CBC, complete blood count; DMT, disease-modifying therapy; ePRO, electronic PRO; Gd+, gadolinium enhancing; IFN, interferon; LLN = lower limit of normal; MFIS-5, Modified Fatigue Impact Scale – 5-item version; MRI, magnetic resonance imaging; MS, multiple sclerosis; MS-TAQ, MS Treatment Adherence Questionnaire; PDDS, Patient Determined Disease Steps; PPMS, primary progressive MS; PRO, patient-reported outcome; PY, patient years; RMS, relapsing forms of MS; RRMS, relapsing-remitting MS; SD, standard deviation; SF-36, 36-Item Short Form Health Survey; SPMS, secondary progressive MS; TEAE, treatment emergent AE; TSQM, 14-Item Treatment Satisfaction Questionnaire for Medication; Tx, treatment; USPI, United States Prescribing Information; WPAI-MS, Work Productivity Activity Impairment – MS; yrs, years

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