P055

# Cladribine Tablets in Patients with Relapsing Forms of Multiple Sclerosis Who Had Suboptimal Response to Injectable Disease-Modifying Drug (CLICK-MS)

A.A. Miravalle,[1] J. Katz,[2] J.A. Sloane,[3] B. Hayward,[4] J.S. Walsh,[4] D.E. Harlow[4]

[1]Advanced Neurology of Colorado, University of Colorado, Fort Collins, CO, US; [2]Elliot Lewis Center for Multiple Sclerosis Care, Wellesley, MA, US; [3]BIDMC Department of Neurology, Harvard Medical School, Boston, MA, US; [4]EMD Serono, Inc., Rockland, MA, US

## BACKGROUND INFORMATION

- The cladribine tablets developmental program studies have demonstrated the efficacy, safety, and tolerability of cladribine tablets 10 mg (3.5 mg/kg cumulative dose over 2 years) in patients with relapsing forms of MS
  - **CLARITY**[1]
    - **After 96 weeks, cladribine tablets significantly reduced relapse rates, risk of disability progression, and MRI measures of disease activity versus placebo in patients with RRMS**
  - **CLARITY Extension (EXT)**[2]
    - In CLARITY EXT, eligible patients who received placebo in CLARITY were assigned to cladribine tablets 3.5 mg/kg, and patients treated with cladribine tablets in CLARITY were re-randomized (2:1) to cladribine tablets 3.5 mg/kg or placebo
    - In a 2-year extension of CLARITY, AE rates were generally similar between groups
    - Of the patients who originally received cladribine tablets 3.5 mg/kg in the CLARITY trial, those who received additional doses of cladribine tablets 3.5 mg/kg during the extension phase had higher rates of Grade ≥3 lymphopenia (40.9%) than those who received placebo in the extension (5.1%)
      - ◇ All groups showed similar lymphocyte recovery by the end of each year
      - ◇ >90% of those treated with cladribine tablets and all treated with placebo recovered to Grade 0–1 by study end
    - **Treatment with cladribine tablets 3.5 mg/kg for 2 years followed by 2 years of placebo produced durable clinical benefits that were similar to 4 years of cladribine tablets treatment, with a lower risk of severe lymphopenia**
- In March 2019, the US Food and Drug Administration approved cladribine tablets 3.5 mg/kg for the treatment of adult patients with relapsing-remitting disease and active secondary progressive disease. Treatment with cladribine tablets 3.5 mg/kg is generally recommended for patients who have had an inadequate response to, or are unable to tolerate, an alternate drug indicated for the treatment of MS[3]

## RATIONALE

- Real-world studies are designed to complement randomized controlled trials by providing information on relative and long-term effectiveness of MS treatments[4]
- **Real-world data on the effectiveness and safety of cladribine tablets are limited**
- Data on treatment switching is also limited, as the majority of patients in the Phase 3 trials were treatment naïve

## CLICK-MS STUDY DESIGN & ENDPOINTS[5]

A 30-month, prospective, single-arm, observational, Phase 4 study, to be conducted in the US to examine real-world effectiveness, safety, and PROs of cladribine tablets in patients with RMS who transition to cladribine tablets after suboptimal response to **injectable** DMDs

**PATIENTS**

**Main inclusion criteria**
- Age ≥18 years
- Diagnosed with RRMS or active secondary progressive MS for ≥12 months
- Suboptimal response (investigator-assessed) to previous treatment with an injectable DMD
- Received last DMD injection ≥3 months ago
- Decision to initiate cladribine tablets treatment made during routine clinical care (i.e. before enrollment)

**Main exclusion criteria**
- Previous cladribine treatment (any dose)
- Decision to transition from previous injectable DMD made for administrative reasons only (e.g. relocation)
- Have any clinical condition or medical history noted as contraindication on cladribine tablets USPI

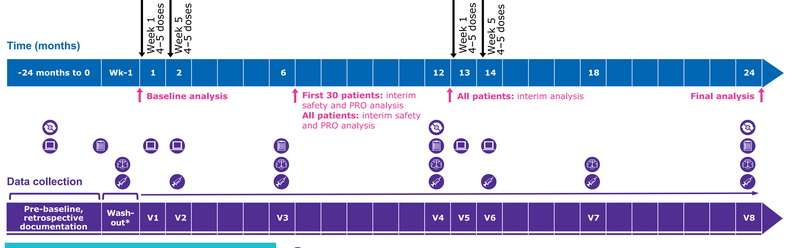
**Sample size**

**~200** patients across **50 sites** **~160** patients with evaluable data for the primary outcome

Patients will receive cladribine 10 mg tablets
(3.5 mg/kg cumulative dose [1.75 mg/kg per year for two years]), as per USPI[4]

**Cladribine tablets, YEAR 1**
Marketed per USPI: 1.75 mg/kg per year, 2 treatment courses of 4 or 5 days each, patient receives 10 or 20 mg (1 or 2 tablets) as single daily dose, depending on body weight

**Cladribine tablets, YEAR 2**
Marketed per USPI: 1.75 mg/kg per year, same 2 courses as during Year 1
Year 2 course may be delayed for some patients, based on patient ALC




**Primary endpoint**
- ARR over 24 months**

Patients will have visits and assessments as per routine clinical practice and in accordance with the USPI. All patients, including those who discontinue cladribine tablets 3.5 mg/kg treatment during the observation, will be followed up to Month 24 (or Month 30 for patients with delayed start of Year 2 treatment)

*Duration between stopping previous injectable DMD and start of cladribine tablets is at the discretion of the investigator
**Relapse as defined by investigator

- **Relapse count** (pre-baseline: last 24 months)
- **Treatment adherence** (via online: MS-TEQ, modified versions)
- **Other PROs** (via eCRF: TSQM, SF-36, MFIS-5, BDI-FS, WPAI-MS, PDDS)
- **MRI data** (as available as per routine practice, assuming documentation at baseline, Months 6, 12, 18, and 24)
- **Blood samples** (as available as per routine practice): expected time points based on required ALC testing as per USPI; additional assessments such as CBC, lymphocyte subsets, JCV status
- **Parameters** collected on an ongoing basis: AEs, concomitant medications (both for MS and overall)

## RECRUITMENT


## MASTER-2 TRIAL

A similarly designed trial (MASTER-2; NCT03933202) is ongoing in patients with RMS who had suboptimal response to prior **oral or infusion** DMDs[6]

## CONCLUSION

**CLICK-MS will describe real-world effectiveness and generate safety, tolerability, and PRO data for cladribine tablets in patients with RMS with suboptimal response to prior injectable DMDs**

**Abbreviations:** AEs = adverse events; ALC = absolute lymphocyte count; ARR = annualized relapse rate; BDI-FS = Beck-Depression Inventory – Fast Screen; CBC = complete blood count; DMD = disease-modifying drug; eCRF = electronic case report form; JCV = John Cunningham Virus; MFIS-5 = Modified Fatigue Impact Scale – 5-item version; MRI = magnetic resonance imaging; MS = multiple sclerosis; MS-TEQ = MS Treatment Experience Questionnaire; PDDS = Patient Determined Disease Steps; PRO = patient reported outcome; RMS = relapsing forms of MS; RRMS = relapsing-remitting MS; SF-36 = 36-Item Short Form Health Survey; TSQM = 14-Item Treatment Satisfaction Questionnaire for Medication; USPI = United States Prescribing Information; V = visit; Wk = week; WPAI-MS = Work Productivity Activity Impairment – MS

**References:** 1. Giovannoni G, et al. *N Engl J Med.* 2010;362:416-26; 2. Giovannoni G, et al. *Mult Scler.* 2018;24:1594-1604; 3. EMD Serono, Inc. Mavenclad.® FDA Prescribing Information. 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/022561s000lbl.pdf. Accessed 1 July 2019; 4. Trojano M, et al. *Nat Rev Neurol.* 2017;13(2):105-118; 5. EMD Serono Research & Development Institute, Inc. A Study of Suboptimally Controlled Participants Previously Taking Injectable Disease-modifying Drugs (DMDs) for Relapsing Forms of Multiple Sclerosis (RMS) (CLICK-MS). Available at: https://clinicaltrials.gov/ct2/show/NCT03933215. NLM identifier: NCT03933215. Accessed 1 Jul 2019; 6. EMD Serono Research & Development Institute, Inc. A Study of Suboptimally Controlled Participants Previously Taking Oral Disease-Modifying Drugs (DMDs) for Relapsing Forms of Multiple Sclerosis (RMS) (MASTER-2). Available at: https://clinicaltrials.gov/ct2/show/NCT03933202. NLM identifier: NCT03933202. Accessed 1 Jul 2019.

**Acknowledgments:** This study was sponsored by EMD Serono, Inc., a business of Merck KGaA, Darmstadt, Germany (in the US), and Merck Serono SA, Geneva, an affiliate of Merck KGaA, Darmstadt, Germany (ROW). Writing and editorial support for the preparation of this poster was provided by Jenna Steere, PhD and Nick White of Ashfield (New York, NY, US); funding was provided by EMD Serono. EMD Serono reviewed and provided feedback on the poster. The authors had full control of the poster, and provided their final approval of all content.

**Disclosures: AAM:** Consultant/research grants/speaker for EMD Serono, Genzyme, Genentech, Novartis, Alexion, and Celgene; **JK:** Member of speaker's bureau for EMD Serono, Sanofi-Genzyme, Biogen, Genentech, and Novartis; **JAS**: Served as a consultant for Biogen, EMD Serono/Merck KGaA, Celgene, Genzyme, Genentech, and Teva, and has received grant funding from Biogen, Genzyme, and the National MS Society; **BH, JSW,** and **DEH:** Employees of EMD Serono, Inc., Rockland, MA, US (an affiliate of Merck KGaA, Darmstadt, Germany)



**Presented at ACTRIMS 2020; February 27-29, West Palm Beach, Florida, US**