Incidence of Infections and Severe Lymphopenia in Patients Newly Initiating Cladribine Tablets or Fingolimod for Treatment of Multiple Sclerosis: CLARION Study

J. Hillert[1], H. Butzkueven[2], M. Soilu-Hänninen[3], T. Ziemssen[4], J. Kuhle[5], J.R. Berger[6], A. Aydemir[7], J. Sõnajalg[8], I. Bezemer[9], M. Sabidó[10]

[1]Department of Clinical Neuroscience, Karolinska Institute, Stockholm, Sweden; [2]Monash University, Melbourne, VIC, Australia; [3]Neurocenter, Turku University Hospital and Clinical Neurosciences, University of Turku, Turku, Finland; [4]Center of Clinical Neuroscience, Neurological University Clinic Carl Gustav Carus, University of Technology, Dresden, Germany; [5]Neurology Clinic and Policlinic, MS Center and Research Center for Clinical Neuroimmunology and Neuroscience Basel (RC2NB), University Hospital of Basel, Basel, Switzerland; [6]Department of Neurology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; [7]EMD Serono Research and Development Institute, Inc., Billerica, MA, USA (an affiliate of Merck KGaA); [8]Global Database Studies, IQVIA, Tartu, Estonia; [9]Global Epidemiology and Outcomes Research, IQVIA, Amsterdam, The Netherlands; [10]Merck Healthcare KGaA, Darmstadt, Germany

CONCLUSION

Despite the limitation of a short follow-up period for this first assessment, as of the cut-off date no new safety signal has been identified.

INTRODUCTION

- Several studies have reported on the safety profile of cladribine tablets 10 mg (3.5 mg/kg cumulative dose over 2 years) during clinical development for relapsing MS.[1,2]
- **CLARION** is a long-term post-authorisation safety study that aims to compare the incidence of adverse events of special interest of patients with MS newly initiating cladribine tablets versus patients newly initiating fingolimod.

CLARION

OBJECTIVES

To estimate the incidence rate of severe infections, herpes zoster, PML, TB, and opportunistic infections in patients with MS and newly initiating cladribine tablets or fingolimod.

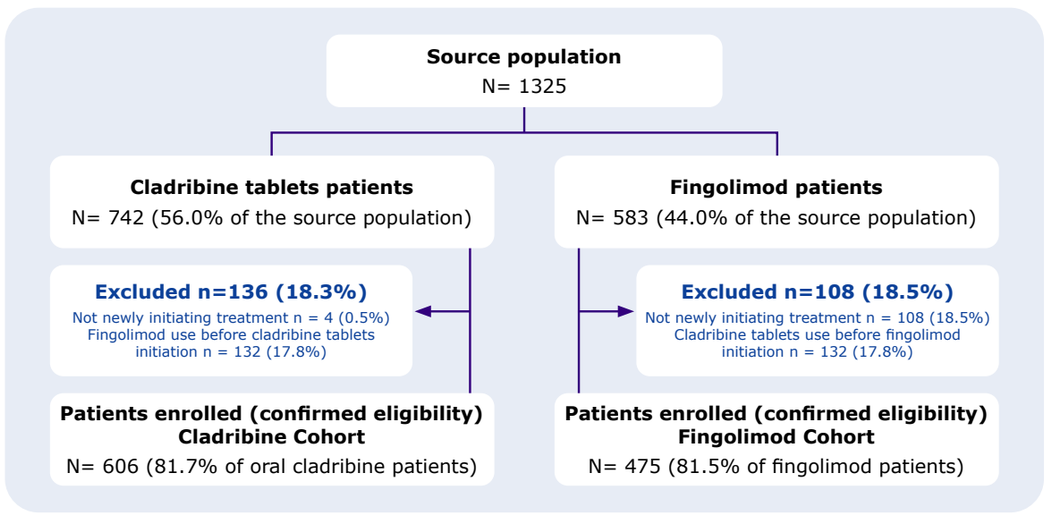
To estimate the incidence rate of severe lymphopenia in those newly initiating cladribine tablets.

METHODS

- Two cohorts of MS patients newly initiating cladribine tablets or fingolimod were identified from 6 MS registries participating in CLARION.
- Patient time-at-risk was counted from cohort entry time to the earliest date of first event, last visit date, or cut-off date (1 April 2020).
- Incidence rates of each outcome per 1000 PY were estimated for each cohort using Poisson regression. All outcomes were analysed as ITT, except severe lymphopenia (ALC <0.5x10^9 cells/L) analysed as-treated in cladribine tablets-treated patients only.
  - ITT: Patients are classified according to treatment received at cohort entry (enrolment).
  - As-treated: Exposure is time-dependent and patients are classified per on-going treatment at a given time: current exposure to cladribine tablets; current exposure to fingolimod; or no current exposure to study treatment.
  - The analysis of severe lymphopenia was performed using data of 4 MS registries (not available in Swedish MS Registry and Norwegian MS Registry).

RESULTS

Figure 1. Patient Disposition



Source population: Patients with fingolimod or cladribine tablets between cladribine tablets launch date (country-specific) and date of data cut-off (1 April 2020).

Table 1. Patient Demographics

	Cladribine cohort N=606	Fingolimod cohort N=475
Age at enrolment, years		
Range (min, max)	(19.0, 76.0)	(16.0, 78.0)
Mean (SD)	41.0 (12.6)	40.0 (11.0)
Female, n (%)	449 (71.4)	331 (69.7)
Data source, n (%)		
MSBase	132 (21.8%)	49 (10.3%)
MSDS3D (and NTD)	130 (21.5%)	104 (21.9%)
Norwegian MS Registry	183 (30.2%)	136 (28.6%)
Swiss MS Cohort	8 (1.3%)	13 (2.7%)
Finnish MS Registry	73 (12.0%)	123 (25.9%)
Swedish MS Registry	80 (13.2%)	50 (10.5%)
Duration of follow-up at the time of data cut-off, years		
Range (min, max)	(0.0, 2.3)	(0.0, 2.5)
Mean (SD)	0.9 (0.5)	1.3 (0.7)
Person-years	545.5	613.1

DMT, disease-modifying therapy; **MS**, multiple sclerosis; **MSD3D**, Multiple Sclerosis Management System 3D; **N**, total number of patients; **n**, number of occurrences; **NTD**, NeuroTransData database; **SD**, standard deviation

- There were no differences in baseline characteristics between the cohorts

Table 2. Incidence Rate of Infections: ITT Exposure Definition

	Cladribine cohort N=606			Fingolimod cohort N=475			IR difference (95% CI)
	Total number of first severe events	Total time at risk (PY)	IR per 1000 PY (95% CI)	Total number of first severe events	Total time at risk (PY)	IR per 1000 PY (95% CI)	Cladribine cohort relative to fingolimod cohort
Severe infections	4	543	7.37 (2.76, 19.63)	4	611	6.55 (2.46, 17.44)	0.82 (-10.29, 12.95)
Herpes zoster	3	544	5.51 (1.78, 17.09)	2	611	3.27 (0.82, 13.09)	2.24 (-6.98, 13.14)
Opportunistic infections	0	546	0 (NA)	1	612	1.63 (0.23, 11.60)	-1.63 (-9.20, 5.37)

CI, confidence interval; **IR**, incidence rate; **ITT**, intention-to-treat; **N**, total number of patients; **n**, number of occurrences; **NA**, not applicable; **PML**, progressive multifocal leukoencephalopathy; **PY**, patient-years; **TB**, tuberculosis

- There were no events of PML or TB recorded. No recurrent events were observed.

Table 3. Incidence Rate of Infections: 6-month As-treated Exposure Definition (Sensitivity Analysis)

	Cladribine cohort N=623			Fingolimod cohort N=475			IR difference (95% CI)
	Total number of first severe events	Total time at risk (PY)	IR per 1000 PY (95% CI)	Total number of first severe events	Total time at risk (PY)	IR per 1000 PY (95% CI)	Cladribine cohort relative to fingolimod cohort
Severe infections	4	553	7.23 (2.71, 19.26)	4	536	7.46 (2.80, 19.88)	-0.23 (-12.64, 11.88)
Herpes zoster	3	555	5.41 (1.74, 16.76)	2	536	3.73 (0.93, 14.92)	1.68 (-8.65, 12.47)
Opportunistic infections	0	555	0 (NA)	1	538	1.86 (0.26, 13.20)	-1.86 (-10.46, 5.03)

*Defined as ITT with patient follow-up time censored at 6 (or 12) months after first discontinuation or switch (only the first treatment episode is considered). **CI**, confidence interval; **IR**, incidence rate; **ITT**, intention-to-treat; **N**, total number of patients; **n**, number of occurrences; **NA,** not applicable; **PML**, progressive multifocal leukoencephalopathy; **PY**, patient-years; **TB**, tuberculosis

- There were no events of PML or TB recorded. No recurrent events were observed. Similar results were obtained using the 12-month as-treated* exposure definition.

Table 4. Incidence Rate of Severe Lymphopenia: As-treated Exposure Definition

	Cladribine cohort N=349			
	Number of patients	Total number of first severe events	Total time at risk (PY)	IR per 1000 PY (95% CI)
6 months as-treated	349	19	298	63.86 (40.73, 100.12)
12 months as-treated (sensitivity analysis)	346	19	297	63.97 (40.80, 100.29)

CI, confidence interval; **IR**, incidence rate; **PY**, patient-years

- No recurrent events were observed.

REFERENCE
1. Cook S, et al. *Mult Scler Relat Disord*. 2019;29:157-167. 2. Leist T, et al. *Mult Scler Relat Disord*. 2020;46:102572.

Disclosures: HB's Institution (Monash University) received compensation for consulting, talks, and advisory/steering board activities from Alfred Health, Biogen, Genzyme, Merck, and Novartis; research support from Biogen, Merck, MS Research Australia, National Health and Medical Research (Australia), Novartis, the Oxford Health Policy Forum, and Roche. Personal compensation for steering group activities from Merck and Oxford Health Policy Forum. **JH** has received honoraria for serving on advisory boards for Biogen, Bristol-Myers-Squibb, Merck, Novartis, Sandoz and Sanofi-Genzyme, and speaker's fees from Bayer, Biogen, Merck, Novartis, Sanofi-Genzyme, and Teva. He has served as P.I. for projects, or received unrestricted research support from Bayer, Biogen, Merck, Novartis, Sanofi-Genzyme, and Teva. His MS research is funded by the Swedish Research Council and the Swedish Brain foundation. **JS** and **IB** are employees of IQVIA, a contract research organization that performs commissioned pharmacoepidemiological studies for several pharmaceutical companies. **MS-H** has served on scientific advisory boards for Biogen, Celgene (BMS), Merck, Sanofi, and Roche, and has received honoraria for lecturing from Biogen, Merck, Sanofi, and Teva, and has received research support and support for congress participation from Biogen, Merck, Novartis, and Roche. **AA** is an employee or EMD Serono Research and Development Institute, Inc., Billerica, MA, USA (an affiliate of Merck KGaA). **TZ** has received grants and personal fees from Almirall, Bayer, Biogen, Celgene (BMS), Merck, Novartis, Roche, Sanofi, and Teva. **JK** has received speaker fees, research support, travel support, and/or served on advisory boards by Swiss MS Society, Swiss National Research Foundation (320030_189140/1), University of Basel, Progressive MS Alliance, Bayer, Biogen, Celgene (BMS), Merck, Novartis, Roche, and Sanofi. **MM** has served on scientific advisory boards and served as consultant for, received support for congress participation or received speaker honoraria from AbbVie, Alexion (Janssen/J&J), Biogen, Merck, Roche, and Sanofi. **SW** has received honoraria for serving on advisory boards for Biogen and Sanofi-Genzyme, speaker fees from Biogen and Novartis, and research support from Biogen and Novartis. **MS** is an employee of Merck Healthcare KGaA, Darmstadt, Germany.

Medical writing assistance was provided by Joseph Ward of inScience Communications, Springer Healthcare Ltd, UK, and was funded by Merck Healthcare KGaA, Darmstadt, Germany. CLARION study: EU PAS Register No. EUPAS24484.

Presented at ECTRIMS 2021 Virtual Congress | 13–15 October

This study was sponsored by Merck (CrossRef Funder ID: 10.13039/100009945)