DXT27

Integrated Lymphopenia Analysis in Younger and Older Patients with Multiple Sclerosis Treated with Cladribine Tablets

G. Giovannoni,[1] P.K. Coyle,[2] P. Vermersch,[3] B. Walker,[4] J. Aldridge,[5] A. Nolting,[6] S. Syed,[5] A. Galazka,[7] D.L. Jones,[8] C. Lemieux,[9] T.P. Leist[9]

[1]Blizard Institute of Cell and Molecular Science, London, UK; [2]Department of Neurology, Stony Brook University, Stony Brook, NY, USA; [3]Université de Lille, Lille, France; [4]Duke University School of Medicine, Durham, NC, USA; [5]EMD Serono Research & Development Institute, Inc., Billerica, MA, USA, an affiliate of Merck KGaA, Darmstadt, Germany; [6]Merck KGaA, Darmstadt, Germany; [7]Merck, Aubonne, Switzerland, an affiliate of Merck KGaA, Darmstadt, Germany; [8]EMD Serono, Inc., Rockland, MA, USA, an affiliate of Merck KGaA, Darmstadt, Germany; [9]EMD Inc., Mississauga, ON, Canada, an affiliate of Merck KGaA, Darmstadt, Germany; [10]Jefferson University Hospital, Philadelphia, PA, USA

GET POSTER PDF
Copies of this poster obtained through QR (Quick Response) code are for personal use only and may not be reproduced without written permission of the authors.

CONCLUSIONS

- Changes in absolute lymphocyte count in patients treated with cladribine tablets 3.5 mg/kg in the Phase 3 CLARITY, CLARITY EXT, and ORACLE-MS studies, including those followed up in the PREMIERE registry, were similar in older and younger patients (age ≤50 and >50) relative to baseline levels during two years of active treatment
- Recovery time from Grade ≥3 lymphopenia following cladribine tablets 3.5 mg/kg treatment to Grade ≤2 lymphopenia was also similar between younger and older age groups
- Although there are anticipated changes in the immune system as patients age, this exploratory analysis found that older and younger patients treated with cladribine tablets had similar kinetics of lymphocyte reduction and recovery. However, these results should be interpreted with caution as the number of patients were lower in the aged >50 group versus ≤50 group (110 vs. 813)

INTRODUCTION

- Physiological aging is associated with a decline in immune system function[1]
- Cladribine tablets 10 mg (3.5 mg/kg cumulative dose over 2 years) are approved in >70 countries for various indications related to relapsing forms of MS
  - During the 96-week, Phase 3 CLARITY study, cladribine tablets were administered at 0.875 mg/kg per week in Weeks 1 and 5 of treatment Year 1, followed by Weeks 48 and 52 (the two treatment weeks in Year 2). In CLARITY, dosing in Year 2 occurred irrespective of the lymphocyte count at the end of Year 1; however, in clinical practice, the Year 2 dose can be delayed for up to six months to allow for recovery of ALC[2,3]
- Due to its mechanism of action, lymphopenia is expected in patients treated with cladribine tablets which preferentially reduce B and T lymphocyte counts[4]
- As the immune system undergoes changes with aging, it is not currently well understood whether the impact of cladribine tablets on lymphocyte counts differs in younger versus older patients

OBJECTIVES

- This *post hoc* analysis examined changes in lymphocyte levels following treatment with cladribine tablets 3.5 mg/kg or placebo in patients by baseline age ≤50 and >50 years who were enrolled in the Phase 3 CLARITY, CLARITY EXT, or ORACLE-MS studies, and participated in long-term follow-up in the PREMIERE registry

METHODS

- Combined data from patients treated with cladribine tablets 3.5 mg/kg (i.e., the monotherapy oral cohort) or placebo in two years of Phase 3 studies (CLARITY, CLARITY EXT, and ORACLE-MS),[2,5,6] including long-term follow-up data from the PREMIERE registry,[7] on levels of ALC, incidence of Grade ≥3 lymphopenia, and time to recovery from severe lymphopenia were analyzed by baseline age group (≤50 and >50 years)
  - Both CLARITY and ORACLE-MS studies evaluated the efficacy and safety of cladribine tablets 3.5 mg/kg versus placebo[2,6]
  - The CLARITY EXT study investigated long-term safety and efficacy of cladribine tablets 3.5 mg/kg versus placebo in eligible patients who completed CLARITY and were then re-randomized to placebo or additional cladribine tablets 3.5 mg/kg treatment[5]
  - The PREMIERE registry was a long-term observational safety study of patients who participated in the Phase 3 studies of cladribine tablets[7]
- Severity of lymphopenia was determined in accordance with the NCI CTCAE v3.0 toxicity grading system
- All analyses were performed using SAS® software version 9.4 or higher

RESULTS

Patients

- This analysis was carried out in 1564 patients (**Table 1**)

RESULTS (cont.)

Table 1. Demographics and Disease Characteristics of Patients in the ≤50 and >50 Years Age Groups at Entry into CLARITY/ORACLE-MS

	Age ≤50		Age >50	
	Placebo (N=566)	Cladribine tablets 3.5 mg/kg (N=813)	Placebo (N=75)	Cladribine tablets 3.5 mg/kg (N=110)
Age (years), mean (SD)	34.9 (8.0)	34.7 (8.4)	54.3 (3.1)	54.6 (3.7)
Female, n (%)	367 (64.8)	531 (65.3)	57 (76.0)	81 (73.6)
Disease duration (years), mean (SD)	7.91 (6.46)[a]	7.84 (5.82)[a]	14.31 (9.53)[a]	14.54 (10.20)[a]
Prior use of DMDs, n (%)	116 (20.5)	163 (20.0)	15 (20.0)	21 (19.1)
Relapse number at baseline, n (%)				
0	201 (35.5)	382 (47.0)	7 (9.3)	37 (33.6)
1	254 (44.9)	305 (37.5)	52 (69.3)	58 (52.7)
2	94 (16.6)	104 (12.8)	16 (21.3)	12 (10.9)
≥3	17 (3.0)	22 (2.7)	0	3 (2.7)
EDSS score, mean (SD)	2.41 (1.29)	2.43 (1.33)	3.39 (1.30)	3.64 (1.41)
Number of T1 Gd+ lesions, mean (SD)	0.9 (2.3)[b]	1.2 (3.4)[c]	0.3 (0.9)[d]	0.3 (1.0)
Patients with 0 or ≥1 T1 Gd+ lesions, n (%)				
0	377 (66.7)[b]	524 (64.5)[c]	62 (83.8)[d]	95 (86.4)
≥1	188 (33.3)[b]	288 (35.5)[c]	12 (16.2)[d]	15 (13.6)
Number of T2 lesions, mean (SD)	27.7 (22.0)[b]	30.1 (22.3)[c]	21.9 (14.0)[e]	26.2 (13.3)
Patients with <9 or ≥9 T2 lesions, n (%)				
<9	80 (14.2)[b]	104 (12.8)[c]	11 (15.1)[e]	6 (5.5)
≥9	485 (85.8)[b]	708 (87.2)[c]	62 (84.9)[e]	104 (94.5)
Volume of T2 lesions (cm³), mean (SD)	10.6 (12.2)[b]	11.9 (14.0)[c]	12.8 (12.2)[e]	16.3 (18.8)

[a]Disease duration is defined as the time since first attack; it is not applicable to subjects from the ORACLE-MS study
Percentages calculated based on [b]n=565, [c]n=812, [d]n=74 and [e]n=73 subjects due to missing data

Absolute Lymphocyte Count

- In both age groups, the nadir for ALC occurred soon after completing the second treatment week of each treatment year of cladribine tablets, for the cladribine tablets 3.5 mg/kg group, with ALC gradually increasing thereafter to above the lower limit of normal by the end of each year in most patients (**Figure 1, Table 2**)

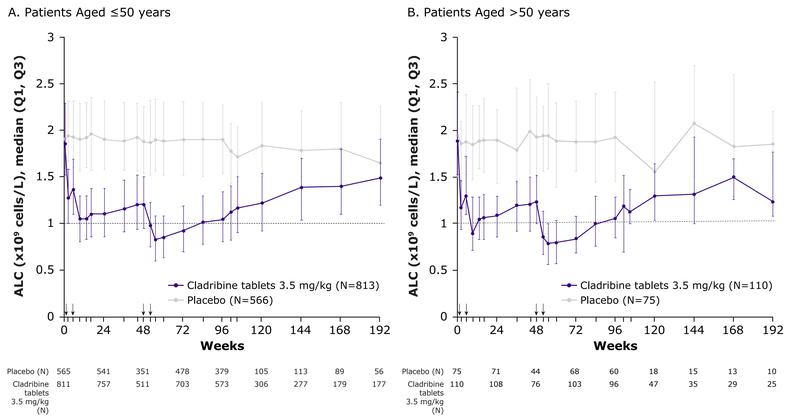
Table 2. Nadir and End-of-Year Recovery of ALC in Years 1 and 2 by Age Group

ALC (x10⁹/L), median (Q1, Q3)	Age ≤50		Age >50	
	Placebo (N=566)	Cladribine tablets 3.5 mg/kg (N=813)	Placebo (N=75)	Cladribine tablets 3.5 mg/kg (N=110)
Baseline				
n	565	811	75	110
ALC	1.91 (1.57, 2.33)	1.86 (1.52, 2.29)	1.95 (1.50, 2.31)	1.89 (1.53, 2.41)
Year 1 post dose				
Week 9[a,c], n	535	766	72	107
ALC	1.90 (1.56, 2.29)	1.05 (0.80, 1.30)	1.85 (1.48, 2.27)	0.90 (0.72, 1.29)
% change vs. baseline	−0.5%	−43.5%	−5.1%	−52.4%
Week 48[b,c], n	351	511	44	76
ALC	1.87 (1.54, 2.25)	1.21 (0.95, 1.50)	1.93 (1.51, 2.36)	1.24 (1.0, 1.52)
% change vs. baseline	-2.1%	−34.9%	−1.0%	−34.4%
Year 2 post dose				
Week 55[a,c], n	251	478	29	60
ALC	1.90 (1.56, 2.33)	0.83 (0.60, 1.08)	1.95 (1.59, 2.50)	0.79 (0.57,1.0)
% change vs. baseline	−0.5%	−55.4%	0	−58.2%
Week 96[b,c], n	379	573	60	96
ALC	1.90 (1.54, 2.27)	1.04 (0.80, 1.34)	1.93 (1.46, 2.41)	1.06 (0.85, 1.29)
% change vs. baseline	−0.5%	−44.1%	−1.0%	−43.9%

Percentages calculated based on subjects with a valid measurement in the period
lower limit of normal = 1.0 x10⁹/L
[a]Nadir for ALC in patients treated with cladribine tablets 3.5 mg/kg; [b]Recovery of ALC in patients treated with cladribine tablets 3.5 mg/kg; [c]Week number represents from the start of the study

RESULTS (cont.)

Figure 1. Changes in ALC over Time from First Dose



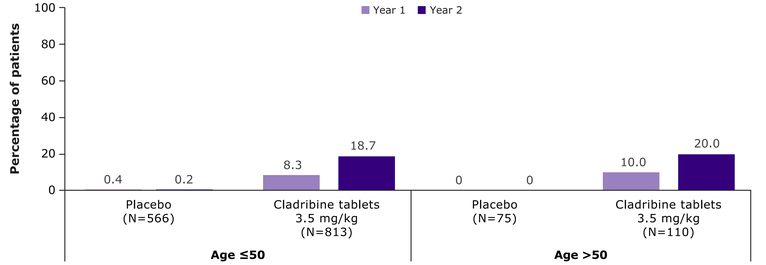
Weeks	0	24	48	72	96	120	144	168	192
Placebo (N)	565	541	351	478	379	105	113	89	56
Cladribine tablets 3.5 mg/kg (N)	811	757	511	703	573	306	277	179	177
Placebo (N)	75	71	44	68	60	18	15	13	10
Cladribine tablets 3.5 mg/kg (N)	110	108	76	103	96	47	35	29	25

Only visits with sample size ≥10 are displayed
Reference line corresponds to lower normal limit of 1.0 x10⁹/L
Arrows represent dosing of cladribine tablets at Weeks 1 and 5 (the two treatment weeks in study year 1) and Weeks 48 and 52 (the two treatment weeks in study year 2)

Severity of Lymphopenia

- Treatment with cladribine tablets 3.5 mg/kg was associated with Grade ≥3 lymphopenia in Years 1 and 2 of treatment at similar rates for the two age groups (**Figure 2**)

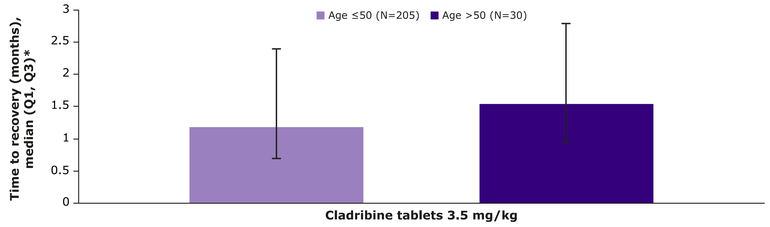
Figure 2. Grade ≥3 Lymphopenia during Year 1 and Year 2 by Treatment and Age Group



Time to Recovery

- Median time to recovery from Grade ≥3 to Grade ≤2 lymphopenia was 1.18 and 1.54 months for cladribine tablets 3.5 mg/kg-treated patients in the age ≤50 and >50 groups, respectively (**Figure 3**)

Figure 3. Time to Recovery from Grade ≥3 to Grade ≤2 Lymphopenia



*First lymphopenia only
Time to recovery = episode end date (or period end date if censored) - episode start date + 1 (in months)

Abbreviations: ALC, absolute lymphocyte count; **CTCAE**, Common Terminology Criteria for Adverse Events; **DMD**, disease-modifying drug; **EDSS**, Expanded Disability Status Scale; **EXT**, Extension; **Gd+**, gadolinium-enhancing; **MS**, multiple sclerosis; **NCI**, National Cancer Institute; **SD**, standard deviation

Acknowledgments: This study was sponsored by EMD Serono, Inc., USA, an affiliate of Merck KGaA, Darmstadt, Germany. Writing and editorial support for the preparation of this poster was provided by Ying Jean, PhD and Nick White of Ashfield Healthcare Communications (New York, NY, USA); funding was provided by EMD Serono, Inc., USA, an affiliate of Merck KGaA, Darmstadt, Germany. EMD Serono, Inc. reviewed and provided feedback on the poster. The authors had full control of the poster, and provided their final approval of all content.

Disclosures: GG has received speaker honoraria and consulting fees from Abbvie, Actelion, Atara Bio, Almirall, Bayer Schering Pharma, Biogen Idec, FivePrime, GlaxoSmithKline, GW Pharma, Merck & Co., Merck KGaA (Darmstadt, Germany), Pfizer Inc., Protein Discovery Laboratories, Teva Pharmaceutical Industries Ltd, Sanofi-Genzyme, UCB, Vertex Pharmaceuticals, Ironwood, and Novartis; and has received research support unrelated to this study from Biogen Idec, Merck & Co, Novartis, and Ironwood. **PKC** declares being an advisor or consultant for Accordant, Acorda Therapeutics, Bayer HealthCare, Biogen, Celgene, EMD Serono, Inc., USA (an affiliate of Merck KGaA, Darmstadt, Germany), Genentech/Roche, Genzyme/Sanofi, Novartis, and Teva Pharmaceuticals USA, and receiving grants for clinical research from Actelion, Alkermes, Genentech/Roche, MedDay, NINDS, and Novartis. **PV** has received honoraria or consulting fees from Biogen, Sanofi-Genzyme, Teva, Novartis, Merck KGaA (Darmstadt, Germany), Celgene, Roche and Almirall; and research support from Biogen, Sanofi-Genzyme, Teva, and Merck KGaA (Darmstadt, Germany). **BW** has received consulting fees from Biogen, Celgene, EMD Serono, Inc., USA (an affiliate of Merck KGaA, Darmstadt, Germany), Novartis, and Sanofi-Genzyme. **JA** is an employee of EMD Serono Research & Development Institute, Inc., Billerica, MA, USA, an affiliate of Merck KGaA, Darmstadt, Germany. **AN** is an employee of Merck KGaA, Darmstadt, Germany. **SS** is an employee of Sanofi USA, Cambridge, MA, USA; former employee of EMD Serono Research & Development Institute, Inc., Billerica, MA, USA; an affiliate of Merck KGaA, Darmstadt, Germany. **AG** is an employee of Merck, Aubonne, Switzerland, an affiliate of Merck KGaA, Darmstadt, Germany. **DLJ** is an employee of Apellis Pharmaceuticals, Waltham, MA, USA; former employee of EMD Serono, Inc., Rockland, MA, USA; an affiliate of Merck KGaA, Darmstadt, Germany. **CL** is an employee of EMD Inc. Mississauga, ON, Canada, an affiliate of Merck KGaA, Darmstadt, Germany. **TPL** received consultancy fees or clinical research grants from Alkermes, Bayer, Biogen, EMD Serono, Inc., USA (an affiliate of Merck KGaA, Darmstadt, Germany), Genentech, Genzyme, and Novartis. The CLARITY study: NCT00213135; The CLARITY Extension study: NCT00641537; The ORACLE-MS study: NCT00725985; The PREMIERE registry: NCT01013350

References: 1. Valiathan R, et al. *Scand J Immunol* 2016;83:255–66. **2.** Giovannoni G, et al. *N Engl J Med* 2010;362:416–26. **3.** Mavenclad [package insert]. Rockland, MA: EMD Serono, Inc.; 2019. **4.** Comi G, et al. *Mult Scler Relat Disord* 2019;29:168–74. **5.** Giovannoni G, et al. *Mult Scler* 2018;24:1594–604. **6.** Leist TP, et al. *Lancet Neurol* 2014;13:257–67. **7.** Cook S, et al. *Mult Scler Relat Disord* 2019;29:157–67.

Presented at the CMSC 2020 Virtual Poster/Platform Session, August 3, 2020