Poster No. 39

Lymphopenia Rates in CLARITY/CLARITY Extension are Unrelated to Disease Activity at Baseline

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INTRODUCTION

- In CLARITY, treatment with Cladribine Tablets showed strong efficacy in patients with relapsing multiple sclerosis (RMS) versus placebo over 2 years.[1]
- In CLARITY Extension, Cladribine Tablets produced durable clinical benefits.[2]
  - There was no difference in clinical efficacy between treatment with Cladribine Tablets in CLARITY followed by placebo in CLARITY Extension, vs. treatment with Cladribine Tablets in both CLARITY and CLARITY Extension.
- Patients with RMS and high disease activity (HDA) may be at higher risk of relapses and disability progression.
- In a *post hoc* analysis of CLARITY, patients with HDA had clinical and magnetic resonance imaging responses to Cladribine Tablets 10 mg (3.5 mg/kg cumulative dose over 2 years; referred to as Cladribine Tablets 3.5 mg/kg) that were generally better than, or comparable with, the overall CLARITY population.[3]
- Lymphopenia is an anticipated side effect of cladribine treatment due to its pharmacological properties leading to selective depletion of lymphocytes, as observed in CLARITY and CLARITY Extension.[1,2]
- While there does not appear to be a direct link between lymphocyte count reduction and clinical or MRI outcomes, it is relevant to investigate whether HDA patients are more likely to experience lower lymphocyte counts.

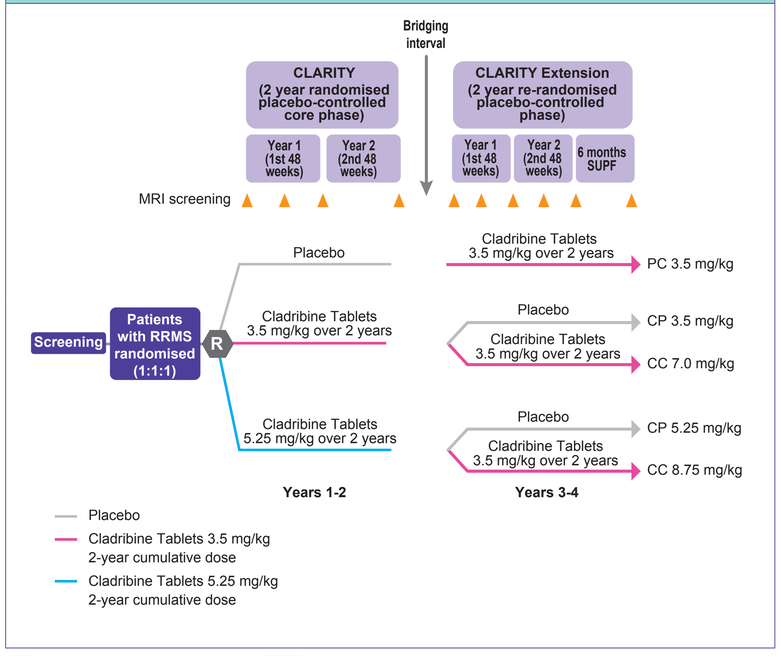
OBJECTIVE

- To determine the rate of lymphopenia in patients with HDA in the CLARITY/CLARITY Extension studies in patients receiving Cladribine Tablets 3.5 mg/kg in CLARITY and either Cladribine Tablets 3.5 mg/kg or placebo in CLARITY Extension.

METHODS

- In this *post hoc* analysis, patients exposed to Cladribine Tablets 3.5 mg/kg in CLARITY or CLARITY Extension in Years 1 and 2 only are referred to as the CT 3.5 group (n = 685) and a subgroup of these patients who received further courses of Cladribine Tablets 3.5 mg/kg in Years 3 and 4 are referred to as the CT 7.0 group (n = 186) (see **Figure 1** for study design).

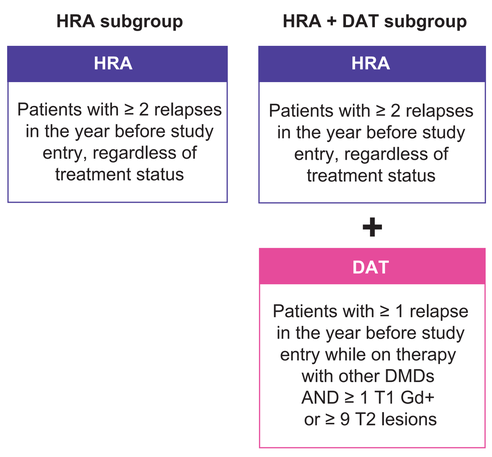
Figure 1. CLARITY/CLARITY Extension Study Design



MRI, magnetic resonance imaging; **RRMS**, relapsing remitting multiple sclerosis.

- Two overlapping sets of criteria (**Figure 2**) were applied in the analysis of baseline disease characteristics to subdivide patients into HDA groups based upon:
  1. High relapse activity (HRA), defined as ≥ 2 relapses in the year before study entry whether on disease modifying drug (DMD) treatment or not.
  2. HRA + disease activity on treatment (DAT) defined as ≥ 1 relapse in the year before study entry while on therapy with other DMDs AND ≥ 1 T1 gadolinium-enhancing or ≥ 9 T2 lesions.

Figure 2. Definitions of High Disease Activity



NB These definitions are not exclusive and include a large overlap of patients.
DMD, disease modifying drug; **Gd+**, Gadolinium-enhancing; **HRA**, high relapse activity; **HRA+DAT**, high relapse activity plus disease activity on treatment.

- Lymphopenia in HDA and non-HDA subgroups was analysed based on the Adverse Event of Special Interest (AESI) lymphopenia (all Medical Dictionary for Regulatory Activities [MedDRA] preferred terms describing a drop in lymphocytes) and on laboratory data for absolute lymphocyte count (ALC) across CLARITY and CLARITY Ext.

RESULTS

Lymphopenia based on adverse event reporting

- In the CT 3.5 group, the incidence rates of AESI lymphopenia were similar for the two HDA subgroups and the corresponding HDA and non-HDA subgroups (**Table 1**).
- In CT 3.5 at Year 2, AESIs/100 patient-years were similar in the HRA (n = 196) and HRA+DAT (n = 219) subgroups (11.50 and 13.09 respectively) and similar between corresponding non-HDA groups (14.08 [n = 489] and 13.46 [n = 466]).
- In CT 7.0 at Year 4, rates were approximately double the CT 3.5 at Year 2, but not different between HDA and non-HDA subgroups.
- There was a low rate of serious AESI lymphopenia in the CT 3.5 HRA and non-HRA groups and no incidences in the CT 7.0 HRA and non-HRA groups (**Table 1**).

Table 1. AESI Lymphopenia for HDA and Corresponding Non-HDA Subgroups Over 2 years*

	HRA		Non-HRA	
	CT 3.5 n = 196	**CT 7.0 n = 51**	**CT 3.5 n = 489**	**CT 7.0 n = 135**
Any AESI lymphopenia	47 (**11.50**)	19 (**23.64**)	144 (**14.08**)	55 (**26.68**)
Serious AESI lymphopenia	2 (**0.39**)	0	2 (**0.15**)	0
	HRA+DAT		**Non-HRA+DAT**	
	CT 3.5 n = 219	**CT 7.0 n = 56**	**CT 3.5 n = 466**	**CT 7.0 n = 130**
Any AESI lymphopenia	58 (**13.09**)	20 (**21.78**)	133 (**13.46**)	54 (**27.74**)
Serious AESI lymphopenia	2 (**0.35**)	0	2 (**0.16**)	0

Data shown are number of patients (**Adjusted AESI per 100 patient years**).
*Data reported for 2 years of active treatment (CT 3.5) or 2 years of additional active treatment (CT 7.0).
AESI Lymphopenia from AE is a custom query generated as a subset from MedDRA by using all preferred terms which describe drop of lymphocytes.
AE, adverse event; **AESI**, Adverse event of special interest; **CT 3.5**, Cladribine Tablets 3.5 mg/kg; **CT 7.0**, Cladribine Tablets 7.0 mg/kg; **HDA**, high disease activity; **HRA**, high relapse; **HRA+DAT**, high relapse activity plus disease activity on treatment; **MedDRA**, Medical Dictionary for Regulatory Activities.

Lymphopenia based on laboratory data

- Baseline median (minimum, maximum) absolute lymphocyte count (ALC) (×10^9/L) in the overall CT 3.5 population was 1.86 (0.60, 5.30).
- Median ALC nadir (×10^9/L) for HRA and HRA+DAT CT 3.5 patients at Year 2 were 0.71 and 0.70 respectively; median ALC nadirs were 0.65 in both corresponding non-HDA subgroups (**Table 2**).

Table 2. Absolute Lymphocyte Count Nadirs (×10^9/L) for HDA and Corresponding Non-HDA Subgroups

	HRA		Non-HRA	
	CT 3.5 n = 196	**CT 7.0 n = 51**	**CT 3.5 n = 489**	**CT 7.0 n = 135**
Year 1, Median (Min, Max)	0.82 (0.3, 2.7) n = 194	-	0.83 (0.2, 2.3) n = 489	-
Year 2, Median (Min, Max)	0.71 (0.2, 1.9) n = 175	-	0.65 (0.2, 2.1) n = 443	-
Year 3, Median (Min, Max)	-	0.70 (0.2, 1.4) n = 51	-	0.62 (0.2, 1.6) n = 135
Year 4, Median (Min, Max)	-	0.66 (0.2, 1.3) n = 42	-	0.56 (0.2, 1.4) n = 110
	HRA+DAT		**Non-HRA+DAT**	
	CT 3.5 n = 219	**CT 7.0 n = 56**	**CT 3.5 n = 466**	**CT 7.0 n = 130**
Year 1, Median (Min, Max)	0.82 (0.3, 2.7) n = 217	-	0.83 (0.2, 2.3) n = 466	-
Year 2, Median (Min, Max)	0.70 (0.2, 1.9) n = 197	-	0.65 (0.2, 2.1) n = 421	-
Year 3, Median (Min, Max)	-	0.70 (0.2, 1.4) n = 56	-	0.61 (0.2, 1.6) n = 130
Year 4, Median (Min, Max)	-	0.66 (0.2, 1.3) n = 46	-	0.57 (0.2, 1.4) n = 106

CT 3.5, Cladribine Tablets 3.5 mg/kg; **CT 7.0**, Cladribine Tablets 7.0 mg/kg; **HDA**, high disease activity; **HRA**, high relapse; **HRA+DAT**, high relapse activity plus disease activity on treatment; **Max**, maximum; **Min**, minimum.

- A similar pattern was seen in the CT 7.0 group at Year 4, but with lower nadirs than for CT 3.5 at Year 2. However, it should be noted that this difference is not profound and that patient numbers in the CT 7.0 group were lower than in the CT 3.5 group.
- There were only small differences in time to ALC nadir between HDA subgroups (**Table 3**).

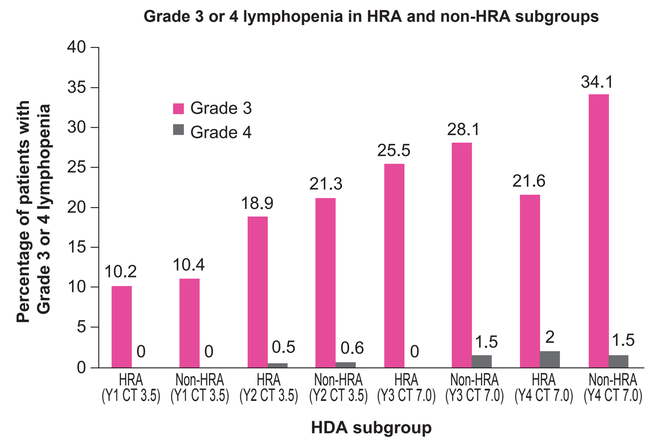
Table 3. Time to Absolute Lymphocyte Count Nadirs (Days) for HDA and Corresponding Non-HDA Subgroups

	HRA		Non-HRA	
	CT 3.5 n = 196	**CT 7.0 n = 51**	**CT 3.5 n = 489**	**CT 7.0 n = 135**
Year 1, Median (Min, Max)	105.0 (7, 345) n = 190	-	86.0 (6, 381) n = 484	-
Year 2, Median (Min, Max)	85.0 (23, 608) n = 166	-	84.0 (8, 884) n = 437	-
Year 3, Median (Min, Max)	-	57.0 (6, 302) n = 51	-	83.0 (6, 335) n = 133
Year 4, Median (Min, Max)	-	85.0 (29, 225) n = 42	-	76.0 (23, 337) n = 109
	HRA+DAT		**Non-HRA+DAT**	
	CT 3.5 n = 219	**CT 7.0 n = 56**	**CT 3.5 n = 466**	**CT 7.0 n = 130**
Year 1, Median (Min, Max)	104.0 (7, 345) n = 213	-	86.0 (6, 381) n = 461	-
Year 2, Median (Min, Max)	85.0 (23, 608) n = 188	-	84.0 (8, 884) n = 415	-
Year 3, Median (Min, Max)	-	57.0 (6, 302) n = 55	-	83.0 (6, 335) n = 129
Year 4, Median (Min, Max)	-	80.0 (29, 225) n = 46	-	77.0 (23, 337) n = 105

CT 3.5, Cladribine Tablets 3.5 mg/kg; **CT 7.0**, Cladribine Tablets 7.0 mg/kg; **HDA**, high disease activity; **HRA**, high relapse; **HRA+DAT**, high relapse activity plus disease activity on treatment; **Max**, maximum; **Min**, minimum.

- For the CT 3.5 group, incidence of Grade 3 lymphopenia was similar or numerically lower in the HDA subgroups compared with non-HDA subgroups (**Figure 3**).
- In CT 7.0 at Year 4, Grade 3 lymphopenia incidence was lower in the HDA than the non-HDA subgroups.
- Overall, Grade 3 lymphopenia incidence was lower in CT 3.5 at Year 2 than for CT 7.0 at Year 4.
- Grade 4 lymphopenia incidence was low in all HDA and non-HDA subgroups.

Figure 3. Percentage of Patients with Grade 3 or 4 Lymphopenia for HDA and Corresponding Non-HDA Subgroups



Grade 3 lymphopenia < 500 cells/mm^3; Grade 4 lymphopenia < 200 cells/mm^3.
CT 3.5, Cladribine Tablets 3.5 mg/kg; **CT 7.0**, Cladribine Tablets 7.0 mg/kg; **HDA**, high disease activity; **HRA**, high relapse; **HRA+DAT**, high relapse activity plus disease activity on treatment.

CONCLUSIONS

- **There were no relevant differences between the HDA and non-HDA subgroups with regard to incidence of the AESI lymphopenia, ALC nadir, and time to ALC nadir.**
- **There were no relevant differences between the HRA and HRA+DAT subgroups with regard to incidence of the AESI lymphopenia and ALC nadir, suggesting that the inclusion of previously-treated patients did not change the risk and the severity of lymphopenia.**
  - **It should be noted, however, that DAT patients represented only a small proportion of additional HDA patients.**
- **Patients who received CT 3.5 mg/kg had a lower incidence of AESI lymphopenia than patients who received CT 7.0.**

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DISCLOSURES

SC: has received honoraria for lectures/consultations from Merck, Bayer HealthCare, Sanofi-Aventis, Neurology Reviews, Biogen Idec, Teva Pharmaceuticals, and Actinobac Biomed Inc.; has served on advisory boards for Bayer HealthCare, Merck, Actinobac Biomed, Teva Pharmaceuticals, and Biogen Idec; and received grant support from Bayer HealthCare. **GG**: has received speaker honoraria and consulting fees from Abbvie, Actelion, Atara Bio, Almirall, Bayer Schering Pharma, Biogen Idec FivePrime, GlaxoSmithKline, GW Pharma, Merck, 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, Novartis, and Ironwood. **PV**: has received honoraria or consulting fees from Biogen, Sanofi-Genzyme, Bayer, Novartis, Merck, Celgene, Roche and Almirall; and research support from Biogen, Sanofi-Genzyme, Bayer, and Merck. **PS-S**: has served on advisory boards for Biogen, Merck, Novartis, Teva, MedDay Pharmaceuticals, and GSK; on steering committees or independent data monitoring boards in trials sponsored by Merck, Teva, GSK, and Novartis; has received speaker honoraria from Biogen Idec, Merck, Teva, Sanofi-Aventis, Genzyme, and Novartis. His department has received research support from Biogen, Merck, Teva, Novartis, Roche, and Genzyme. **BK** and **EM**: are employees of Merck KGaA, Darmstadt, Germany.

The CLARITY study: NCT00213135
The CLARITY Extension study: NCT00641537

Cladribine Tablets are approved by the European Commission for the treatment of adult patients with highly active relapsing multiple sclerosis (MS) as defined by clinical or imaging features.

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