Poster No. 41

Sustained Efficacy in Relapsing Remitting Multiple Sclerosis Following Switch to Placebo Treatment from Cladribine Tablets in Patients with High Disease Activity at Baseline

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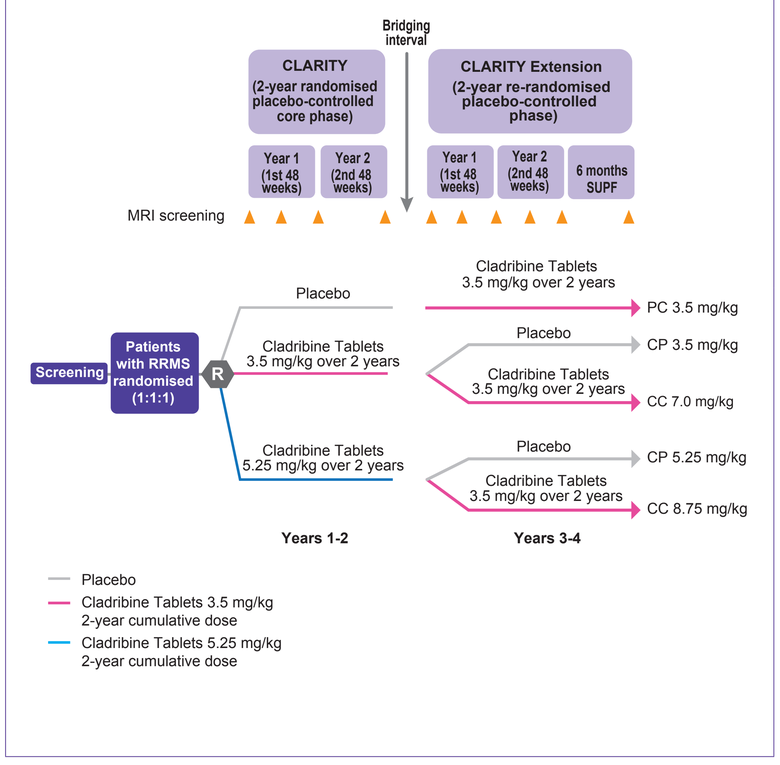
INTRODUCTION

- The Phase III CLARITY study in patients with relapsing remitting multiple sclerosis (RRMS) demonstrated that Cladribine Tablets 10 mg (3.5 mg/kg cumulative dose over 2 years; referred to as Cladribine Tablets 3.5 mg/kg), given as two short (4 or 5 days) weekly treatments annually over 2 years, significantly reduced relapse rates, disability progression and outcomes assessed by magnetic resonance imaging (MRI) versus placebo.[1]
- Patients completing CLARITY could enter the CLARITY Extension study (**Figure 1**), where they were re-randomised to Cladribine Tablets or placebo.
  - The effects of Cladribine Tablets were shown to be durable, as efficacy was sustained in years 3 and 4 in patients that received no further active treatment.[2]
- Patients with RRMS who show an increased rate of relapse or MRI activity can be described as having high disease activity (HDA) and are at higher risk of disease progression.[3]

Figure 1. CLARITY/CLARITY Extension Study Design



CC, Cladribine Tablets in CLARITY and in CLARITY Ext; **CP**, Cladribine Tablets in CLARITY and placebo in CLARITY Ext; **MRI**, magnetic resonance imaging; **PC**, placebo in CLARITY and Cladribine Tablets in CLARITY Ext; **RRMS**, relapsing-remitting multiple sclerosis; **SUPF**, supplementary follow-up.

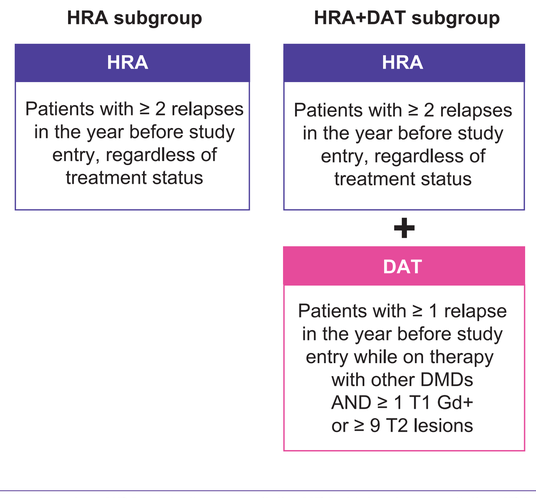
OBJECTIVE

- The aim of this *post hoc* analysis was to determine whether the clinical efficacy of Cladribine Tablets 3.5 mg/kg in CLARITY was sustained long-term in patients switched to placebo in CLARITY Extension (years 3 and 4), in a subgroup of patients with HDA at CLARITY study baseline.

METHODS

- The CLARITY study enrolled patients aged 18–65 years with a definite diagnosis of RRMS according to the McDonald criteria, including:[1]
  - ≥ 1 relapse in the 12 months before study entry, but no relapses within the 28 days before entry.
  - Neurological lesions detectable by MRI consistent with MS.
  - An Expanded Disability Status Scale (EDSS) score of 0–5.5.
- Patients were excluded if they had received a disease-modifying drug (DMD) within 3 months before study entry, or if treatment with > 1 DMD had failed.
- Patients randomised to Cladribine Tablets 3.5 mg/kg in CLARITY who then switched to placebo in CLARITY Extension were retrospectively analysed using two HDA definitions based on relapse history, prior treatment, and MRI characteristics.
- 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 patients with ≥ 2 relapses during the year before study entry, regardless of prior use of DMDs.
  2. HRA plus disease activity on treatment (HRA+DAT), defined as patients with ≥ 2 relapses in the year before study entry, regardless of prior use of DMDs, plus patients with ≥ 1 relapse in the year before study entry AND ≥ 1 T1 gadolinium (Gd+) or ≥ 9 T2 lesions while on DMD therapy.

Figure 2. Definitions of High Disease Activity



Gd+, Gadolinium-enhancing; **HDA**, high disease activity; **HRA**, high relapse activity; **HRA+DAT**, high relapse activity plus disease activity on treatment.

- The ability of these criteria to retrospectively identify patients with HDA, and the effects of Cladribine Tablets 3.5 mg/kg versus placebo on relapse rates and disability outcomes in these patient groups has been presented previously.[3]
- Clinical outcomes were analysed for patients randomised to CLARITY Extension who fulfilled HRA and HRA+DAT criteria at CLARITY baseline and who received Cladribine Tablets 3.5 mg/kg in CLARITY and placebo in CLARITY Extension.
- The CLARITY data are for assessments at the end of the 96-week double blind period. The CLARITY Extension data covers the 96-week double-blind period and the 6-month supplemental follow-up (including the gap between periods).

RESULTS

Patients

- A total of 98 patients received Cladribine Tablets 3.5 mg/kg in CLARITY and placebo in CLARITY Extension.
- Baseline demographics and disease characteristics at baseline of the CLARITY study are shown in **Table 1**.
- Of these 98 patients, 29 were retrospectively classified as HRA and 31 were classified as HRA+DAT.
  - Both HDA subgroups (HRA and HRA+DAT) had a lower mean age and a higher proportion of females compared with the corresponding non-HDA subgroups and the overall subgroup.
  - There was a higher proportion of patients with prior MD use in both HDA subgroups compared with the corresponding non-HDA sugroups.

Table 1. Patient Demographics and Disease Characteristics by HDA Definitions for Patients who Received Cladribine Tablets 3.5 mg/kg in CLARITY and Placebo in CLARITY Extension

	Overall N = 98	HRA n = 29	Non-HRA n = 69	HRA+DAT n = 31	Non-HRA+DAT n = 67
Age, years; mean (SD)	38.1 (10.6)	35.4 (11.2)	39.2 (10.3)	36.2 (11.3)	39.0 (10.3)
Female, %	68.4	75.9	65.2	74.2	65.7
Disease duration, years; mean (SD)	3.86 (4.68)	2.13 (3.07)	4.59 (5.05)	2.16 (2.97)	4.65 (5.12)
Prior use of DMDs, n (%)	18 (18.4)	7 (24.1)	11 (15.9)	9 (29.0)	9 (13.4)
Relapses in prior 12 months, n (%)					
0	0	0	0	0	0
1	69 (70.4)	0	69 (100)	2 (6.5)	67 (100)
2	20 (20.4)	20 (69.0)	0	20 (64.5)	0
≥ 3	9 (9.2)	9 (31.0)	0	9 (29.0)	0
EDSS score; mean (SD)	3.01 (1.35)	2.88 (1.53)	3.06 (1.27)	2.94 (1.50)	3.04 (1.28)
Number of T1 Gd+ lesions; mean (SD)	1.2 (2.6)	1.7 (2.9)	1.0 (2.4)	1.6 (2.8)	1.0 (2.5)
Number of T2 lesions; mean (SD)	28.4 (20.8)	33.0 (24.0)	26.5 (19.1)	32.2 (23.5)	26.7 (19.3)
T2 lesion volume; mean (SD)	18.35 (17.60)	18.42 (15.36)	18.32 (18.57)	18.06 (15.01)	18.48 (18.79)

DMD, disease modifying drug; **EDSS**, Expanded Disability Status Scale; **Gd+**, Gadolinium-enhancing; **HRA**, high relapse activity; **HRA+DAT**, high relapse activity plus disease activity on treatment; **SD**, standard deviation.
Data presented relate to baseline of the CLARITY study.

Sustained clinical efficacy from CLARITY to CLARITY Extension

- Clinical outcomes in CLARITY and at the end of CLARITY Extension were similar in the overall population randomised to Cladribine Tablets 3.5 mg/kg and in corresponding HDA subgroups (**Tables 2 and 3**).

Relapses

- At the end of CLARITY Extension, the annualised relapse rate (ARR) for qualifying relapses for the overall patient population who switched to placebo in CLARITY Extension from Cladribine Tablets 3.5 mg/kg in CLARITY was 0.15 (95% confidence interval [95% CI]; 0.11, 0.21). This was equal to or similar to the ARRs for HDA and non-HDA patients (**Tables 2 and 3**).
  - ARRs for HRA and non-HRA patients were 0.15 (95% CI; 0.08, 0.28) and 0.15 (95% CI; 0.10, 0.22), respectively (**Table 2**).
  - For HRA+DAT and non-HRA+DAT patients, ARRs were 0.14 (95% CI; 0.08, 0.26) and 0.15 (95% CI; 0.10, 0.22), respectively (**Table 3**).

Table 2. Outcomes for Patients Overall and Those Classified by HRA Status in CLARITY and CLARITY Extension

		Overall	HRA	Non-HRA
Cladribine Tablets 3.5 mg/kg in CLARITY	**N**	**573**	**130**	**303**
	ARR [adjusted]; (95% CI)	0.14 (0.12; 0.17)	0.16 (0.11; 0.22)	0.14 (0.11; 0.18)
	Proportion with 3-month EDSS progression, n (%)	62 (14.3)	12 (9.2)	50 (16.5)
	Proportion with 6-month EDSS progression, n (%)	56 (9.8)	6 (4.6)	33 (10.9)
Cladribine Tablets 3.5 mg/kg in CLARITY Placebo in CLARITY Extension	**N**	**98**	**29**	**69**
	ARR [adjusted]; (95% CI)	0.15 (0.11; 0.21)	0.15 (0.08; 0.28)	0.15 (0.10; 0.22)
	Proportion with 3-month EDSS progression, n (%)	18 (18.4)	4 (13.8)	14 (20.3)
	Proportion with 6-month EDSS progression, n (%)	13 (13.3)	4 (13.8)	9 (13.0)

N.B. These definitions are not exclusive; to a large extent, the subgroups comprise the same patients. **ARR**, annualised relapse rate; **CI**, confidence intervals; **DMD**, disease modifying drug; **EDSS**, Expanded Disability Status Scale; **HRA**, high relapse activity. The CLARITY data are for assessments at the end of the 96-week double blind period. The CLARITY Extension data cover the 96-week double-blind period and the 6-month supplemental follow-up (including the gap between periods).

EDSS Progression

- At the end of CLARITY Extension, numerically fewer patients in the HRA (13.8%) and HRA+DAT (12.9%) subgroups had confirmed 3-month EDSS progression relative to the non-HRA (20.3%), non-HRA+DAT (20.9%) and overall groups (18.4%) (**Table 2 and 3**).
- The proportions of patients with confirmed 6-month EDSS progression were similar in the HRA (13.8%), HRA+DAT (12.9%), non-HRA (13.0%), non-HRA+DAT (13.4%) and overall groups (13.3%) (**Table 2 and 3**).

Table 3. Outcomes for Patients Overall and Those Classified by HRA+DAT Status in CLARITY and CLARITY Extension

		Overall	HRA+DAT	Non-HRA+DAT
Cladribine Tablets 3.5 mg/kg in CLARITY	**N**	**573**	**140**	**293**
	ARR [adjusted]; (95% CI)	0.14 (0.12; 0.17)	0.16 (0.12; 0.22)	0.14 (0.11; 0.18)
	Proportion with 3-month EDSS progression, n (%)	62 (14.3)	12 (8.6)	50 (17.1)
	Proportion with 6-month EDSS progression, n (%)	56 (9.8)	6 (4.3)	33 (11.3)
Cladribine Tablets 3.5 mg/kg in CLARITY Placebo in CLARITY Extension	**N**	**98**	**31**	**67**
	ARR [adjusted]; (95% CI)	0.15 (0.11; 0.21)	0.14 (0.08; 0.26)	0.15 (0.10; 0.22)
	Proportion with 3-month EDSS progression, n (%)	18 (18.4)	4 (12.9)	14 (20.9)
	Proportion with 6-month EDSS progression, n (%)	13 (13.3)	4 (12.9)	9 (13.4)

N.B. These definitions are not exclusive; to a large extent, the subgroups comprise the same patients. **ARR**, annualised relapse rate; **CI**, confidence intervals; **DMD**, disease modifying drug; **EDSS**, Expanded Disability Status Scale; **HRA+DAT**, high relapse activity plus disease activity on treatment. The CLARITY data are for assessments at the end of the 96-week double blind period. The CLARITY Extension data cover the 96-week double-blind period and the 6-month supplemental follow-up (including the gap between periods).

CONCLUSIONS

- **At the end of CLARITY Extension, sustained clinical efficacy was observed both in the overall population and in HDA patients treated with Cladribine Tablets 3.5 mg/kg in CLARITY and placebo in CLARITY Extension.**
- **Fewer patients with HDA had 3-month confirmed EDSS progression throughout CLARITY and CLARITY Extension than patients without HDA at baseline.**
  - **It should be noted, however, that the subgroups used in this analysis represent a small number of patients and therefore these results should be viewed with caution.**

REFERENCES

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DISCLOSURES

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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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