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Reasons for and safety of treatment continuation with cladribine tablets (CladT) in year 5 – first interim analysis of the CLIP-5 study

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RESEARCH IN CONTEXT

1. **In patients with RMS, safety and effectiveness data following administration of cladribine tablets in year 5 were consistent with prior data from administration in years 1 and 2.**
2. **Treatment continuation with CladT has not induced new safety signals in comparison with the first treatment phase.**

INTRODUCTION

Cladribine tablets (CladT) are administered in two short treatment courses one year apart, followed by 2 treatment-free years.

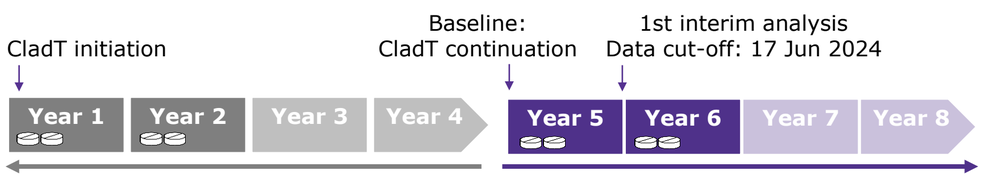
CLIP-5 is an ongoing non-interventional study (NIS) in Germany in patients with relapsing multiple sclerosis (RMS) who received the full dosage of CladT according to the SmPC in year 1 and 2 and are **continuing CladT therapy in year 5**.

Effectiveness and safety data are presented up to and including year 5 of treatment with CladT.

OBJECTIVES

This first interim analysis assesses reasons for treatment continuation with CladT, lymphocyte counts and safety data.

METHODS



Retrospective data collection included baseline characteristics, lymphocyte counts and occurrence of relapses at CladT initiation and at month 12, 24, 36, and 48 following CladT initiation.

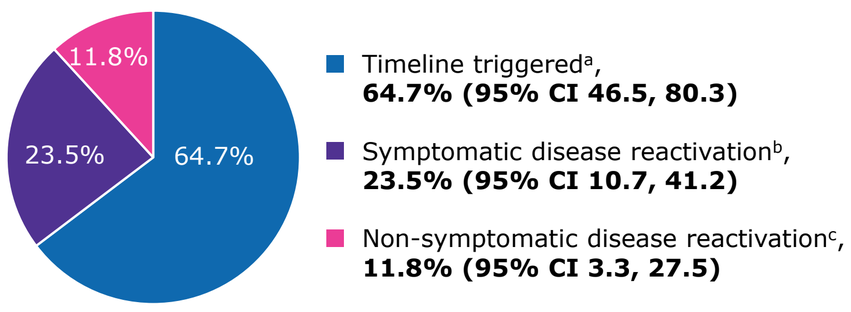
Prospective data collection included assessment of the primary reason for treatment continuation, AE, lymphocyte counts and occurrence of relapses at CladT continuation (baseline) and month 6 and 12 following CladT continuation.

RESULTS

- 85.3% Female
- Mean (±SD) age 43.0 ±11.9 years
- 97.1% RRMS
- 2.9% rSPMS

N=34

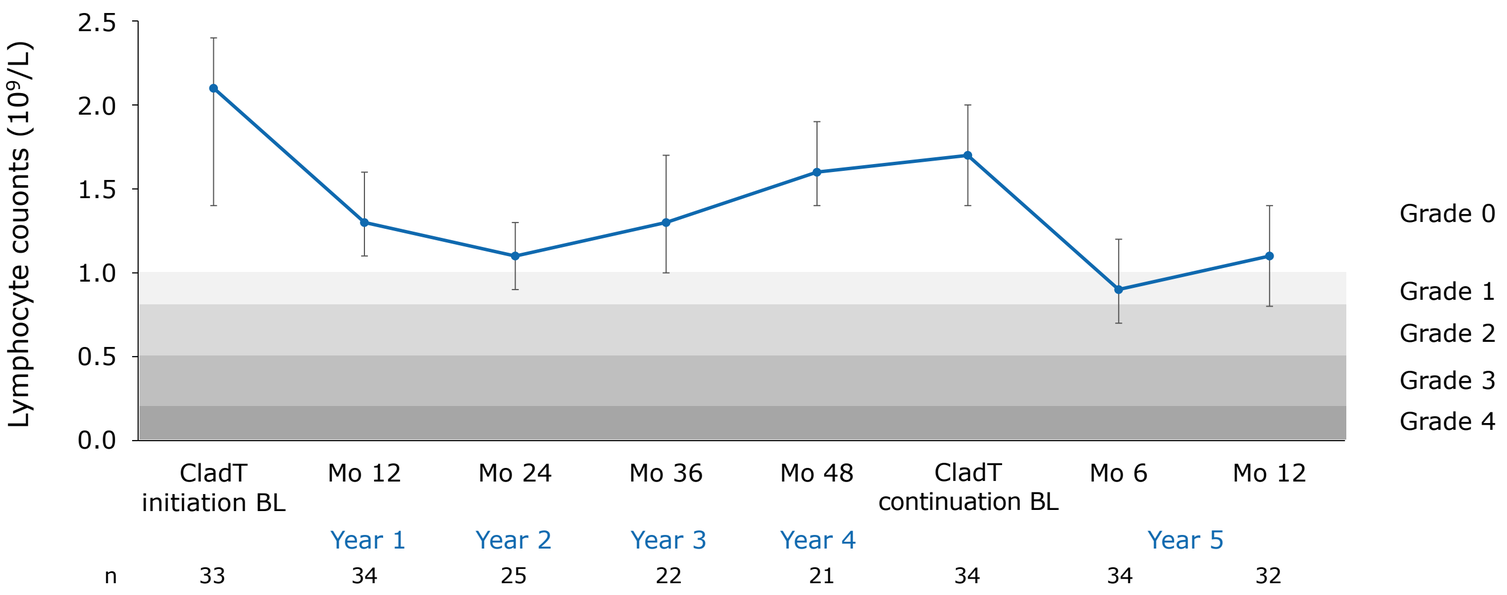
Figure 1. The primary reason for CladT continuation was timeline triggered



- Timeline triggered[a], **64.7% (95% CI 46.5, 80.3)**
- Symptomatic disease reactivation[b], **23.5% (95% CI 10.7, 41.2)**
- Non-symptomatic disease reactivation[c], **11.8% (95% CI 3.3, 27.5)**

N=34; [a]no specific signs of disease reactivation are assessed; the intention is to prolong/further extend the achieved disease control or to prevent disease reactivation; [b]clinically evaluated by EDSS; relapse rate; symptomatic parameters; [c]evaluated by MRI
CI, confidence interval; CladT, cladribine tablets; EDSS, Expanded Disability Status Scale; MRI, magnetic resonance imaging

Figure 2. The lymphocyte profile following CladT continuation is comparable to the profile following CladT initiation



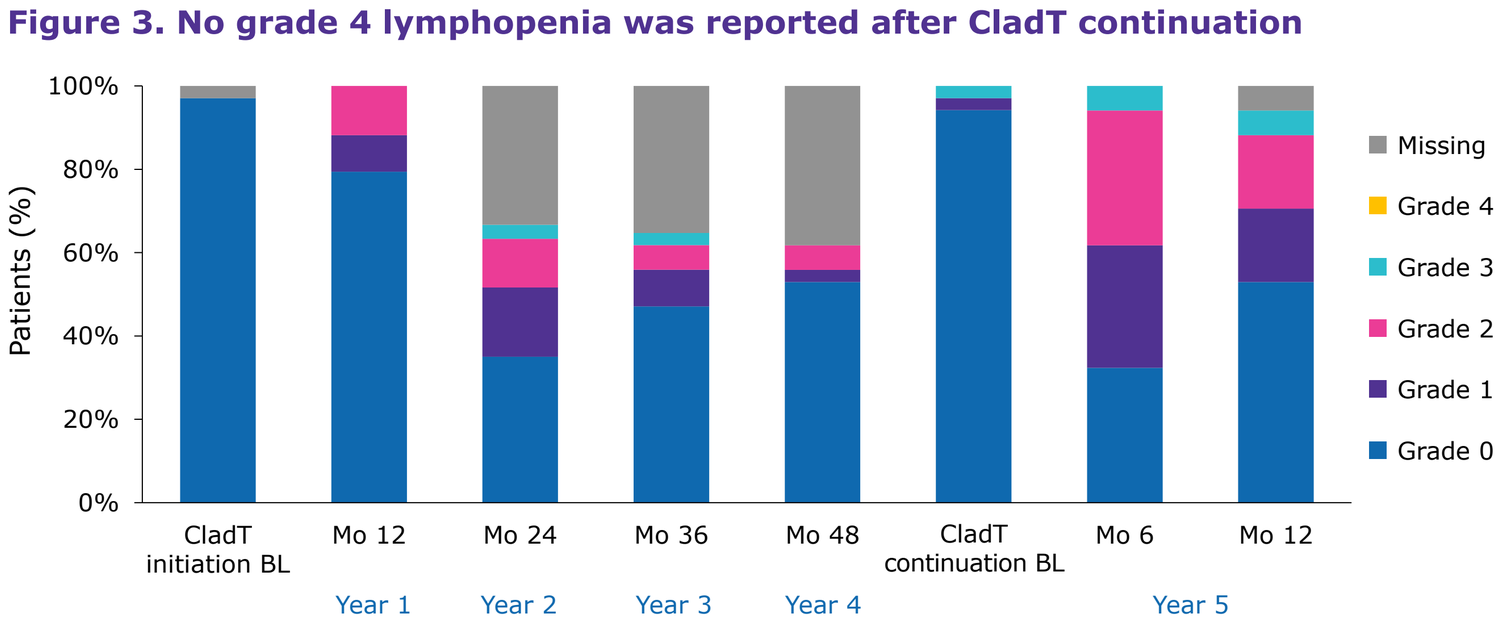
Data are presented as median. Bars represent Q1 and Q3. CladT, cladribine tablets, Mo, month

Table 1. Overview of adverse events reported in year 5

Adverse event, n (%)	N=34
Any TEAE	15 (44.1)
Mild	3 (8.8)
Moderate	7 (20.6)
Severe	5 (14.7)
Any study treatment related TEAE	13 (38.2)
Mild	4 (11.8)
Moderate	4 (11.8)
Severe	5 (14.7)
Any serious TEAE	2 (5.9)
Any related serious TEAE	1 (2.9)
Any TEAE leading to death	0 (0.0)
Any related TEAE leading to death	0 (0.0)

TEAE, treatment-emergent adverse events

Figure 3. No grade 4 lymphopenia was reported after CladT continuation



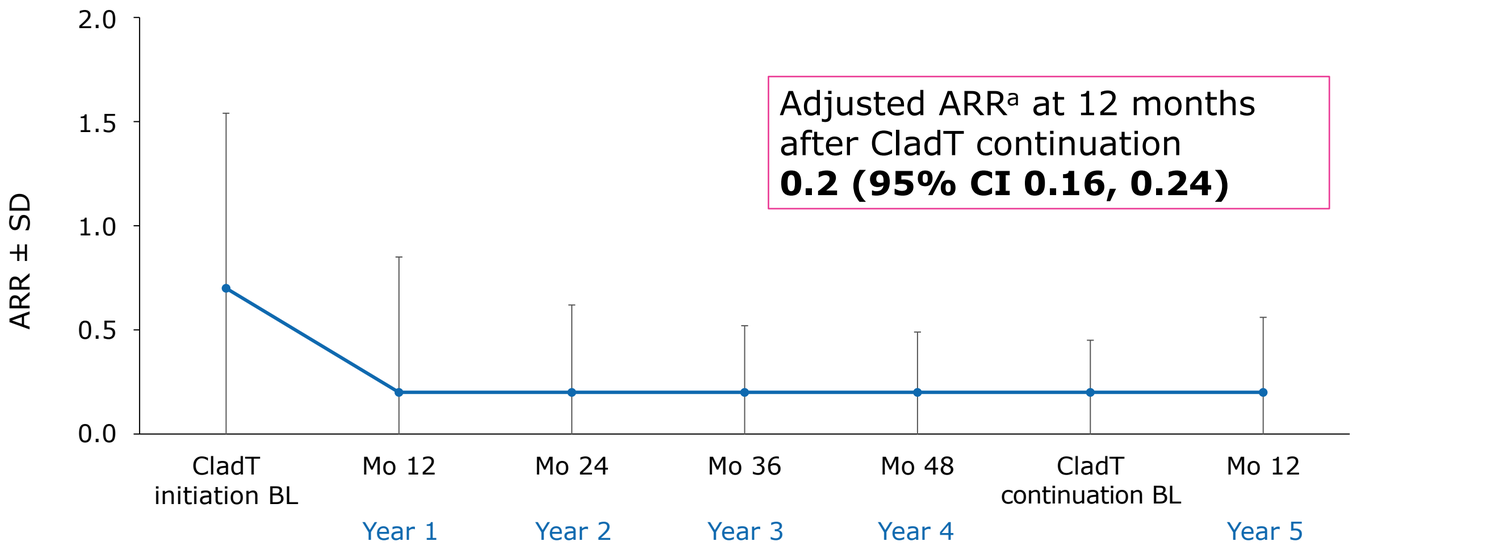
N=34; CladT, cladribine tablets

Table 2. Reported adverse events after CladT continuation

Adverse events (PT), n (%)	N=34
Subjects with at least one related TEAE	**13 (38.2)**
Lymphopenia	6 (17.6)
Nausea	2 (5.9)
Fatigue	1 (2.9)
COVID-19	1 (2.9)
Herpes zoster	1 (2.9)
Influenza	1 (2.9)
Oral herpes	1 (2.9)
Headache	2 (5.9)
Alopecia	2 (5.9)
Rash	1 (2.9)
Subjects with at least one serious related TEAE	**1 (2.9)**
Lymphopenia	1 (2.9)

TEAE, treatment-emergent adverse events

Figure 4. The relapse rate remained low throughout the study period



Adjusted ARR[a] at 12 months after CladT continuation
0.2 (95% CI 0.16, 0.24)

N=34; [a]The estimated Annual Relapse Rate is estimated with a Poisson regression model with count of patient-reported, clinician-confirmed relapses as dependent variable and and fixed effects for age (in years) and EDSS at Baseline [>3 vs. <=3 as reference]. The log of the duration of the treatment period in days is the offset variable in the model.
ARR, annualised relapse rate; CI, confidence interval; CladT, cladribine tablets; Mo, month; SD, standard deviation

- Median EDSS remained stable at 2.0 over the study period of 5 years.

CONCLUSIONS

- **The decision to continue with CladT therapy was made by most of the patients on a timeline basis and not due to acute clinical or paraclinical symptoms.**
- **Lymphopenia has been detected in line with the mechanism of action. No grade 4 lymphopenia has been reported.**

Concflicts of interest

CK received speaker honoraria and travel support from Biogen, Roche, Merck, Sanofi, BMS and research support Merck, Novartis; NR and AC declare that they have no conflicts of interest; JK received personal compensation for consulting as well as speaker honoraria from Bayer, Biogen, Bristol Myers Squibb, Grifols, Janssen, Merck Serono, Novartis, Roche, Sanofi Genzyme, Takeda and Teva; TW, BM and APF are employees of Merck or its affiliates.

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