October 2023.

Time to Qualifying Relapse by Previous Disease-Modifying Therapy Status in Patients with Relapsing Multiple Sclerosis Treated with Cladribine Tablets Over 2 Years in the CLARIFY-MS Study

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CONCLUSIONS

Overall, the number of qualifying relapses were low across pre-treatment naïve and DMT pre-treated patients treated with CladT during the CLARIFY-MS study

DMT pre-treated patients experienced similar benefits (in terms of relapses) to pre-treatment naïve patients after treatment with CladT

No specific prior DMT was associated with an increased risk of relapses with CladT

INTRODUCTION

- Relapses are the most common clinical manifestation of multiple sclerosis (MS). It is of high prognostic significance as incomplete remission of relapses may often result in residual disability[1]
- Relapse recurrence is an important parameter to assess treatment efficacy in MS and is influenced by the patient's disease status,[1] prior disease-modifying therapy (DMT) experience and by the type of previous DMTs used[2]
- Previous studies have shown that treatment with cladribine tablets (CladT) was associated with reduced frequency and severity of relapses versus placebo in people with relapsing MS (PwRMS)[3,4]
- In this *post-hoc* analysis of the data from the Phase IV CLARIFY-MS study, we investigated the effects of prior DMTs on the onset of relapses following CladT treatment in PwRMS (please refer **Supplementary Figure 1** for study design)

OBJECTIVE

To evaluate the onset of relapses based on prior DMT experience in PwRMS treated with CladT over 2 years in the CLARIFY-MS study

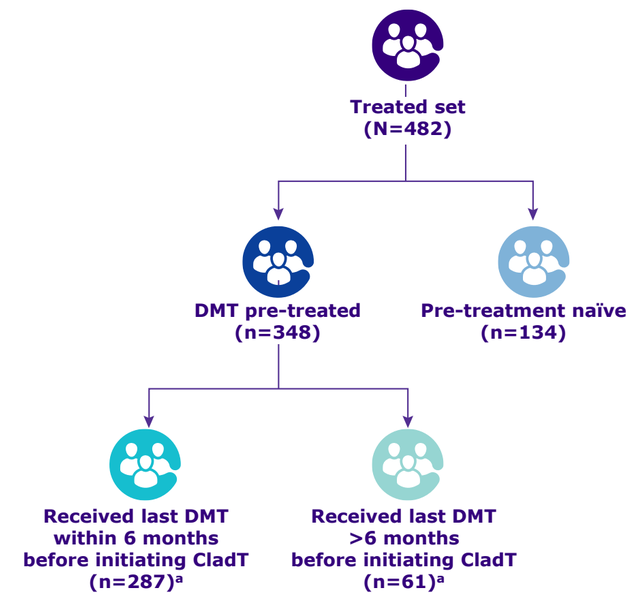
METHODS

Patients

Based on the prior DMT experience, patients were grouped as (**Figure 1; Supplementary Table 1**):

- **DMT pre-treated:** *those who received DMTs any time before initiating CladT treatment*
  - Based on the treatment history, they were further subgrouped as those who received last DMT:
    - within 6 months before initiating CladT and
    - >6 months before initiating CladT
- **Pre-treatment naïve:** *those who did not receive any DMTs before initiating CladT*

Figure 1: Patient Population Analysed



[a] Last DMT administered within or >6 months before CladT initiation include interferons, glatiramer acetate, fingolimod, teriflunomide, dimethyl fumarate, other DMTs.
CladT, cladribine tablets; **DMT**, disease-modifying therapy.

Outcomes Analysed	Statistics Applied
Time to first qualifying relapse by previous DMT use	Kaplan–Meier estimates[a]
Occurrence of time to qualifying relapse by previous DMT use	MCF[b]
ARR for qualifying relapses by previous DMT use and type of DMT	Poisson regression model[c]

[a] Survival curves, point estimates and percentiles with corresponding 2-sided 95% CIs.
[b] Estimates with 95% CIs and increase in MCF in each month. An MCF of 0.3 indicate patients have on average 0.3 relapses up to the respective point in time. This model includes all recurrent qualifying relapses.
[c] Model adjusted for age (in years) and Expanded Disability Status Scale scores at Baseline (>3 versus ≤3).
ARR, annualised relapse rate; **CI,** confidence interval; **DMT,** disease-modifying therapy; **MCF,** mean cumulative function

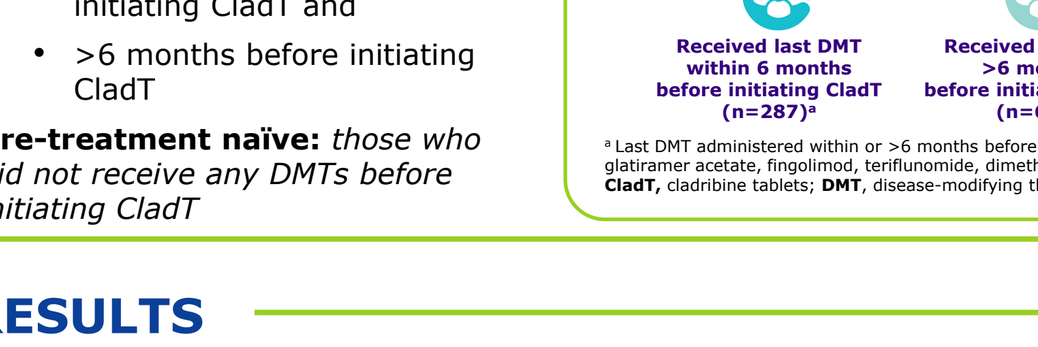
RESULTS

- Patient demographics and baseline characteristics are presented in **Supplementary Table 2**

Time to First Qualifying Relapse and Occurrence of Qualifying Relapse

- The probability of patients experiencing a first qualifying relapse (**Figure 2**) and the estimate of cumulative relapses per patient (**Supplementary Figure 2**) was low after treatment with CladT; this was independent of whether the patients were treatment naïve or pre-treated with DMT within or >6 months before initiating CladT treatment
- In patients who received their last DMT within 6 months before initiating CladT, there were no notable differences between the previous DMTs in the time to first qualifying relapse (**Figure 3**) and the estimate of cumulative relapses per patient (**Supplementary Figure 3**). The highest point values were from patients previously treated with glatiramer acetate
  - Similar results were observed in patients who received their last DMT >6 months before initiating CladT (**Supplementary Figures 4 and 5**)

Figure 2: Time to First Qualifying Relapse by Prior DMT Experience

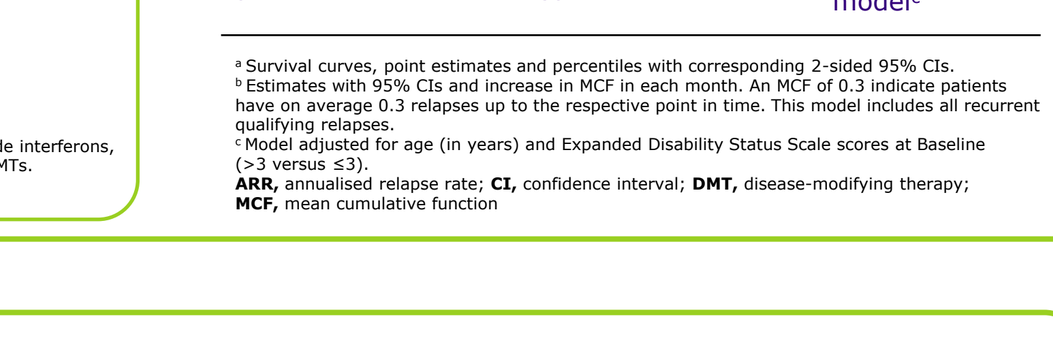


Number of patients at risk (number of events):

DMT pre-treated: Last DMT before previous 6 months	61 (0)	56 (4)	55 (5)	55 (5)	52 (8)	51 (8)	50 (9)	50 (9)	46 (12)
DMT pre-treated: Last DMT within previous 6 months	287 (0)	268 (17)	260 (25)	256 (28)	245 (38)	238 (44)	232 (48)	226 (53)	217 (56)
Total	482 (0)	450 (29)	437 (42)	432 (46)	415 (62)	406 (68)	397 (75)	389 (82)	364 (89)
Pre-treatment naïve	134 (0)	126 (8)	122 (12)	121 (13)	118 (16)	117 (16)	115 (18)	113 (20)	101 (21)

Months are defined using 30 days, i.e. Month 1 (30 days), Month 2 (60 days) up to Month 24 (720 days).
DMT, disease-modifying therapy.

Figure 3: Time to First Qualifying Relapse in Patients Receiving Last DMT Within 6 Months Before Initiating CladT



Number of patients at risk (number of events):

Glatiramer acetate	41 (0)	35 (4)	32 (7)	31 (8)	29 (10)	28 (11)	27 (12)	26 (13)	26 (13)
Fingolimod	38 (0)	34 (4)	34 (4)	34 (4)	32 (6)	31 (7)	29 (7)	29 (7)	27 (8)
Dimethyl fumarate	63 (0)	60 (3)	60 (3)	59 (3)	54 (7)	52 (9)	51 (10)	49 (12)	47 (12)
Interferons	84 (0)	81 (3)	79 (5)	78 (6)	76 (8)	75 (8)	73 (10)	72 (10)	69 (11)
Teriflunomide	39 (0)	38 (1)	38 (1)	37 (2)	37 (2)	36 (3)	36 (3)	35 (4)	33 (5)

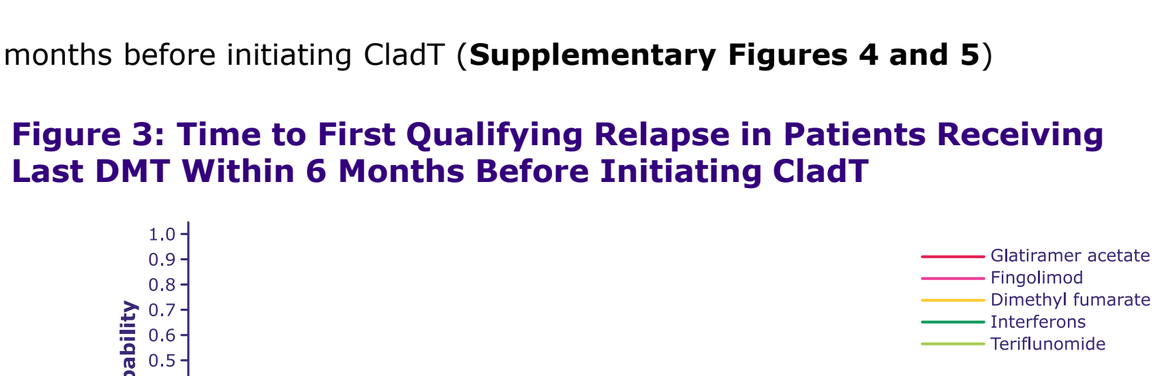
Months are defined using 30 days, i.e. Month 1 (30 days), Month 2 (60 days) up to Month 24 (720 days). Data for other DMTs (where the number of patients taking each DMT within 6 months before initiating CladT were ≤12) are not presented here.
In the subgroup of patients who received last DMT within 6 months before initiating CladT, data for 22 such patients (natalizumab: n=7; daclizumab: n=5; investigational drug: n=5; diroximel fumarate: n=3; methotrexate: n=1 and ozanimod: n=1) are not shown here.
CladT, cladribine tablets; **D,** day; **DMT,** disease-modifying therapy.

Anualised Relapse Rates (ARRs) for Qualifying Relapses

- In total, 91 out of 482 patients (18.9%) experienced a qualifying relapse during the study. The estimated ARRs for qualifying relapses were low for both pre-treatment naïve and all DMT pre-treated subgroups (**Supplementary Figure 6**)
- Similarly, ARRs were low in patients who received their last DMT within 6 months before initiating CladT, with highest estimates for glatiramer acetate and fingolimod (**Figure 4**). Due to small sample sizes and overlapping CIs, differences in ARRs were not apparent. No obvious rebound effect in patients switching from fingolimod to CladT were observed

Supplementary material available here:

Figure 4: ARRs in Patients Receiving Last DMT Within 6 Months Before Initiating CladT[a]



[a] Only qualifying relapses as reported in the electronic case report form were analyzed. Model adjusted for age (in years) and Expanded Disability Status Scale score at Baseline (>3 vs. ≤3). Data for other DMTs (where the number of patients taking each DMT within or >6 months before initiating CladT were ≤12) are not presented here. In the subgroup of patients who received last DMT within 6 months before initiating CladT, data for 22 such patients (natalizumab: n=7; daclizumab: n=5; investigational drug: n=5; diroximel fumarate: n=3; methotrexate: n=1 and ozanimod: n=1) are not shown here.
ARR, annualised relapse rate; **CI,** confidence interval; **CladT,** cladribine tablets; **DMT,** disease-modifying therapy

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Disclosures: FP has served on scientific advisory boards for Almirall, Bayer, Biogen, Celgene (BMS), Merck, Novartis, Roche, Sanofi, and Teva; and has received speaker honoraria from the same companies and non-personal research grants for his department from Biogen, Merck, Novartis, and Sanofi. **BB** has received consultancy fees, speaker fees, research grants (non-personal), or honoraria from Biogen, Celgene (BMS), Merck, Novartis, Roche, and Sanofi. **EKH** has received honoraria/research support from Actelion (Janssen/J&J), Biogen, Celgene (BMS), Merck, Novartis, Roche, Sanofi, and Teva; has served on advisory boards for Actelion (Janssen/J&J), Biogen, Celgene (BMS), Merck, Novartis, Roche, and Sanofi. **AS** has served on advisory boards for Merck, Novartis, and Sanofi and has been invited to speak on behalf of Almirall, Biogen, Excemed, Merck, and Teva. **RH** has received institutional research grants and fees for lectures and advisory boards from Biogen, Merck, and Sanofi. **DL** has participated in speaker bureau for Almirall, Bayer, Biogen, Merck, Novartis, Roche, Sanofi, and Teva; has received consultancy fees from Bayer, Biogen, Merck, Novartis, and Teva; and has received research grants from Bayer, Biogen, Merck, and Novartis. **JL-S** has accepted travel compensation from Biogen, Merck, and Novartis. Her institution receives the honoraria for talks and advisory board commitment as well as research grants from Biogen, Celgene (BMS), Merck, Novartis, Roche, Sanofi, and Teva. **FPi** has received research grants from Janssen, Merck, and Sanofi and fees as a member of the DMC in clinical trials with Lundbeck, Chugai and Roche. **KS** has received honoraria for speaking, consulting and serving for advisory boards for Biogen, Celgene (BMS), Merck, Novartis, Roche, and TG Therapeutics. **AL** and **ASm** are employees of Merck Healthcare KGaA, Darmstadt, Germany. **XM** has received speaking honoraria and travel expenses for participation in scientific meetings, has been a steering committee member of clinical trials or participated in advisory boards of clinical trials in the past years with AbbVie, Actelion, Alexion, Biogen, Celgene (BMS), EMD Serono Research & Development Institute, Inc., Billerica, MA, USA an affiliate of Merck KGaA, Genzyme, Hoffmann-La Roche, Immunic, Janssen Pharmaceuticals, MedDay, Merck, Mylan, Nervgen, Novartis, Sandoz, Sanofi-Genzyme, Teva Pharmaceutical, TG Therapeutics, Excemed, MSIF and NMSS.

Medical writing assistance was provided by Vimal Kumar Muthyala and Pritorthi Bhattacharjee of Merck Specialties Pvt. Ltd., Bangalore, India, an affiliate of Merck KGaA. ClinicalTrials.gov identifier: NCT03369665

Presented at the 9th Joint ECTRIMS-ACTRIMS Meeting | 11 – 13 October, 2023 | Milan, Italy

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

Supplementary Table 1: Subgroups of Previous DMT use

Statistic	Pre-Treatment naïve (n=134)	DMT pre-treated (n=348)		Total (N=482)
		Received last DMT >6 months before initiating CladT treatment (n=61)	Received last DMT within 6 months before initiating CladT treatment (n=287)	
Previous DMT				
Interferons, n (%)	-	11 (18.0)	84 (29.3)	95 (19.7)
Glatiramer acetate, n (%)	-	8 (13.1)	41 (14.3)	49 (10.2)
Fingolimod, n (%)	-	6 (9.8)	38 (13.2)	44 (9.1)
Teriflunomide, n (%)	-	8 (13.1)	39 (13.6)	47 (9.8)
Dimethyl Fumarate, n (%)	-	10 (16.4)	63 (22.0)	73 (15.1)
Other DMTs	-	18 (29.6)	22 (7.6)	40 (8.3)

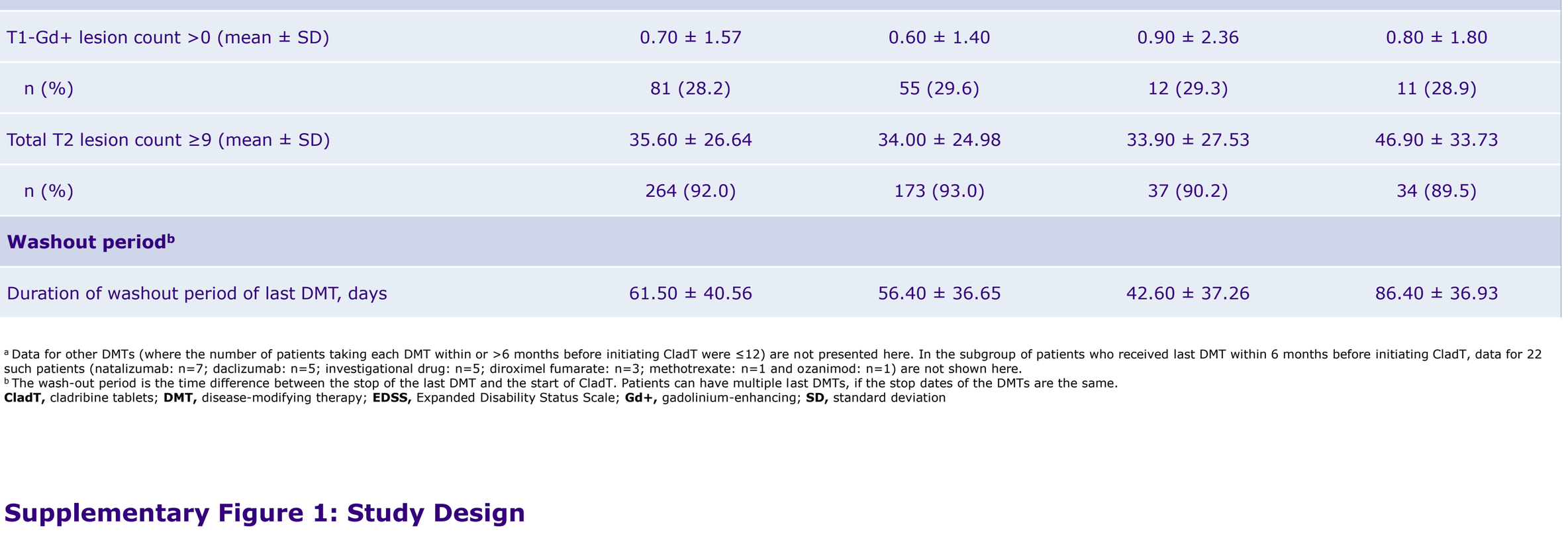
Data for other DMTs (where the number of patients taking each DMT within or more than 6 months before initiating CladT were ≤12) are not presented in detail here.
CladT, cladribine tablets; **DMT,** disease-modifying therapy.

Supplementary Table 2: Patient Demographics and Baseline Characteristics[a]

By last DMT within 6 months before initiating CladT				
	Total (n=287)	**Interferons, teriflunomide and dimethyl fumarate (n=186)**	**Glatiramer acetate (n=41)**	**Fingolimod (n=38)**
Demographic Characteristics				
Age (mean ± SD), years	38.40 ± 10.09	38.30 ± 10.23	37.10 ± 10.86	37.2 ± 8.38
Female, n (%)	200 (69.7)	129 (69.4)	28 (68.3)	27 (71.1)
Disease Characteristics				
Time since onset of MS (mean ± SD), months	118.69 ± 92.52	119.36 ± 91.63	81.42 ± 64.45	127.37 ± 83.30
EDSS ≤3 at Baseline, n (%)	201 (70.0)	143 (76.9)	29 (70.7)	22 (57.9)
MRI parameters at Screening				
T1-Gd+ lesion count >0 (mean ± SD)	0.70 ± 1.57	0.60 ± 1.40	0.90 ± 2.36	0.80 ± 1.80
n (%)	81 (28.2)	55 (29.6)	12 (29.3)	11 (28.9)
Total T2 lesion count ≥9 (mean ± SD)	35.60 ± 26.64	34.00 ± 24.98	33.90 ± 27.53	46.90 ± 33.73
n (%)	264 (92.0)	173 (93.0)	37 (90.2)	34 (89.5)
Washout period[b]				
Duration of washout period of last DMT, days	61.50 ± 40.56	56.40 ± 36.65	42.60 ± 37.26	86.40 ± 36.93

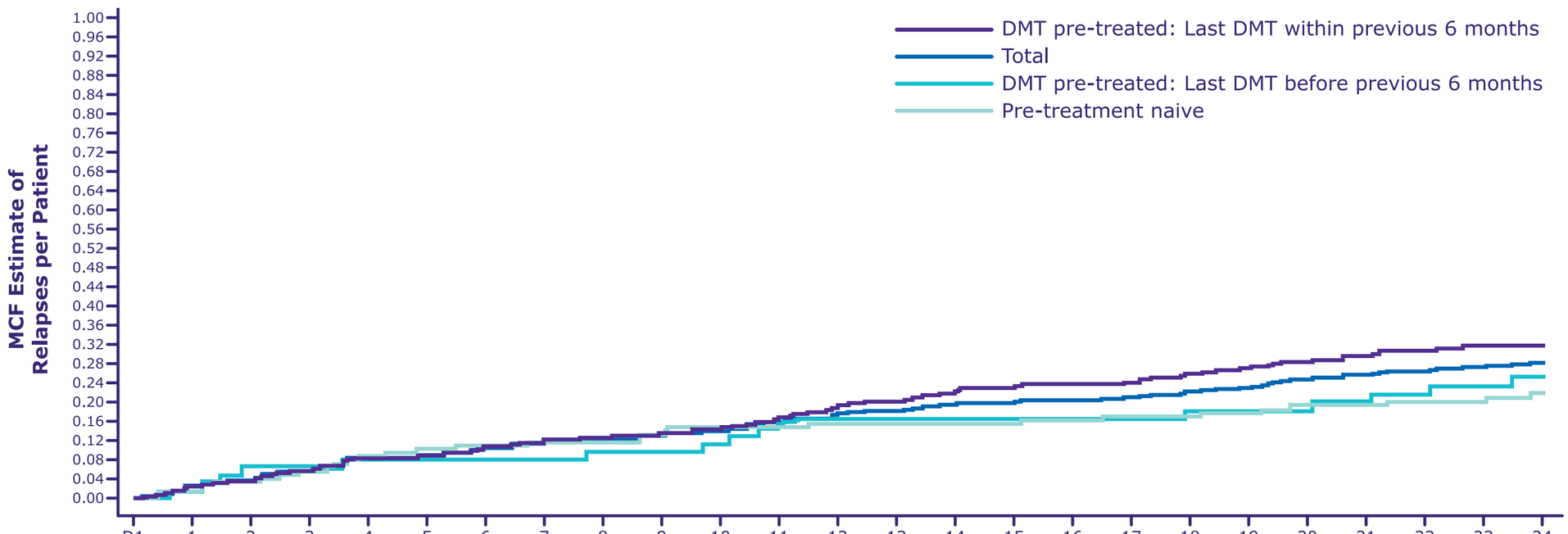
[a] Data for other DMTs (where the number of patients taking each DMT within or >6 months before initiating CladT were ≤12) are not presented here. In the subgroup of patients who received last DMT within 6 months before initiating CladT, data for 22 such patients (natalizumab: n=7; daclizumab: n=5; investigational drug: n=5; diroximel fumarate: n=3; methotrexate: n=1 and ozanimod: n=1) are not shown here.
[b] The wash-out period is the time difference between the stop of the last DMT and the start of CladT. Patients can have multiple last DMTs, if the stop dates of the DMTs are the same.
CladT, cladribine tablets; **DMT,** disease-modifying therapy; **EDSS,** Expanded Disability Status Scale; **Gd+,** gadolinium-enhancing; **SD,** standard deviation

Supplementary Figure 1: Study Design



[a] 0–3 month window for these trial visits. [b] Second treatment course may be delayed for some patients.
9-HPT, Nine-Hole Peg Test; **BICAMS,** Brief International Cognitive Assessment for Multiple Sclerosis; **DMT,** disease-modifying therapy; **EDSS,** Expanded Disability Status Scale; **FSS,** Fatigue Severity Scale; **HADS,** Hospital Anxiety and Depression Scale; **HRQoL,** health-related quality of life; **MRI,** magnetic resonance imaging; **MSQoL-54,** Multiple Sclerosis Quality of Life-54 instrument; **RMS,** relapsing multiple sclerosis; **SPC,** summary of product characteristics; **T25FW,** Timed 25-Foot Walk; **TSQM,** Treatment Satisfaction Questionnaire for Medication.
Figure adapted from: Brochet B, et al. *Mult Scler Relat Disord.* 2022. (CC BY 4.0)

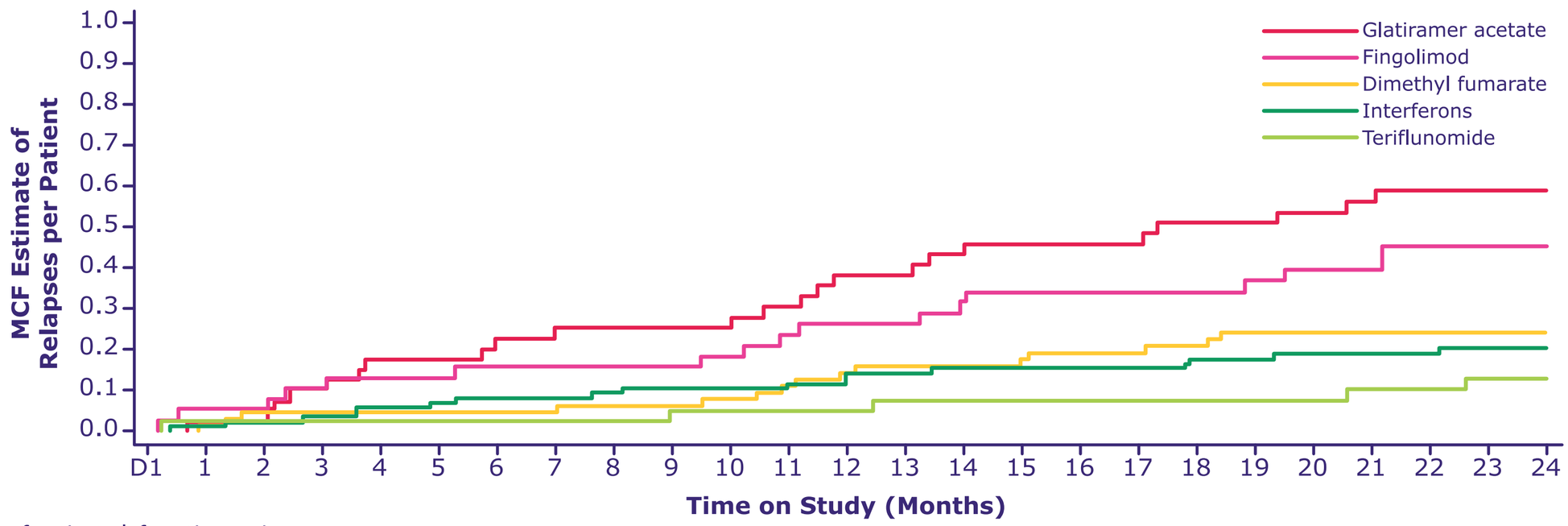
Supplementary Figure 2: Estimate of Cumulative Relapses in Patients by their Prior DMT Experience



Number of patients left at time point																									
DMT pre-treated: Last DMT within previous 6 months	287	287	286	285	285	285	285	284	284	284	283	283	282	280	280	280	280	280	276	276	276	274	274	274	263
Total	482	482	480	479	479	479	479	477	477	476	475	475	474	471	470	470	469	469	465	465	465	463	461	460	437
DMT pre-treated: Last DMT before previous 6 months	61	61	60	60	60	60	60	60	60	60	60	60	60	59	59	59	58	58	58	58	58	58	58	58	57
Pre-treatment naïve	134	134	134	134	134	134	134	133	133	132	132	132	132	132	131	131	131	131	131	131	131	131	129	128	117

Months are defined using 30 days, i.e. Month 1 (30 days), Month 2 (60 days) up to Month 24 (720 days).
DMT, disease-modifying therapy; **MCF,** Mean Cumulative Function I

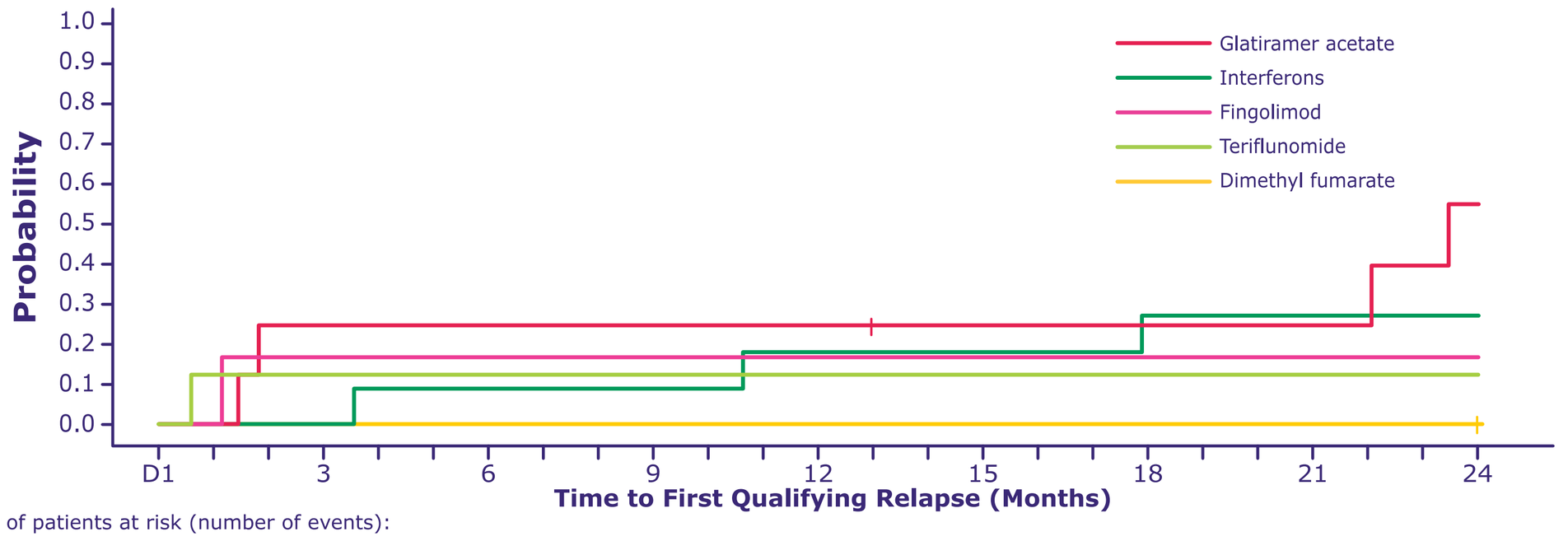
Supplementary Figure 3: Estimate of Cumulative Relapses in Patients Receiving Last DMT Within 6 Months Before Initiating CladT



Number of patients left at time point:																									
Glatiramer acetate	41	41	40	39	39	39	39	39	39	39	39	39	39	39	39	39	39	39	38	38	38	37	37	37	36
Fingolimod	38	38	38	38	38	38	38	38	38	38	38	38	38	38	38	38	38	38	36	36	36	36	36	36	32
Dimethyl fumarate	63	63	63	63	63	63	63	62	62	62	62	62	61	61	61	61	61	61	60	60	60	60	60	60	57
Interferons	84	84	84	84	84	84	84	84	84	84	84	84	84	83	83	83	83	83	83	83	83	82	82	82	80
Teriflunomide	39	39	39	39	39	39	39	39	39	39	39	39	39	39	39	39	39	39	39	39	39	39	39	39	38

Months are defined using 30 days, i.e. Month 1 (30 days), Month 2 (60 days) up to Month 24 (720 days). An MCF of 0.3 means indicate patients have on average 0.3 relapses up to the respective point in time. This model includes all recurrent qualifying relapses. Data for other DMTs (where the number of patients taking each DMT within 6 months before initiating CladT were ≤12) are not presented here. In the subgroup of patients who received last DMT within 6 months before initiating CladT, data for 22 such patients (natalizumab: n=7; daclizumab: n=5; investigational drug: n=5; diroximel fumarate: n=3; methotrexate: n=1 and ozanimod: n=1) are not shown here.
CladT, cladribine tablets; **D,** day; **DMT,** disease-modifying therapy; **MCF,** Mean Cumulative Function

Supplementary Figure 4: Time to First Qualifying Relapse in Patients Receiving Last DMT >6 Months Before Initiating CladT



Number of patients at risk (number of events):									
Glatiramer acetate	8 (0)	6 (2)	6 (2)	6 (2)	6 (2)	5 (2)	5 (2)	5 (2)	3 (4)
Interferons	11 (0)	11 (0)	10 (1)	10 (1)	9 (2)	9 (2)	8 (3)	8 (3)	8 (3)
Fingolimod	6 (0)	5 (1)	5 (1)	5 (1)	5 (1)	5 (1)	5 (1)	5 (1)	5 (1)
Teriflunomide	8 (0)	7 (1)	7 (1)	7 (1)	7 (1)	7 (1)	7 (1)	7 (1)	7 (1)
Dimethyl fumarate	10 (0)	10 (0)	10 (0)	10 (0)	10 (0)	10 (0)	10 (0)	10 (0)	9 (0)

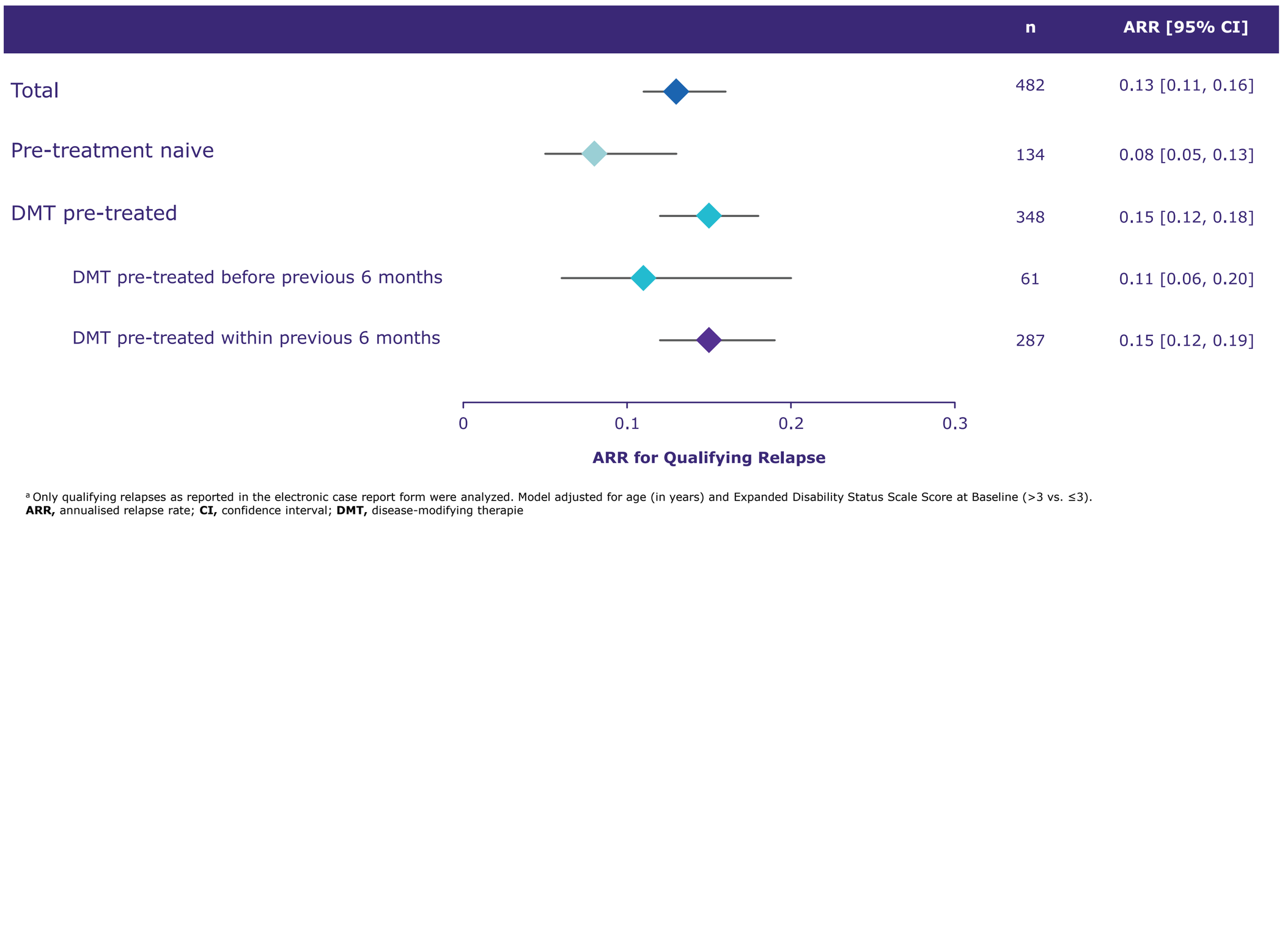
Months are defined using 30 days, i.e. Month 1 (30 days), Month 2 (60 days) up to Month 24 (720 days). Data for other DMTs (where the number of patients taking each DMT >6 months before initiating CladT were ≤12) are not presented here.
CladT, cladribine tablets; **D,** day; **DMT,** disease-modifying therapy.

Supplementary Figure 5: Estimate of Cumulative Relapses in Patients Receiving Last DMT >6 Months Before Initiating CladT

Number of patients at risk (number of events):																									
Glatiramer acetate	8	8	8	8	8	8	8	8	8	8	8	8	8	7	7	7	6	6	6	6	6	6	6	6	6
Interferons	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11
Fingolimod	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Teriflunomide	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8
Dimethyl Fumarate	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	9

Months are defined using 30 days, i.e. Month 1 (30 days), Month 2 (60 days) up to Month 24 (720 days). Data for other DMTs (where the number of patients taking each DMT >6 months before initiating CladT were ≤12) are not presented here.
CladT, cladribine tablets; **D,** day; **DMT,** disease-modifying therapy; **MCF,** Mean Cumulative Function

Supplementary Figure 6: ARRs for Qualifying Relapses by Prior DMT Experience and in the DMT Pre-treated Subgroups[a]



[a] Only qualifying relapses as reported in the electronic case report form were analyzed. Model adjusted for age (in years) and Expanded Disability Status Scale Score at Baseline (>3 vs. ≤3).
ARR, annualised relapse rate; **CI,** confidence interval; **DMT,** disease-modifying therapie