

Supplementary webappendix

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Supplement to: Leist TP, Comi G, Cree BAC, et al, on behalf of the oral cladribine for early MS (ORACLE MS) Study Group. Effect of oral cladribine on time to conversion to clinically definite multiple sclerosis in patients with a first demyelinating event (ORACLE MS): a phase 3 randomised trial. *Lancet Neurol* 2014; published online Feb 4. [http://dx.doi.org/10.1016/S1474-4422\(14\)70005-5](http://dx.doi.org/10.1016/S1474-4422(14)70005-5).

Supplementary material

Section 1: Patients were recruited at 160 centres in 34 countries

Trial centres: Argentina (2), Austria (2), Belgium (4), Bosnia and Herzegovina (1), Bulgaria (9), Canada (1), Croatia (2), Czech Republic (6), Estonia (2), Finland (4), France (3), Georgia (3), Germany (2), India (6), Italy (19), Korea (5), Lebanon (1), Macedonia (1), Norway (2), Poland (9), Portugal (4), Romania (4), Russia (25), Serbia (3), Singapore (1), Spain (2), Sweden (3), Taiwan (3), Thailand (1), Turkey (2), Ukraine (3), United Arab Emirates (1), United Kingdom (1), United States (23).

Section 2: Changes to the conduct of the trial and planned analyses

The original protocol, 14 July 2008, was amended five times; the key amendments were:

- Protocol amendment 5 (all countries; 3 August 2011): the main purpose of this amendment was to ensure that all patients in all countries were treated and assessed in a uniform manner following suspension of treatment with cladribine tablets in all phases of this study. The main changes made to the protocol were: to implement in all participating countries the termination of all dosing with blinded study medication and open-label cladribine; to terminate the double-blind treatment period and to make provisions for a maximum of up to 48 weeks of subcutaneous interferon beta-1a treatment (instead of cladribine tablets) for patients converting to multiple sclerosis (MS; McDonald 2005 criteria) during the double-blind and long-term follow-up (LFU) treatment periods and for patients who converted to clinically definite MS (CDMS) in the double-blind treatment period; and to adapt the statistical analysis accordingly. Amendment 5 was not implemented at any site until after the 15 August 2011 data cut-off date for the primary analysis.
- Protocol amendment 3 (all countries; 8 January 2010) included revisions provided in inclusion and exclusion criteria aimed at providing further clarification to frequently asked questions from recruiting sites for patient enrolment and eligibility.
- Three statistical analyses were originally planned for the different study periods: double-blind period (primary analysis); double-blind period (second analysis); and open-label maintenance period (OLMP) and LFU analyses. Following the sponsor's decision to stop the cladribine programme in June 2011, it was decided to perform two abbreviated analyses: the double-blind primary analysis, which was conducted based on data captured up to 15 August 2011, and a post-double-blind period end-of-study final analysis including the analyses of baseline assessments, efficacy (where appropriate), and safety endpoints for each of the three study periods. These analyses were conducted based on the final database, which includes at least 24 weeks' follow-up data after the last dose of cladribine for all patients.

Section 3: Laboratory abnormalities

In the event of a grade 1 or 2 toxicity that was determined to be potentially attributable to study medication, the patient was treated as deemed appropriate by the treating physician. If a grade 3 toxicity potentially associated with study medication occurred, treatment was interrupted and the patient was monitored closely with follow-up laboratory tests every 2 weeks until the toxicity resolved to grade 0 or 1. Treatment was permanently discontinued if the grade 3 toxicity attributable to study medication recurred within the same year or persisted after 4 weeks' interruption of therapy. A grade 4 toxicity resulted in permanent discontinuation of study medication. For patients who experienced grade 3 or 4 lymphopenia, treatment was interrupted and laboratory values were re-tested every 2 weeks until resolution of toxicity to grade 0 or 1. Treatment was permanently discontinued if grade 4 lymphopenia occurred and was confirmed by a second test, if grade 3 lymphopenia persisted (as described above), or if a decrease in lymphocyte count was associated with medical complications, such as infection. Other pre-defined criteria for permanent treatment withdrawal were pregnancy, evidence of latent or active tubercular infection, or initiation of another disease-modifying therapy for MS. All patients who discontinued study medication were encouraged to remain on study for evaluations and procedures.

Section 4: Patient study disposition

The time patients spent on the study in the double-blind treatment period exceeded 48 weeks for the majority of patients. The proportion of patients on study more than 48 weeks and up to 96 weeks was lower in the placebo group (n=145; 70.9%) compared with the cladribine 3.5-mg/kg (179; 86.9%) and 5.25-mg/kg (173; 84.8%) groups. The percentage of patients whose participation exceeded 96 weeks (includes final 4-week follow-up visit) was lower in the placebo group (n=41; 19.9%) than in the cladribine 3.5-mg/kg (n=72; 35.0%) or 5.25-mg/kg (n=63; 30.9%) groups.

Section 5: Further secondary MRI endpoints

The available data on brain volume change are shown in supplementary table 1. Because of the reduced numbers of patients completing 96 weeks of the double-blind period, these results should be interpreted with caution. Furthermore, based on past experience with cladribine, pseudoatrophy is likely during the first year and the analysis shown did not adjust for this phenomenon.

Supplementary table 1: Baseline brain volume and change from baseline at weeks 48 and 96

	Cladribine 5·25 mg/kg (n=204)	Cladribine 3·5 mg/kg (n=206)	Placebo (n=206)
Baseline normalised brain volume (cm³)			
n (missing)	203 (1)	206 (0)	204 (2)
Mean (SD)	1533·4 (71·0)	1532·4 (64·6)	1533·2 (69·5)
Median (Q1, Q3)	1538·2 (1496·3, 1583·4)	1538·6 (1489·4, 1579·5)	1535·0 (1491·0, 1583·9)
Change from baseline (%) at week 48			
n (missing)	163 (41)	171 (35)	140 (66)
Mean (SD)	-0·48 (0·6)	-0·48 (0·7)	-0·33 (0·7)
Median (Q1, Q3)	-0·40 (-0·74, -0·18)	-0·38 (-0·86, -0·10)	-0·29 (-0·65, 0·00)
Change from baseline (%) at week 96			
n (missing)	67 (137)	76 (130)	47 (159)
Mean (SD)	-0·58 (0·7)	-0·68 (0·6)	-0·70 (0·5)
Median (Q1, Q3)	-0·61 (-0·77, -0·40)	0·61 (-0·83, -0·40)	-0·61 (-0·94, -0·42)

Only patients with brain volume assessments at both visits were included in analyses of change from baseline.
SD=standard deviation.

Other secondary MRI endpoints are shown in supplementary table 2. Concerning the T1 hypointense lesions, there was a statistically significant treatment difference between the cladribine 5.25 mg/kg and placebo groups. There was no significant difference between the cladribine 3.5 mg/kg group and placebo. It is unclear why the apparent greater number of T1 hypointense lesions is seen in the cladribine 5.25 mg/kg group, although it is worth bearing in mind that this endpoint assessed total lesion number rather than persistent lesions.

Supplementary table 2: Other secondary MRI endpoints (ITT population)

		Cladribine 5.25 mg/kg (n=204)		Cladribine 3.5 mg/kg (n=206)		Placebo (n=206)
Volume of T1 gadolinium-enhancing lesions and change from baseline by visit, mm ³						
Statistic	Observed	Change	Observed	Change	Observed	Change
Baseline						
n (missing)	204 (0)		206 (0)		206 (0)	
Median	0.0		0.0		0.0	
Q1, Q3	0.0, 104.5		0.0, 62.9		0.0, 68.7	
Week 24						
n (missing)	181 (6)	181 (6)	193 (1)	193 (1)	170 (6)	170 (6)
Median	0.0	0.0	0.0	0.0	0.0	0.0
Q1, Q3	0.0, 0.0	-88.7, 0.0	0.0, 0.0	-51.5, 0.0	0.0, 57.2	-14.3, 11.4
Week 48						
n (missing)	164 (6)	164 (6)	171 (3)	171 (3)	141 (12)	141 (12)
Median	0.0	0.0	0.0	0.0	0.0	0.0
Q1, Q3	0.0, 0.0	-97.3, 0.0	0.0, 0.0	-35.9, 0.0	0.0, 54.4	0.0, 20.0
Early termination						
n	82	82	78	78	68	68
Median	0.0	0.0	0.0	0.0	0.0	0.0
Q1, Q3	0.0, 0.0	-65.8, 0.0	0.0, 0.0	-60.1, 0.0	0.0, 38.7	-37.2, 0.0
Week 96						
n (missing)	68 (41)	68 (41)	76 (33)	76 (33)	47 (35)	47 (35)
Median	0.0	0.0	0.0	0.0	0.0	0.0
Q1, Q3	0.0, 0.0	-123.1, 0.0	0.0, 0.0	-36.6, 0.0	0.0, 57.2	0.0, 45.8
Volume of T2 lesions and change from baseline by visit, mm ³						
Statistic	Observed	Change	Observed	Change	Observed	Change
Baseline						
n (missing)	204 (0)		206 (0)		206 (0)	
Mean (SD)	3825.7 (5093.5)		3435.2 (5184.1)		3436.7 (4613.4)	
Median	1820.5		1692.4		1793.9	
Q1, Q3	819.7, 4772.7		855.5, 4028.3		721.0, 3790.8	
Min, Max	51.5, 31991.5		57.2, 46492.0		54.4, 26819.0	
Week 24						
n (missing)	181 (6)	181 (6)	193 (1)	193 (1)	170 (6)	170 (6)
Mean (SD)	0.0 (0.0)	-3727.3 (4844.1)	0.0 (0.0)	-3502.9 (5317.2)	32.4 (314.6)	-3298.6 (4515.1)
Median	0.0	-1827.1	0.0	-1691.0	0.0	-1693.7
Q1, Q3	0.0, 0.0	-4714.9, -769.6	0.0, 0.0	-4028.3, -869.8	0.0, 0.0	-3707.9, -692.4
Min, Max	0.0, 0.0	-27366.2, -51.5	0.0, 0.0	-46492.0, -57.2	0.0, 3679.5	-26819.0, 155.4
Week 48						
n (missing)	164 (6)	164 (6)	171 (3)	171 (3)	141 (12)	141 (12)
Mean (SD)	3142.6 (4189.4)	-630.7 (2361.0)	2857.4 (3576.5)	-664.4 (3444.8)	3115.2 (3382.4)	-61.9 (2861.1)
Median	1665.1	-45.7	1605.2	-74.4	2042.7	114.5

Q1, Q3	579.4, 4105.6	-320.5, 37.2	812.6, 3506.3	-429.2, 108.8	789.7, 4260.1	-62.9, 632.4
Min, Max	0.0, 25683.0	-18815.4, 2723.7	0.0, 24708.0	-35672.0, 5047.3	0.0, 14017.5	-17658.0, 7126.7
Early termination						
n	83	83	79	79	68	68
Mean (SD)	776.1 (2935.4)	-3886.7 (5769.0)	420.4 (1760.1)	-4418.1 (6802.0)	99.5 (365.3)	-3973.6 (5944.7)
Median	0.0	-1356.2	0.0	-1796.7	0.0	-1639.4
Q1, Q3	0.0, 0.0	-5373.5, -366.1	0.0, 0.0	-6079.6, -663.8	0.0, 0.0	-4049.9, -506.5
Min, Max	0.0, 18196.0	-27366.2, 2243.4	0.0, 10812.0	-35680.0, 3132.4	0.0, 2423.5	-26819.0, 503.6
Week 96						
n (missing)	68 (41)	68 (41)	76 (33)	76 (33)	47 (35)	47 (35)
Mean (SD)	1347.4 (1744.1)	-1173.7 (2543.7)	1225.4 (1850.9)	-1299.4 (2786.1)	2013.0 (2575.8)	-677.3 (2875.8)
Median	748.6	-250.3	680.9	-410.6	1196.0	-71.5
Q1, Q3	53.0, 1652.3	-979.9, -24.3	0.0, 1513.6	-1183.1, -14.4	0.0, 3444.7	-707.7, 363.4
Min, Max	0.0, 7573.1	-14995.8, 664.0	0.0, 9673.1	-15689.6, 2151.5	0.0, 11370.0	-13550.9, 3241.6
Proportion of patients with no new or enlarging T2 lesions						
n/M (%)	109/203 (53.7)		104/202 (51.5)		54/196 (27.6)	
95% CI of proportion	(46.6, 60.7)		(44.4, 58.6)		(21.4, 34.4)	
Proportion of patients with no new T1 gadolinium-enhancing lesions						
n/M (%)	165/203 (81.3)		142/202 (70.3)		62/196 (31.6)	
95% CI of proportion	(75.2, 86.4)		(63.5, 76.5)		(25.2, 38.6)	
Number of T1 hypointense lesions						
Median (Q1–Q3) cumulative number of lesions	3.0 (0.0–11.0)		2.0 (0.0–10.0)		2.0 (0.0–10.0)	
Treatment group comparison: cladribine/placebo, ratio (SE)*	1.510 (1.117–2.040)		1.026 (0.758–1.388)		–	
Risk increase versus placebo, %	51.0		2.6		–	
p value*	0.0073		0.8681		–	

CI=confidence interval, ITT=intention-to-treat; M=number of patients with at least one post-baseline MRI scan for the parameter; MRI=magnetic resonance imaging; SD=standard deviation; SE=standard error.
 *From the analysis of the cumulative number of lesions, using a negative binomial model with treatment, region, and baseline lesion count as covariates, and the log number of scans as an offset variable.

Section 6: Lymphocyte count as a haematological laboratory toxicity

As a haematological laboratory parameter, lymphopenia, reported as a decreased lymphocyte count, occurred in all three treatment arms (supplementary figure 1).

Other haematopoietic cytopenias occurred only in the cladribine groups, including neutropenia (2·0% in the 5·25-mg/kg group and 2·4% in the 3·5-mg/kg group) and leucopenia (2·5% in the 5·25-mg/kg group and 1·0% in the 3·5-mg/kg group). In addition, thrombocytopenia (1·0%), microcytic anaemia, and monocytopenia (0·5% each) occurred only in the cladribine 5·25-mg/kg group, while normochromic normocytic anaemia (1·0%), decreased platelet count (0·5%), and decreased lymphocyte count (0·5%) occurred only in the cladribine 3·5-mg/kg group.

Section 7: OLMP and LFU

OLMP

Supplementary table 3: Patient disposition in the OLMP

	Cladribine 5·25 mg/kg (n=24)	Cladribine 3·5 mg/kg (n=25)	Placebo (n=60)	All patients (N=109)
Completed OLMP subcutaneous interferon beta-1a treatment (96 weeks)	6 (25·0)	2 (8·0)	7 (11·7)	15 (13·8)
Discontinued subcutaneous interferon beta-1a treatment	18 (75·0)	23 (92·0)	53 (88·3)	94 (86·2)
Reason for discontinuation				
Adverse event	2 (8·3)	2 (8·0)	5 (8·3)	9 (8·3)
Lost to follow-up	1 (4·2)	0 (0·0)	0 (0·0)	1 (0·9)
Protocol violation	0 (0·0)	0 (0·0)	0 (0·0)	0 (0·0)
Disease progression	0 (0·0)	0 (0·0)	4 (6·7)	4 (3·7)
Death	0 (0·0)	1 (4·0)	0 (0·0)	1 (0·9)
Other	15 (62·5)	20 (80·0)	44 (73·3)	79 (72·5)

All values are n (%).

OLMP, open-label maintenance period.

Among the eight patients with non-fatal serious AEs (SAEs), there was one (0·9%) report each of the following SAEs: increased blood creatine phosphokinase (CPK), increased blood uric acid, hyperprolactinaemia, gastric ulcer perforation, injection-site necrosis, erysipelas, benign pituitary tumour, ureteric calculus, nasal cyst, and psoriasis. All events were considered unrelated or unlikely to be related to study treatment. Cardio-respiratory arrest (leading to death), injection-site necrosis, erysipelas, and increased blood CPK were considered severe. Lymphopenia occurred in 8·3%, 4·0%, and 3·3% of patients previously exposed to cladribine 5·25 mg/kg, cladribine 3·5 mg/kg, or placebo, respectively. No malignancies developed in the OLMP. Benign neoplasms were reported in one patient in the cladribine 5·25-mg/kg group (mild skin papillomas) and one patient in the cladribine 3·5-mg/kg group (mild benign pituitary tumour). Both were considered unrelated to treatment. Two patients became pregnant during the OLMP; both had been treated with placebo. One gave birth to a healthy infant, the outcome of the other pregnancy is unknown because the patient refused follow-up.

Supplementary table 4: Overall incidence of TEAEs in the OLMP

Events, n (%)	Cladribine 5·25 mg/kg (n=24)	Cladribine 3·5 mg/kg (n=25)	Placebo (n=60)	All patients (N=109)
Any TEAE	18 (75·0)	20 (80·0)	47 (78·3)	85 (78·0)
Any drug-related TEAE	15 (62·5)	16 (64·0)	41 (68·3)	72 (66·1)
Any severe TEAE	1 (4·2)	2 (8·0)	4 (6·7)	7 (6·4)
Any serious TEAE	1 (4·2)	4 (16·0)	4 (6·7)	9 (8·3)
Any TEAE from SOC infections and infestations	9 (37·5)	4 (16·0)	22 (36·7)	35 (32·1)
Any TEAE leading to OLMP treatment discontinuation	2 (8·3)	2 (8·0)	2 (3·3)	6 (5·5)
Death	0 (0·0)	1 (4·0)	0 (0·0)	0 (0·0)

OLMP=open-label maintenance period; SOC=system organ class; TEAE=treatment-emergent adverse event.

Supplementary table 5: Most common TEAEs (reported by ≥5% patients) in the OLMP

Events, n (%)	Cladribine 5·25 mg/kg (n=24)	Cladribine 3·5 mg/kg (n=25)	Placebo (n=60)	All patients (N=109)
Influenza-like illness	7 (29·2)	9 (36·0)	21 (35·0)	37 (33·9)
Headache	5 (20·8)	8 (32·0)	10 (16·7)	23 (21·1)
Pyrexia	1 (4·2)	5 (20·0)	5 (8·3)	11 (10·1)
Myalgia	3 (12·5)	0 (0·0)	7 (11·7)	10 (9·2)
Influenza	2 (8·3)	0 (0·0)	6 (10·0)	8 (7·3)
Nasopharyngitis	2 (8·3)	1 (4·0)	5 (8·3)	8 (7·3)
Injection-site reaction	2 (8·3)	0 (0·0)	4 (6·7)	6 (5·5)
Insomnia	1 (4·2)	1 (4·0)	4 (6·7)	6 (5·5)
ALT increased	1 (4·2)	0 (0·0)	4 (6·7)	5 (4·6)
Back pain	2 (8·3)	0 (0·0)	3 (5·0)	5 (4·6)
Injection-site pain	2 (8·3)	0 (0·0)	3 (5·0)	5 (4·6)
Lymphopenia	2 (8·3)	1 (4·0)	2 (3·3)	5 (4·6)
Musculoskeletal pain	0 (0·0)	2 (8·0)	3 (5·0)	5 (4·6)
Nausea	1 (4·2)	1 (4·0)	3 (5·0)	5 (4·6)
Pharyngitis	2 (8·3)	0 (0·0)	3 (5·0)	5 (4·6)
Arthralgia	0 (0·0)	2 (8·0)	2 (3·3)	4 (3·7)
Cough	2 (8·3)	1 (4·0)	1 (1·7)	4 (3·7)
Fatigue	3 (12·5)	0 (0·0)	1 (1·7)	4 (3·7)
Injection-site erythema	0 (0·0)	2 (8·0)	2 (3·3)	4 (3·7)
Leucopenia	0 (0·0)	2 (8·0)	2 (3·3)	4 (3·7)
Dental caries	2 (8·3)	0 (0·0)	1 (1·7)	3 (2·8)
Eye pain	0 (0·0)	0 (0·0)	3 (5·0)	3 (2·8)

ALT=alanine aminotransferase; OLMP=open-label maintenance period; TEAE=treatment-emergent adverse event.

LFU

The mean (standard deviation [SD]) and median cumulative cladribine doses received among all patients were 1·54 (0·44) mg/kg and 1·81 mg/kg, respectively. The means and medians were similar across the three double-blind treatment groups. The overall mean (SD) and median times on cladribine were 4·7 (3·1) weeks and 5·7 weeks, respectively. No malignancies developed in the LFU. No serious or severe infections occurred.

Supplementary table 6: Patient disposition in the LFU—patients treated at LFU entry

LFU treatment status		Cladribine 5·25 mg/kg (n=9)	Cladribine 3·5 mg/kg (n=9)	Placebo (n=17)	All patients (N=35)
Treated at LFU entry – cladribine*		9 (100·0)	9 (100·0)	16 (94·1)	34 (97·1)
	Cladribine only	9 (100·0)	9 (100·0)	15 (88·2)	33 (94·3)
	Cladribine and switched to subcutaneous interferon beta-1a [†]	0 (0·0)	0 (0·0)	0 (0·0)	0 (0·0)
	CDMS conversion in LFU and received subcutaneous interferon beta-1a after conversion [‡]	0 (0·0)	0 (0·0)	1 (5·9)	1 (2·9)
Treated at LFU entry – subcutaneous interferon beta-1a[§]		0 (0·0)	0 (0·0)	1 (5·9)	1 (2·9)
	Received subcutaneous interferon beta-1a at LFU entry	0 (0·0)	0 (0·0)	1 (5·9)	1 (2·9)
LFU study treatment completion/discontinuation					
	Completed	0 (0·0)	0 (0·0)	0 (0·0)	0 (0·0)
	Discontinued	9 (100·0)	9 (100·0)	17 (100·0)	35 (100·0)

All values are n (%). Patients are summarised according to their randomised treatment group from the double-blind period.

*Converted to McDonald MS in double-blind period, completed 96-week double-blind period and received study drug upon entering LFU: 1) entered LFU prior to Amendment 5 and received cladribine only; 2) entered LFU prior to Amendment 5 and received cladribine and switched to subcutaneous interferon beta-1a after Amendment 5; 3) converted to CDMS during LFU and received subcutaneous interferon beta-1a.

[†]Excludes patients with CDMS conversion during LFU.

[‡]Patient 138-0002 received cladribine at entry and then subcutaneous interferon beta-1a after conversion to CDMS.

[§]Converted to McDonald MS in double-blind period, completed 96-week double-blind period and received study drug upon entering LFU: 1) entered LFU after Amendment 5 and received subcutaneous interferon beta-1a.

CDMS=clinically definite multiple sclerosis; LFU=long-term follow-up.

Note: With Amendment 5, patients who would have qualified under the original protocol for open-label cladribine in the LFU based on McDonald MS status, were instead offered serum-free formulation of subcutaneous interferon beta-1a, 44 µg three times weekly.

Supplementary table 7: Patient disposition in the LFU – patients not treated at LFU entry

LFU treatment status	Cladribine 5·25 mg/kg (n=34)	Cladribine 3·5 mg/kg (n=36)	Placebo (n=14)	All patients (N=84)
CDMS conversion*	1 (2·9)	0 (0·0)	0 (0·0)	1 (1·2)
McDonald MS conversion*	1 (2·9)	0 (0·0)	0 (0·0)	1 (1·2)
Received cladribine or subcutaneous interferon beta-1a after conversion to CDMS or McDonald MS in LFU	0 (0·0)	0 (0·0)	0 (0·0)	0 (0·0)
Discontinued LFU	34 (100·0)	36 (100·0)	14 (100·0)	84 (100·0)

*One patient converted to McDonald MS and then CDMS during the LFU.

CDMS=clinically definite multiple sclerosis; LFU=long-term follow-up.

Note: per protocol, “patients not treated” at LFU entry = patients who completed the double blind period without McDonald MS conversion and entered the LFU.

Supplementary table 8: Overall incidence of TEAEs in the LFU – patients treated at LFU entry

Events, n (%)	Cladribine 5·25 mg/kg (n=9)	Cladribine 3·5 mg/kg (n=9)	Placebo (n=16)	All patients (N=34)
Any TEAE	3 (33·3)	4 (44·4)	7 (43·8)	14 (41·2)
Any drug-related TEAE	0 (0·0)	2 (22·2)	3 (18·8)	5 (14·7)
Any severe TEAE	0 (0·0)	0 (0·0)	2 (12·5)	2 (5·9)
Any serious TEAE	0 (0·0)	0 (0·0)	1 (6·3)	1 (2·9)
Any TEAE from SOC Infections and Infestations	1 (11·1)	2 (22·2)	3 (18·8)	6 (17·6)
Any TEAE leading to LFU treatment discontinuation	0 (0·0)	1 (11·1)	0 (0·0)	1 (2·9)
Death	0 (0·0)	0 (0·0)	0 (0·0)	0 (0·0)

LFU=long-term follow-up; SOC=system organ class; TEAE=treatment-emergent adverse event.

Supplementary table 9: Overall incidence of TEAEs in the LFU – patients not treated at LFU entry

Events, n (%)	Cladribine 5·25 mg/kg (n=34)	Cladribine 3·5 mg/kg (n=36)	Placebo (n=14)	All patients (N=84)
Any TEAE	4 (11·8)	7 (19·4)	2 (14·3)	13 (15·5)
Any drug-related* TEAE	1 (2·9)	2 (5·6)	0 (0·0)	3 (3·6)
Any severe TEAE	0 (0·0)	1 (2·8)	1 (7·1)	2 (2·4)
Any serious TEAE	0 (0·0)	1 (2·8)	0 (0·0)	1 (1·2)
Any TEAE from SOC Infections and Infestations	2 (5·9)	2 (5·6)	0 (0·0)	4 (4·8)
Any TEAE leading to LFU treatment discontinuation	0 (0·0)	0 (0·0)	0 (0·0)	0 (0·0)
Death	0 (0·0)	0 (0·0)	0 (0·0)	0 (0·0)

*Probable or possible relationship with study treatment according to investigator. 3 patients had AEs after LTFU entry date listed as possibly related with study treatment.

LFU=long-term follow-up; SOC=system organ class; TEAE=treatment-emergent adverse event.

Supplementary table 10: Most common TEAEs (reported by ≥5% patients) in the LFU

Events, n (%)	Cladribine 5·25 mg/kg (n=9)	Cladribine 3·5 mg/kg (n=9)	Placebo (n=16)	All patients (N=34)
Headache	2 (22·2)	0 (0·0)	3 (18·8)	5 (14·7)
Upper respiratory tract infection	1 (11·1)	0 (0·0)	2 (12·5)	3 (8·8)
Food poisoning	0 (0·0)	1 (11·1)	1 (6·3)	2 (5·9)
Vaginal candidiasis	0 (0·0)	1 (11·1)	1 (6·3)	2 (5·9)
Acute tonsillitis	0 (0·0)	1 (11·1)		1 (2·9)
ALT increased	0 (0·0)	0 (0·0)	1 (6·3)	1 (2·9)
Bartholin's cyst	1 (11·1)	0 (0·0)	0 (0·0)	1 (2·9)
Blood creatine phosphokinase increased	0 (0·0)	0 (0·0)	1 (6·3)	1 (2·9)
Bronchitis	0 (0·0)	1 (11·1)	0 (0·0)	1 (2·9)
Drug hypersensitivity	0 (0·0)	0 (0·0)	1 (6·3)	1 (2·9)
Gastrointestinal toxicity	0 (0·0)	0 (0·0)	1 (6·3)	1 (2·9)
Hordeolum	0 (0·0)	0 (0·0)	1 (6·3)	1 (2·9)
Hyperhidrosis	0 (0·0)	0 (0·0)	1 (6·3)	1 (2·9)
Hypersensitivity	0 (0·0)	0 (0·0)	1 (6·3)	1 (2·9)
Hypoesthesia	0 (0·0)	0 (0·0)	1 (6·3)	1 (2·9)
Lymphopenia	0 (0·0)	1 (11·1)	0 (0·0)	1 (2·9)
Nasopharyngitis	0 (0·0)	1 (11·1)	0 (0·0)	1 (2·9)
Neurosis	0 (0·0)	1 (11·1)	0 (0·0)	1 (2·9)
Nystagmus	0 (0·0)	0 (0·0)	1 (6·3)	1 (2·9)
Paraesthesia	0 (0·0)	0 (0·0)	1 (6·3)	1 (2·9)
Radicular cyst	0 (0·0)	0 (0·0)	1 (6·3)	1 (2·9)
Respiratory tract infection viral	0 (0·0)	0 (0·0)	1 (6·3)	1 (2·9)

ALT=alanine aminotransferase; LFU=long-term follow-up; TEAE=treatment-emergent adverse event.

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