



Cost Assessment Modelling of Treatments for Highly Active Relapsing Multiple Sclerosis

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ABSTRACT

Introduction: Cost assessment modelling (CAM) of treatments in highly active relapsing multiple sclerosis was conducted.

Methods: The CAM was developed using the R programming language. The PICOSTEPS health technology assessment framework was applied in the CAM. Modelled patients were 280 adults with highly active relapsing multiple sclerosis eligible for disease-modifying treatment. Intervention was cladribine tablets, a new and reimbursed oral treatment for highly active

relapsing multiple sclerosis in Finland. Comparators included fingolimod, the most used oral reimbursed treatment for the highly active disease, and natalizumab, the most used intravenous treatment, and a treatment mix (80% use fingolimod, 20% use natalizumab) in Finland. Outcomes presented expected annual and cumulative drug-associated costs in the overall population and per patient. Setting was modelled public specialist care in Finland. Time was set to 4 years, without discounting. Effects covered expected drug-associated costs (screening, acquisition, administration, monitoring, adverse events, travelling, productivity). Perspective was a limited societal perspective. Sensitivity analyses regarding all PICOSTEPS components were conducted.

Results: Cladribine tablets were projected to be cost saving in comparison to fingolimod,

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natalizumab and treatment mix. The respective modelled savings were €4,598,742, €16,249,701 and €6,928,934 in the overall population, and €16,424, €58,035 and €24,746 per patient, respectively, during the 4 years. The most important cost driver was drug costs, representing 96.3%, 96.0% and 83.4% of modelled costs associated with cladribine tablets, fingolimod and natalizumab, respectively. Cladribine tablets sustained their affordability in the sensitivity analyses. From the perspective of health care payer, cladribine tablets' savings were projected to be €4,514,509, €15,145,366 and €6,640,680 in the overall population, and €16,123, €54,091 and €23,717 per patient in comparison to fingolimod, natalizumab and treatment mix, respectively.

Conclusion: Based on the CAM, cladribine tablets were projected to robustly save modelled drug-associated costs in comparison to fingolimod, natalizumab and their mix in Finland.

Keywords: Cladribine tablets; Cost; Fingolimod; Multiple sclerosis; Natalizumab; Productivity; Travelling

Key Summary Points

Why carry out this study?

Multiple sclerosis results in considerable financial burden.

Research of costs in highly active multiple sclerosis is scarce, especially in the Finnish setting.

Drug-related costs of three multiple sclerosis treatments and a treatment mix of fingolimod and natalizumab in highly active relapsing multiple sclerosis were modelled over 4 years in Finland.

What was learned from the study?

Drug-related costs of cladribine tablets were €71,413 per patient. The respective per-patient costs for fingolimod, natalizumab and treatment mix were €16,424; €58,035; and €24,746 higher, respectively.

Cladribine tablets were robustly projected to be a cost-saving treatment option compared to fingolimod, natalizumab and their treatment mix in the Finnish setting.

INTRODUCTION

Multiple sclerosis (MS) is an immune-mediated disorder of the central nervous system with a wide heterogeneity in the clinical course. Most patients are classified as having a relapsing–remitting MS (RRMS) [1], which is further classified as active or highly active, based on the relapse rate and magnetic resonance imaging (MRI) findings [2]. Approximately 4–14% of all MS patients, depending on the definition used, already have a highly active disease course from the onset [3]. During the disease trajectory, this subgroup of patients is marked by a rapid accumulation of functional deficits and MRI activity, despite treatment with one or more disease-modifying drugs (DMDs) [4].

MS is a leading cause of disability in adults, and requires lifelong treatment [5, 6]. The average time from MS onset to death is 35 years [7]. There is no cure for MS, but DMDs prevent relapses and delay disease progression [8].

According to the Finnish treatment guidelines, patients eligible to receive a DMD for highly active disease need to show one relapse in the previous year and at least one T1 gadolinium-enhancing lesion or 9 or more T2 lesions while on therapy with a DMD, or two or more relapses in the previous year, whether or not on DMD [9]. Three approved DMDs for the highly active disease are used in Finland: cladribine tablets, fingolimod and natalizumab [10–12]. Cladribine tablets are approved for use for the treatment of adult patients with highly active relapsing MS, including RRMS, and relapsing secondary progressive MS populations [10].

Finland is a high-risk MS region with a prevalence of 280/100,000 in southwest parts of the country [13], and a nationwide prevalence

estimate between 10,000 and 11,000 patients, corresponding to a crude prevalence of 180–200/100,000 [14]. The estimated annual economic burden of MS in Finland using a bottom-up approach of costing was €46,994 per patient on average and increasing from €10,835 to €109,901 in parallel with advancing disability [15]. Based on a modelled economic evaluation of RRMS patients who have initiated a DMD, effective and reasonably priced DMDs may compensate for various RRMS-related costs in a 15-year time horizon [16]. The impact of MS medication costs on overall healthcare systems has been assessed by per-member per-period costs, where MS represents the fourth most expensive therapy class following inflammatory conditions, diabetes and cancer [17]. In Finland, the estimated proportion of total costs attributable to DMDs is high over 1-year [15] and moderately high (11–18%, depending on DMD) over 15-year [16] time horizons among RRMS patients who have initiated DMD and were valid for a publicly reimbursed DMD.

The costs and cost-effectiveness of DMDs indicated for highly active disease in Finland have not previously been published. In foreign settings and modelled comparisons, cladribine tablets have been observed to be dominant (i.e. lower cost and higher effectiveness) in various settings: compared to fingolimod in Spanish patients with highly active relapsing disease [18], compared to alemtuzumab and natalizumab in English patients with highly active RRMS [19], and compared to alemtuzumab and fingolimod in patients with highly active RRMS as well as compared to natalizumab in patients with rapidly evolving severe disease in the Dutch setting [20]. A cost assessment model (CAM) was developed to project the costs of DMDs for highly active disease in Finland.

METHODS

The CAM was developed with the programming language *R* to project drug-related costs of selected highly active MS therapies based on input parameters described below. The CAM approach was developed for easy and safe estimation of costs over time. To ensure the

coverage of important features, PICOSTEPS principle [16, 21–23] was applied in the CAM dashboard.

PICOSTEPS (Patients–Intervention–Comparators–Outcomes–Setting–Time–Effects–Perspective–Sensitivity analysis) is a framework for reporting health economic studies. It covers the essential parts of health economic evaluations in their order of importance [16, 21, 23]; (Table 1). PICOSTEPS has been used in multiple Finnish health economic studies and in a Current Care guideline [16, 21, 23].

Patients

The yearly number of Finnish relapsing MS patients with highly active disease, who initiate DMD or switch from another DMD, is estimated to be approximately 280, based on Finnish reimbursement statistics. Based on this estimation, the size of the modelled patient population was chosen to be 280.

Patients were modelled to have cladribine tablets 10 mg (cumulative dose 3.5 mg/kg over 2 years) (intervention), or alternatively (1) fingolimod 0.5 mg, (2) natalizumab 300 mg or (3) a treatment mix consisting of 80% patients using fingolimod and 20% of patients using natalizumab based on the Finnish clinical practice, and their similar patient populations defined in their summaries of product characteristics [10–12] (comparators). Highly active disease patients are defined by clinical or imaging features according to the Finnish treatment guidelines and reimbursement criteria [9, 24, 25]. Seventy-two percent of patients were women in the model input [16]. Patients were assumed to stay alive until the end of follow-up (4 years).

The analysis was based on modelling, and the data utilized were obtained from previously conducted studies. The study did not include any new studies with human participants or animals performed by any of the authors. Thus, the study was not registered with any clinical trial database.

Table 1 PICOSTEPS applied in the highly active relapsing MS cost assessment model (CAM) input

PICOSTEPS [16, 21–23]	Definition	Respective sources
P: patients	Disease: highly active relapsing MS	[9–12, 24, 25]
	Feasible MS population in Finland: 280 patients	Sales statistics estimate for dynamic population
	Gender: 72% women	[16]
	Weight: 86.4 kg male, 72.4 kg female	[26]
I: intervention	Cladribine tablets	[10]
C: comparators	Fingolimod and natalizumab, and a treatment mix (80% use fingolimod, 20% use natalizumab)	[11], Finnish clinical practice for natalizumab, sales statistics for the treatment mix
O: outcomes	Expected annual and cumulative drug-associated costs, cost dispersion	Rationale: [27, 28]
S: setting	Modelled specialist care in Finland	[10–12]; clinical practice
T: time	Four years drug acquisition costs at June 2019 values, hospital district tariffs at 2019 values, other costs at year 2018 values, no discounting	Rationale: [27, 28]
E: effects	Drug-associated costs (screening, acquisition, administration, monitoring, adverse events, travelling, productivity)	SmPCs [10–12] or clinical practice; see Tables 2 and 3
P: perspective	Drug-related costs (partially societal)	Logical assumption
S: sensitivity analyses	P: 50% or 90% female	Assumption
	P: average age 36 years	[16]
	P: age–weight distribution	[26]
	I: adherence decreases 10% each year	As above, assumption
	C: adherence decreases 10% each year	Assumption
	S: no screening	Assumption
	T: 3-year results	Assumption
	E: fingolimod use based on clinical practice	Finnish clinical practice (fingolimod)
	E: natalizumab use based on Tysabri SmPC	[12]
	E: natalizumab administration based on Finnish price tariffs	[29, 30]
	E: All cost inputs \pm 20%	Assumption
	E: fingolimod used after cladribine tablets (sequential approach)	Assumption (risks: [31])
	P: direct costs	[32]
P: direct costs without travelling costs	[32]	
P: drug costs alone	[32]	

Table 2 Monitoring and AEs associated with each drug based on their respective summaries of product characteristics

Treatment	Cladribine				Fingolimod				Natalizumab						
	Screening	Year 1	Year 2	Year 3	Year 4	Screening	Year 1	Year 2	Year 3	Year 4	Screening	Year 1	Year 2	Year 3	Year 4
Monitoring						1									
Electrocardiogram (EKG), 6 h															
Full blood count, FBC	1	2	3			1	1	1	1	1					
JC virus antibodies											1				
Latent infections	1	1													
Magnetic resonance imaging (MRI) of head and spine	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Ophthalmologic examination						1									
Transaminases, bilirubin						1	5	1	1	1					
Varicella zoster (VZ) antibodies	1					1									
VZ vaccination	0.15					0.15									
Test taking	1	2	3	0	0	1	5	1	1	1	1	0	0	2	2
Adverse event							0.0555	0.0555	0.0555	0.0555					
Abnormal laboratory findings related to liver function ^a															
Lymphopenia ^b		0.105	0.105	0.105	0.105		0.0408	0.0408	0.0408	0.0408					

^a [39]^b (cladribine tablets) [40], (fingolimod) [39]

Table 3 Unit costs utilized in the analysis

Cost driver	Expense	Cost (€)	Reference	
Drug acquisition	Cladribine 10 mg, 1 tbl	2433.69	FMT 06/19 [34]	
	Cladribine 10 mg, 4 tbl	9624.82	FMT 06/19 [34]	
	Cladribine 10 mg, 6 tbl	14,418.91	FMT 06/19 [34]	
	Fingolimod 0.5 mg 7tbl	427.62	FMT 06/19 [34]	
	Fingolimod 0.5 mg 28tbl	1612.99	FMT 06/19 [34]	
	Natalizumab 300 mg	2250.00	FMT 06/19 [34]	
Drug administration	Natalizumab NaCl for infusion	0.87	FMT 06/19 [34]	
	Natalizumab infusion administration ^c	309.82	[38] indexed to 2018 value ^a	
Monitoring	Electrocardiogram (EKG), 6 h ^f	587.00	[30]	
	Full blood count, FBC	4.60	[35]	
	JC virus antibodies	70.00	[35]	
	Latent infections	120.53	[35]	
	Magnetic resonance imaging (MRI) of head and spine ^e	320.00	[30]	
	Ophthalmologic examination ^c	215.60	[36] indexed to 2018 value ^a	
	Transaminases, bilirubin	4.00	[35]	
	Varicella zoster (VZ) antibodies	20.00	[35]	
	VZ vaccination ^d	203.68	[36] indexed to 2018 value ^a /FMT 6/2019 [34]	
	Test taking ^d	5.52	[37] indexed to 2018 value ^a	
	Adverse event	Abnormal laboratory findings related to liver function ^d	96.26 ^b	[36] indexed to 2018 value ^a , VSSHP [35]
		Lymphopenia ^d	226.83 ^c	[36] indexed to 2018 value ^a , [35]
	Travelling	Primary care	7.40	[37] indexed to 2018 value ^a
Secondary care		37.80	[37] indexed to 2018 value ^a	
Productivity loss	Primary care (1/4 day)	64.24	[42] indexed to 2018 value ^a	
	Secondary care (half a day)	128.48	[42] indexed to 2018 value ^a	
	Full day	256.96	[42] indexed to 2018 value ^a	

FMT Finnish Medicines Tariff

^a Official Statistics of Finland [41]

^b Blood test, specialist paper consultation, specialist telephone consultation, 5% of patients an additional specialist visit and upper stomach ultrasound

^c Lymphocytes differential count, specialist paper consultation, specialist telephone consultation

^d Productivity loss and travelling cost for this procedure estimated to be ¼ day

^e Productivity loss and travelling cost for this procedure estimated to be ½ day

^f Productivity loss and travelling cost for this procedure estimated to be full day

Resources and Costs

The primary focus on analytical perspective was on drug-related costs. The perspective was partially societal, considering direct drug-related costs, such as drug acquisition and administration costs, monitoring and adverse events (AEs), as well as indirect drug-related costs such as productivity loss (absenteeism) and travelling costs related to the health care resources used. This perspective considers the direct costs to the same extent as the Finnish medicines agency (Fimea) guidelines on the evaluation of hospital products [33].

Drug-associated screening, acquisition, administration (also including infusions where relevant), monitoring, AEs, travelling, and productivity costs (Tables 2 and 3) were based on Finnish practices, sources and price tariffs [16, 29, 30, 34–38], and SmPCs [10–12]. Official Finnish list prices of drugs from June 2019 were applied. No treatment pauses or discontinuations were permitted in the base case, but their impact was tested in the sensitivity analyses.

Cladribine tablets were used according to the Mavenclad SmPC, i.e. two annual treatment courses giving a cumulative dose of 3.5 mg/kg over 2 years and applying 86.4 kg average weight for men and 72.4 kg average weight for women (average adult weight in nationally representative FinTerveys study [26]). In sensitivity analyses, age and age–weight distributions were applied to inform the dosing of cladribine tablets [26]. In addition, 24% of cladribine tablets users were assumed to initiate fingolimod on the fourth year, based on the proportion of relapse-free patients (76%) in a CLARITY extension study [31].

Conservatively (i.e. not benefitting cladribine tablets), fingolimod users collected a 7-tablet pack and 13 28-tablet packs from a community pharmacy during the first year of their treatment, and 13 28-tablet packs annually as per label [11], which is the most affordable treatment practice for fingolimod. In the sensitivity analysis, 14 28-tablet packs were assumed to be collected from a community pharmacy during the first year based on the Finnish clinical practice. Since cladribine tablets and fingolimod have restricted reimbursements in

Finland, and they are used in an outpatient setting [24, 25], the retail prices of Finnish medicine tariff [34] excluding value added tax (VAT 10%) were used.

Likewise, natalizumab was conservatively assumed to be administered 12 times per year in a hospital setting based on the Finnish clinical practice and the most affordable treatment practice for natalizumab. In the sensitivity analysis, 14 natalizumab infusions took place during the first year and 13 during subsequent years based on the 28-day dosing interval described in the SmPC [12]. The official wholesale price was used for hospital-administered natalizumab [34] and its administration cost was accrued from a Finnish study [38]. In the sensitivity analyses, two other sources for the administration costs were applied. The administration costs (€934.50 and €373.00) were based on a drug-inclusive administration cost (€2623.00) found in the price tariff of the Hospital District of Pirkanmaa, Finland, [29] of which the cost of administration was derived from the total cost by subtracting (1) the official wholesale price of natalizumab dose (€2250.00) and (2) the average drug price of natalizumab (€1688.50) found in the price tariff of the hospital district of Uusimaa, Finland [30].

Statistical significance related to risk assessment can be impacted, for example, by assumed statistical power, accrued sample size and follow-up time. Thus, the AEs for CAM were accounted for by annualizing the AE probabilities [43] of clinical trials [39, 40, 44], and by applying an inclusion threshold of $\geq 4\%$ between the active treatment and placebo in the AE probability [16].

Finally, analytical perspective can have a considerable impact on the outcomes of health economic evaluation (e.g. [16, 21, 45–47]). In this modelled assessment, productivity costs were based on absenteeism due to drug-associated screening, infusions, monitoring, AEs, and travelling. Absenteeism was valued based on the human capital approach using a Finnish valuation. Sensitivity analyses covered different costing perspectives.

Outcomes

Primary outcomes included undiscounted modelled annual and cumulative treatment-related costs presented in the overall population of 280 patients and per patient. The cost drivers were defined in year 2018 (unit costs in older than year 2018 values were indexed to the year 2018 real value) and 2019 values. Annual costs were calculated by adding up the cost drivers for each treatment per year, and the cumulative costs by adding up the annual costs and the screening costs for each treatment.

Extensive deterministic sensitivity analyses were conducted for all PICOSTEPS inputs.

RESULTS

Overall, the intervention (cladribine tablets) were projected to reduce the expected drug associated costs in comparison to the comparators (fingolimod, natalizumab, treatment mix) during the 4-year treatment period and associated screening (Figs. 1, 2; Tables 4, 5).

Annual Costs

Annual modelled costs during the 4-year treatment period were relatively stable for the comparators, but not for cladribine tablets (Figs. 1, 2; Tables 4, 5). Cladribine tablets are acquired in

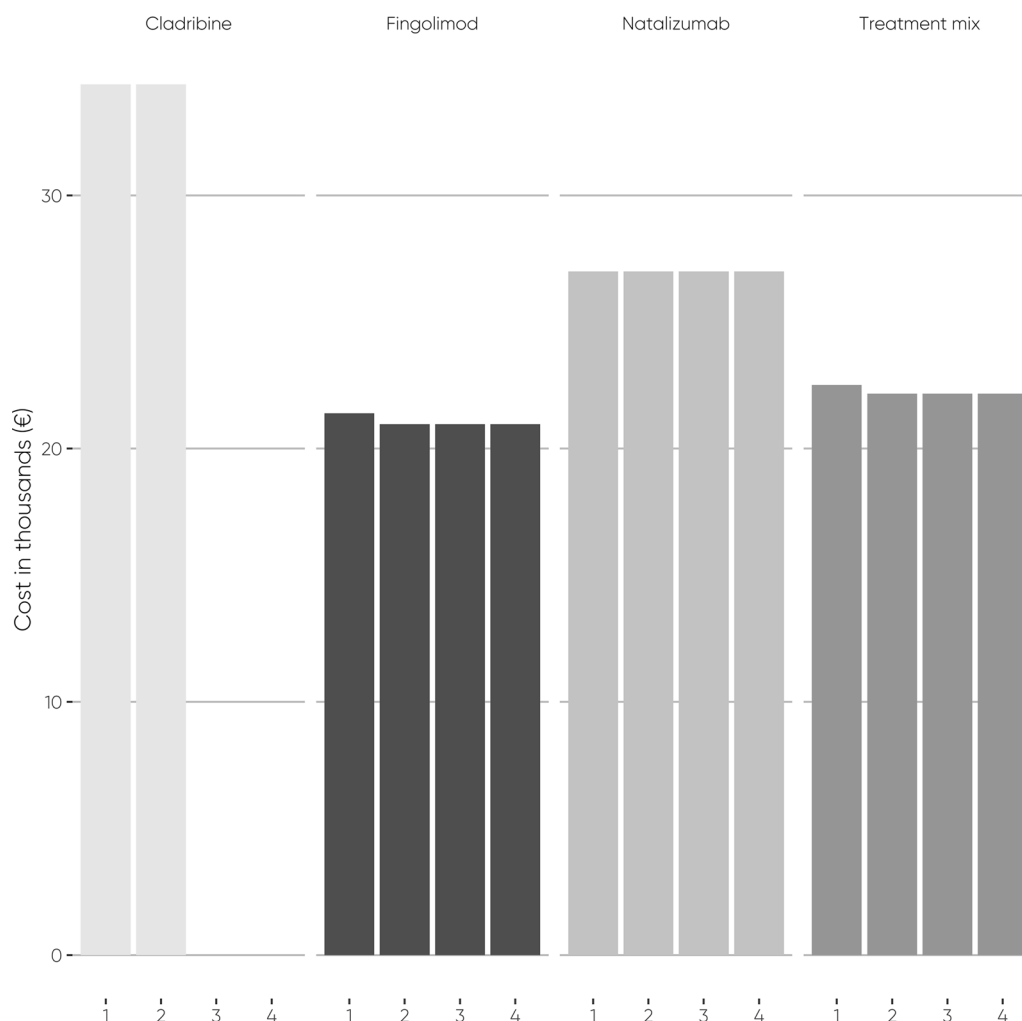


Fig. 1 Annual acquisition costs per patient

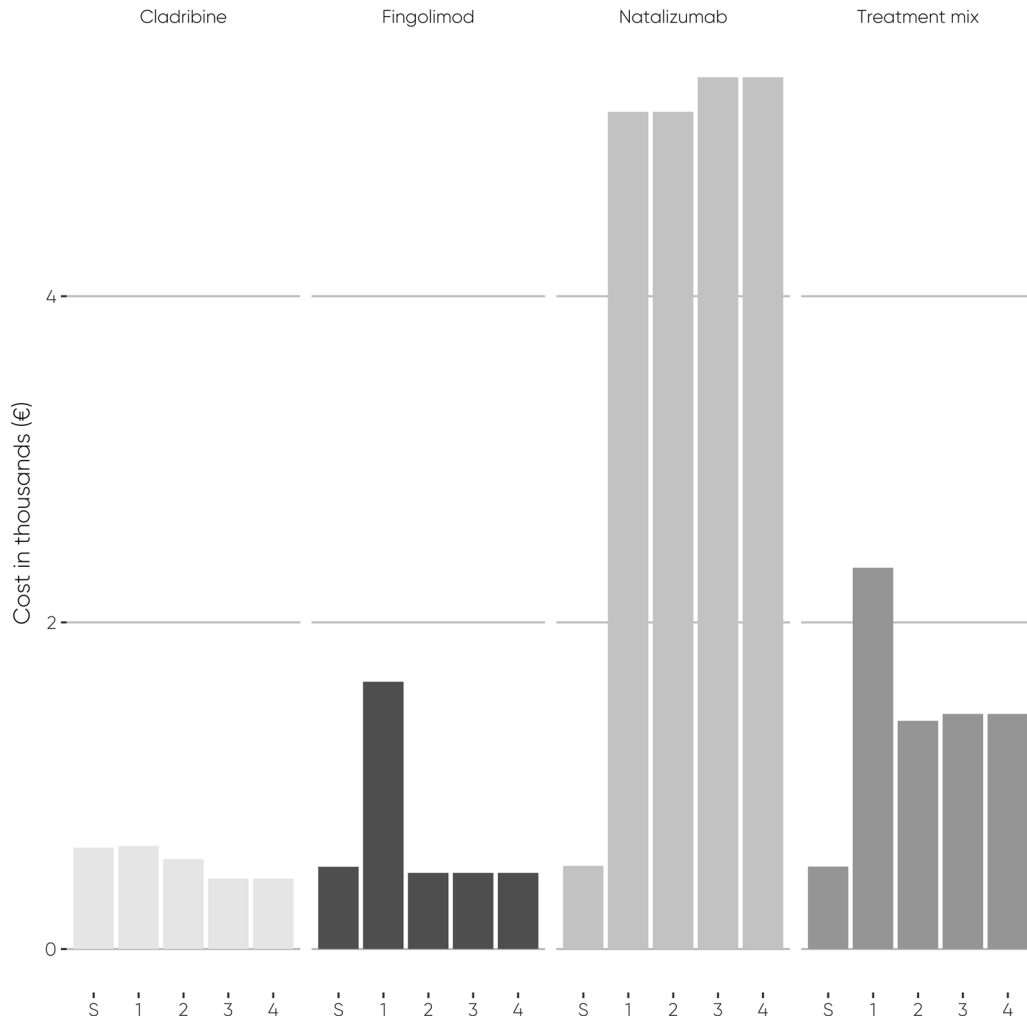


Fig. 2 Drug-associated screening costs, and annual monitoring, administration, AEs, travelling, and productivity costs per patient. S = Screening

the first 2 years, whereas the comparators are acquired continuously.

The modelled total screening costs of cladribine tablets were €619 per patient and €173,303 in the overall population. The modelled total screening costs of fingolimod, natalizumab, and treatment mix were €502, €509, and €504 per patient and €140,674, €142,449, and €141,029, respectively, in the overall population.

In the first year, the modelled costs of cladribine tablets were €35,007 per patient and €9,802,041 in the population. In comparison, the modelled costs of fingolimod, natalizumab, and the treatment mix were €23,034, €32,129,

and €24,853 per patient and €6,449,493, €8,996,169, and €6,958,828 in the overall population, respectively.

The modelled costs in the second year with cladribine tablets were €34,927 per patient and €9,779,547 in the overall population. In comparison, the second-year modelled costs of fingolimod, natalizumab, and the treatment mix were €21,434, €32,129, and €23,573 per patient and €6,001,421, €8,996,169, and €6,600,370 in the overall population, respectively.

During the third and fourth years, the modelled drug-associated costs remained unchanged in both years for each treatment. Because cladribine tablets had no drug-acquisition costs

Table 4 Drug-associated costs (€) per patient

Drug	Screening	Year 1	Year 2	Year 3	Year 4	Sum	Difference to cladribine
Cladribine							
Adverse event	0	24	24	24	24	95	NA
Drug acquisition	0	34,376	34,376	0	0	68,753	NA
Monitoring	501	461	350	320	320	1952	NA
Productivity loss	71	93	116	48	48	376	NA
Travelling	46	53	61	39	39	238	NA
Sum	619	35,007	34,927	430	430	71,413	NA
Fingolimod							
Adverse event	0	15	15	15	15	58	– 37
Drug acquisition	0	21,396	20,969	20,969	20,969	84,303	15,550
Monitoring	385	1175	334	334	334	2562	610
Productivity loss	71	297	70	70	70	579	203
Travelling	46	151	46	46	46	335	98
Sum	502	23,034	21,434	21,434	21,434	87,837	16,424
Natalizumab							
Adverse event	0	0	0	0	0	0	– 95
Drug acquisition	0	27,000	27,000	27,000	27,000	108,000	39,247
Drug administration	0	3728	3728	3728	3728	14,913	14,913
Monitoring	396	320	320	471	471	1978	25
Productivity loss	68	590	590	635	635	2517	2141
Travelling	45	491	491	506	506	2040	1803
Sum	509	32,129	32,129	32,340	32,340	129,448	58,035
Treatment mix							
Adverse event	0	12	12	12	12	47	– 48
Drug acquisition	0	22,517	22,175	22,175	22,175	89,042	20,290
Drug administration	0	746	746	746	746	2983	2983
Monitoring	387	1004	331	362	362	2445	493
Productivity loss	71	355	174	183	183	967	591
Travelling	46	219	135	138	138	676	439
Sum	504	24,853	23,573	23,615	23,615	96,159	24,746

Table 5 Drug-associated costs (€) in the population

Drugs and cost drivers	Screening	Year 1	Year 2	Year 3	Year 4	Sum	Difference to cladribine
Cladribine							
Adverse event	0	6637	6637	6637	6637	26,548	NA
Drug acquisition	0	9,625,384	9,625,384	0	0	19,250,767	NA
Monitoring	140,337	129,016	98,102	89,600	89,600	546,655	NA
Productivity loss	20,001	26,062	32,411	13,363	13,363	105,200	NA
Travelling	12,965	14,942	17,013	10,799	10,799	66,519	NA
Sum	173,303	9,802,041	9,779,547	120,399	120,399	19,995,689	NA
Fingolimod							
Adverse event	0	4074	4074	4074	4074	16,295	– 10,253
Drug acquisition	0	5,991,017	5,871,284	5,871,284	5,871,284	23,604,868	4,354,101
Monitoring	107,708	328,946	93,554	93,554	93,554	717,316	170,662
Productivity loss	20,001	83,153	19,657	19,657	19,657	162,125	56,925
Travelling	12,965	42,304	12,853	12,853	12,853	93,826	27,308
Sum	140,674	6,449,493	6,001,421	6,001,421	6,001,421	24,594,430	4,598,742
Natalizumab							
Adverse event	0	0	0	0	0	0	– 26,548
Drug acquisition	0	7,560,000	7,560,000	7,560,000	7,560,000	30,240,000	10,989,233
Drug administration	0	1,043,902	1,043,902	1,043,902	1,043,902	4,175,607	4,175,607
Monitoring	110,746	89,600	89,600	131,892	131,892	553,730	7075
Productivity loss	19,049	165,089	165,089	177,788	177,788	704,801	599,602
Travelling	12,654	137,578	137,578	141,721	141,721	571,252	504,733
Sum	142,449	8,996,169	8,996,169	9,055,302	9,055,302	36,245,390	16,249,701
Treatment mix							
Adverse event	0	3259	3259	3259	3259	13,036	– 13,512
Drug acquisition	0	6,304,814	6,209,027	6,209,027	6,209,027	24,931,894	5,681,127
Drug administration	0	208,780	208,780	208,780	208,780	835,121	835,121
Monitoring	108,316	281,077	92,763	101,221	101,221	684,599	137,944
Productivity loss	19,811	99,540	48,743	51,283	51,283	270,660	165,460
Travelling	12,903	61,359	37,798	38,626	38,626	189,312	122,793
Sum	141,029	6,958,828	6,600,370	6,612,197	6,612,197	26,924,622	6,928,934

in the third and fourth years, the modelled costs of cladribine tablets plummeted by 99% to €430 per patient and €120,399 in the overall population per year. The modelled costs of fingolimod remained the same as during the second year. Modelled natalizumab costs increased by 0.7% compared to the first and second years and rose to €32,340 per patient and to €9,055,302 in the overall population per year, due to JC virus antibody testing and associated blood sampling, travelling, and productivity loss. The increase of modelled natalizumab costs also increased the total cost of the treatment mix compared to the second year of the treatment period by 0.2% to €23,615 per patient and to €6,612,197 in the overall population per year.

Over the 4-year treatment period, the average modelled annual costs were €17,699 for cladribine tablets, €21,834 for fingolimod, €32,235 for natalizumab and €23,914 for treatment mix. Consequently, cladribine tablets were projected to save 19–45% on the average annual drug-associated costs in comparison to the comparators.

Cumulative Costs

During the 4-year treatment period, cladribine tablets were found to have lower costs than the comparators in terms of cumulative modelled costs (Tables 4, 5). The modelled cumulative costs for the 4 years including screening were: cladribine tablets €71,413 per patient and €19,995,689 in the overall population of 280 patients, fingolimod €87,837 per patient and €24,594,430 in the overall population, natalizumab €129,448 per patient and €36,245,390 in the overall population, and treatment mix €96,159 per patient and €26,924,622 in the overall population. The largest difference for the cumulative costs in the overall population compared to cladribine tablets was with natalizumab (€58,035 per patient, €16,249,701 in the overall population; 81% difference in the cumulative costs), the second largest with the treatment mix (€24,746 per patient, €6,928,934 in the overall population; 35% difference), and the smallest difference was with fingolimod

(€16,424 per patient, €4,598,742 in the overall population; 23% difference).

Comparison of modelled cost drivers between the treatments demonstrates the comparative affordability of cladribine tablets (Tables 4, 5). The modelled cost of cladribine tablets' drug acquisition, monitoring, productivity loss, and travelling was the most affordable. The modelled cost of AEs with natalizumab was the most affordable. Because cladribine tablets and fingolimod are used orally without administration in the health care setting, only natalizumab and the treatment mix have administration costs. Tables 4 and 5 show the differences between the treatments per cost driver.

The most important cost drivers were drug-acquisition costs. The drug-acquisition costs represented 96.3%, 96.0%, 83.4% and 92.6% of modelled costs associated with cladribine tablets, fingolimod, natalizumab and treatment mix, respectively.

Sensitivity Analyses

Cladribine tablets remained affordable in the extensive sensitivity analyses (Tables 6, 7) with the 4-year time horizon.

The only analysis scenario where cladribine tablets were not the most affordable treatment alternative was the time horizon of 3 years, where fingolimod was €4580 less costly per patient and €1,282,280 less costly in the overall population and compared to cladribine tablets.

Cladribine tablets remained affordable after assuming subsequent treatment with fingolimod in the fourth year for a proportion (24%) of patients. The modelled cost of cladribine tablets was €76,959 per patient and €21,548,433 in the overall population. The savings were €10,879, €52,489, and €19,201 per patient and €3,045,997, €14,696,957, and €5,376,189 in the overall population in comparison to fingolimod, natalizumab, and treatment mix, respectively.

From the perspective of health care payer alone, cladribine tablets' modelled savings were projected to be €16,123, €54,091 and €23,717 per patient and €4,514,509, €15,145,366 and €6,640,680 in the overall population in

Table 6 Per-patient results of the sensitivity analyses covering all PICOSTEPS components (€)

Analysis	Cladribine tablets	Fingolimod (difference to cladribine tablets)	Natalizumab (difference to cladribine tablets)	Treatment mix (difference to cladribine tablets)
Base case	71,413	16,424	58,035	24,746
50% of patients women	72,468	15,369	56,980	23,691
90% of patients women	70,550	17,287	58,898	25,609
Age of the population 36 years	72,585	15,252	56,863	23,574
Patient weight based on Finnish real-life distribution instead of on an average	72,065	15,772	57,382	24,094
Annual adherence drop 10% after 1st year	67,976	7280	43,035	14,431
No screening costs	70,794	16,541	58,145	24,861
Time horizon 3 years	70,983	– 4580	26,124	1561
Fingolimod utilization: 14 28-tablet packs during the 1st year, 13 packs thereafter	71,413	17,609	58,035	25,694
Natalizumab utilization: 14 administrations during the 1st year, 13 administrations thereafter	71,413	16,424	71,254	27,390
Cost of natalizumab administration €934.50	71,413	16,424	88,020	30,743
Cost of natalizumab administration €373.00	71,413	16,424	61,068	25,353
All cost inputs -20%	57,131	13,139	46,428	19,797
All cost inputs +20%	85,696	19,709	69,642	29,695
24% of cladribine users assumed to switch to fingolimod on the fourth year	76,959	10,879	52,489	19,201
Direct costs only	71,037	16,221	55,893	24,155
Direct costs only, no travelling costs	70,800	16,123	54,091	23,717

comparison to fingolimod, natalizumab and treatment mix, respectively.

DISCUSSION

Our CAM-based modelled study of DMD-associated costs demonstrates that cladribine tablets

are a cost-saving treatment alternative for patients with highly active relapsing MS compared to fingolimod and natalizumab in the Finnish setting. The average 4-year modelled cost difference of drug-associated costs was €16,424 per patient compared to fingolimod, €58,035 compared to natalizumab, and €24,746 compared to treatment mix. In the overall

Table 7 Per-population results of the sensitivity analysis covering all PICOSTEPS components (€)

Analysis	Cladribine tablets	Fingolimod (difference to cladribine tablets)	Natalizumab (difference to cladribine tablets)	Treatment mix (difference to cladribine tablets)
Base case	19,995,689	4,598,742	16,249,701	6,928,934
50% of patients women	20,291,004	4,303,427	15,954,386	6,633,619
90% of patients women	19,754,067	4,840,363	16,491,322	7,170,555
Age of the population 36 years	20,323,777	4,270,654	15,921,613	6,600,845
Patient weight based on Finnish real-life distribution	20,178,296	4,416,134	16,067,093	6,746,326
Annual adherence drop 10% after 1st year	19,033,150	2,038,510	12,049,898	4,040,788
No screening costs	19,822,386	4,631,370	16,280,555	6,961,207
Time horizon 3 years	19,875,290	– 1,282,280	7,314,798	437,136
Fingolimod utilization: 14 28-tablet packs during the 1st year, 13 packs thereafter	19,995,689	4,930,645	16,249,701	7,194,456
Natalizumab utilization: 14 administrations during the 1st year, 13 administrations thereafter	19,995,689	4,598,742	19,951,070	7,669,207
Cost of natalizumab administration €934.50	19,995,689	4,598,742	24,645,460	8,608,085
Cost of natalizumab administration €373.00	19,995,689	4,598,742	17,098,900	7,098,773
All cost inputs –20%	15,996,551	3,678,993	12,999,761	5,543,147
All cost inputs +20%	23,994,826	5,518,490	19,499,641	8,314,720
24% of cladribine users assumed to switch to fingolimod on the fourth year	21,548,433	3,045,997	14,696,957	5,376,189
Direct costs only	19,890,489	4,541,817	15,650,099	6,763,473
Direct costs only, no travelling costs	19,823,970	4,514,509	15,145,366	6,640,680

population of 280 patients, the respective drug-associated cost differences to cladribine tablets were €4,598,742, €16,249,701, and €6,928,934. The most important cost drivers of modelling were drug-acquisition costs, which accrued 96.3% of the total costs for cladribine tablets, 96.0% for fingolimod, 83.4% for natalizumab, and 92.6% for treatment mix, and drug

administration for natalizumab, which was the only intravenous drug in the study.

Cladribine tablets were also cost saving in all sensitivity analyses with a 4-year time horizon, even when assuming a sequential approach. These findings are supported by cost estimates from other settings [18–20]. The only exception was with the 3-year time horizon, in which

fingolimod was €4580 less costly per patient and €1,282,280 less costly in the overall population compared to cladribine tablets.

As in all health economic modelling, the results of the present study are subject to uncertainty. Although progressive multifocal leukoencephalopathy (PML) is a severe adverse event associated with natalizumab, and to a lesser extent also with other MS drugs [48], the treatment-related risk of PML in MS is still very low [49]. Due to the high uncertainty in the PML incidence data in clinical trials, it was not considered in our analyses. The total cost of natalizumab, therefore, can be an underestimate.

In addition, we did not include MS relapses in the analysis, despite their impact on costs based on Finnish real-world evidence [16], due to the lack of sufficiently comparable evidence regarding relapse incidence. However, as the cost of relapse is likely to be relatively low (€1316 for events not requiring hospitalization and €5619 for events requiring hospitalization [16]) compared to the total costs observed in the present study, the impact of relapses as AEs on the results would most likely have been low.

The inclusion of decreased persistence over time resulted in a decrease in the drug-acquisition and administration costs, and the decrease was more profound in drugs that were used for the whole 4 years, i.e. fingolimod and natalizumab. As the present analysis considered only drug-related costs, decreased persistence narrowed the cost gap between cladribine and comparators, although cladribine tablets remained the most affordable.

In addition, persistence does not only affect costs but also the treatment effects, which were outside the scope of this study. Therefore, the interpretation of the effect of persistence on the results does not reflect cost-effectiveness results.

Furthermore, the inclusion of costs related to disease progression (disability) could have had a significant impact on the total costs (see, e.g., [16]). However, their inclusion would have been complicated and most likely given unreliable results, as there are no direct randomised comparisons between cladribine tablets, fingolimod and natalizumab. However, cladribine tablets have demonstrated a comparable efficacy with

other DMDs for highly active disease in recent indirect comparison analyses [50–52]. Thus, speculatively, the inclusion of treatment effects could have even increased the affordability of cladribine tablets.

In systematic reviews, indirect comparisons, health economic analyses and models, systematic reporting is especially important [21, 50]. PICO is commonly applied in, e.g., evidence synthesis and Finnish current care treatment guidelines. Here, we applied an extended version of PICO (PICOSTEPS) [16, 21] in order to improve the readability of CAM and these results, and to present the core components of CAM. PICOSTEPS has previously been successfully applied in various health economic evaluations [16, 21–23, 46, 47, 53–56], and in real-world data-based predictive cost-effectiveness and cost–benefit assessments of first-line RRMS treatments [16].

In Finland, the prices of hospital-administered drugs may be confidentially negotiated (tendered) by the hospital, which may lead to lower drug costs paid by the hospital than the official drug price list suggests. On the other hand, this may lead to an underestimation of administration costs. As some hospitals' price tariff lists provide a single cost per administration visit (i.e. including both the administration and the drug), the proportion of administration may be higher than that observed by subtracting the official list price from the total cost of the administration visit.

The present study did not address the effectiveness or cost-effectiveness of the treatments, and nor did it include costs related to effectiveness. This was the main limitation of the study. Therefore, further studies are needed to provide this information, and to gain a more complete understanding of the potential of the different treatments.

CONCLUSION

Among patients with highly active relapsing MS, cladribine tablets are projected to robustly save expected drug-associated costs in comparison to fingolimod, natalizumab and their mix in Finland.

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Disclosures. Petri Mankinen is an employee of EsiOR Oy, Kuopio, Finland, but does not hold drug company shares. Tuomas Lundström is an employee of EsiOR Oy, Kuopio, Finland, but does not hold drug company shares. Erkki Soini is an employee of EsiOR Oy, Kuopio, Finland, and is also a shareholder, board member and the CEO of EsiOR Oy. EsiOR carries out studies, statistical analysis, consultancy, education, reporting, health economic evaluations and market access services for several pharmaceutical, food industry, diagnostics and device companies, hospitals, consultancies, academic institutions and projects, including the producers and marketers of MS treatments. However, they do not hold drug company shares. Marja-Liisa Sumelahti is an employee at Suomen Terveystalo, Finland, and a Senior Lecturer in Neurology at Tampere University, Finland. Juhani Ruutiainen is an employee of Finnish Neuro Society, Masku, Finland, and a Senior Lecturer in Neurology at the University of Turku, Turku, Finland. The Finnish Neuro Society looks after the interest of people with

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Compliance with Ethics Guidelines. The analysis in this article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

Data Availability. All data generated or analysed during this study are included in this published article.

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