

Cost-Utility of Cladribine Tablets and Dimethyl Fumarate in the Treatment of Relapsing Remitting Multiple Sclerosis From the Societal Perspective in Spain

Ginestal R¹, Durán O², Rubio-Terrés C³, Rubio-Rodríguez D³, De Los Santos H², Ordoñez C², Sánchez I²

- 1. Hospital Clínico San Carlos, Madrid, Spain
- 2. Merck, S.L.U., Madrid, Spain, an affiliate of Merck KGaA
- 3. HEALTH VALUE, Madrid, Spain

EE586



CONCLUSION



CladT had a 94.4% probability of being cost-effective for a willingness to pay of €25,000 per QALY gained, compared with DMF in the treatment of RRMS in Spain. CladT was also the dominant treatment across all scenarios tested.



Indirect costs, related to losses in productivity, were lower in the CladT arm (24,606 €) than in the DMF arm (37,159 €) in Stage 4 due to a slower disability progression. In fact, at the end of the 10-year horizon, the % of patients in the health state 4 was 18.2% and 30.2% with CladT and DMF respectively.



In the absence of troublesome side effects and excessive cost, this result would recommend a change in the patient's management, prioritizing an early use in terms of efficiency CladT vs DMF.



INTRODUCTION

- Multiple sclerosis can severely affect the patient's quality of life (QoL) due to their impaired functioning in daily living, more so if the help of caregivers is required, impeding family relations, work and social dynamics (1).
- It has been observed that in patients who start early treatment for multiple sclerosis (MS), there is a delay in the progression of the disease compared to patients who start treatment later (2).
- Indirect labor costs are estimated to account for up to 61% of the total cost of RRMS, which is logical considering that the average age of RRMS patients generally ranges between 38 and 45 years, people with full-time employment (3).
- Economic modelling can provide useful information to help decision-makers make informed evaluations on the efficient management strategy that generates savings and therefore contributes to the sustainability of NHS and social services in Spain.



OBJECTIVE

- To analyse the cost-utility of treatment of relapsing remitting multiple sclerosis (RRMS) with cladribine tablets (CladT) and dimethyl fumarate (DMF) from the societal perspective in Spain.



METHODS

- A probabilistic Markov model (second-order Monte Carlo simulation) with a 10-year time horizon and annual Markov cycles was performed, based on a model developed by the Canadian Agency for Drugs and Technologies in Health (CADTH) (4) (Figure 1).
- Data on progression, relapses, treatment adherence, treatment continuation and utilities (quality-adjusted life years [QALYs]) were obtained from the medical literature (4-7).
- The cost of drugs, monitoring, EDSS status, relapses, adverse reactions and indirect costs (loss of work productivity: number of days/hours off work per year and early retirement) were obtained from Spanish sources (8-11) (Table 1).

Figure 1. 5-state Markov model.

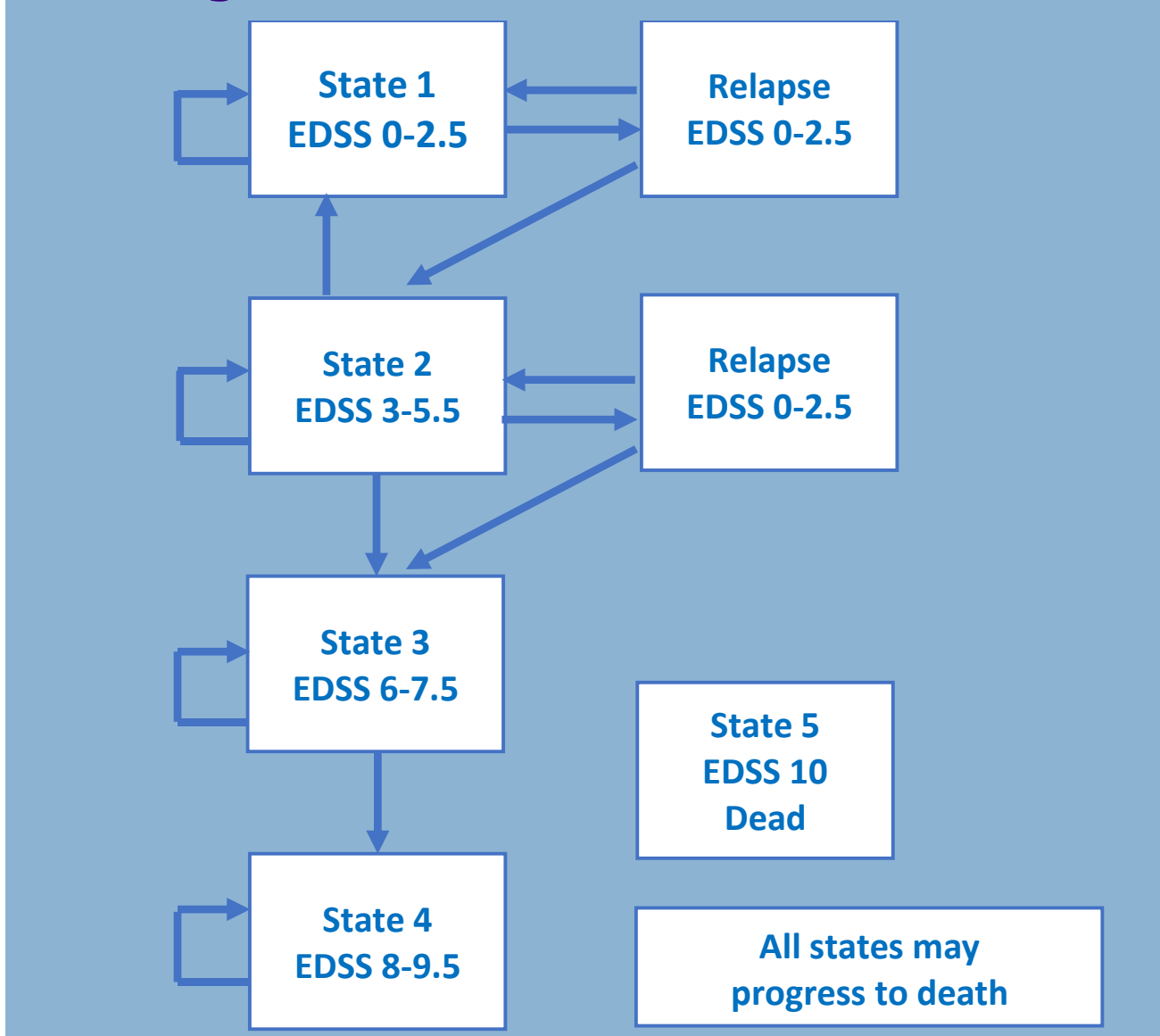


Table 1. Unit costs.

Costs per patient / event	CladT	DMF
Treatment/patient/10 years	92,151 €	153,300 €
Monitoring/patient/year	121.95 €	317.20 €
Adverse reactions/patient/year	852.15 €	862.24 €
Event cost by stage		Social perspective
State 1	11,282 €	
State 2	24,731 €	
State 3	47,387 €	
State 4	65,726 €	
Relapse	7,966 €	

- Univariate sensitivity analyses (modifying time horizon, cost of treatment continuation, and CladT and DMF purchase prices) were performed to confirm and provide robustness to the results.



RESULTS

- CladT was dominant over DMF in 94.1% of simulations, with lower costs (-81,637 € [95% CI -77,452; -88,549 €]) (Figure 2) and greater effectiveness (0.1399 [95% CI -0.2379; 0.2067] QALY) per patient, compared to DMF (Figure 3).

Figure 2. Cost difference per patient

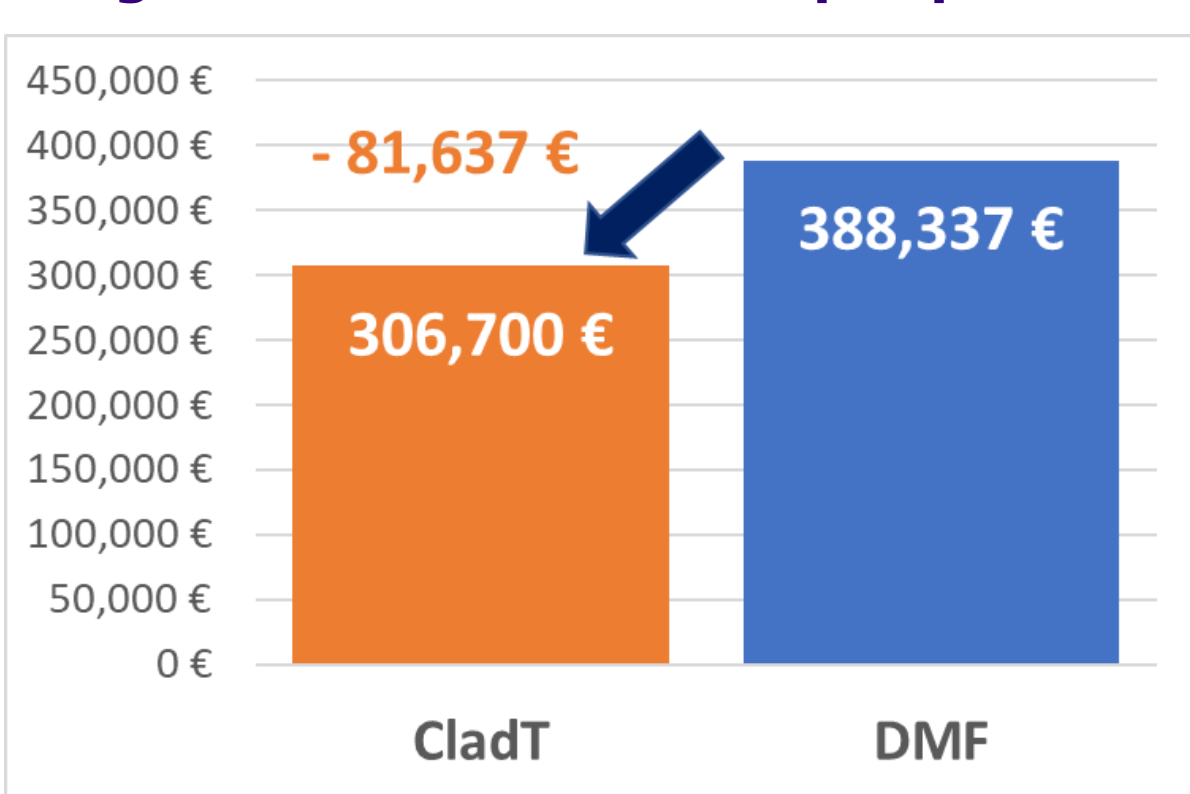
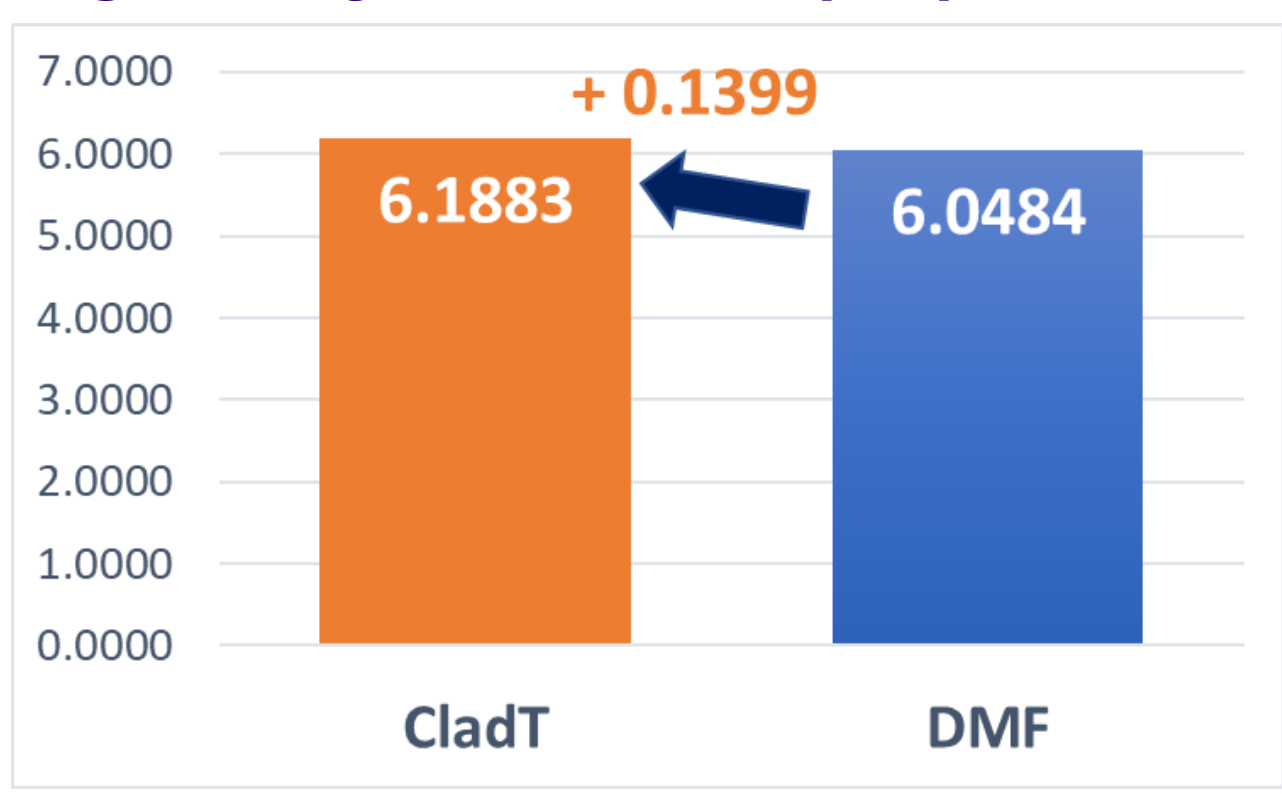


Figure 3. QALY difference per patient



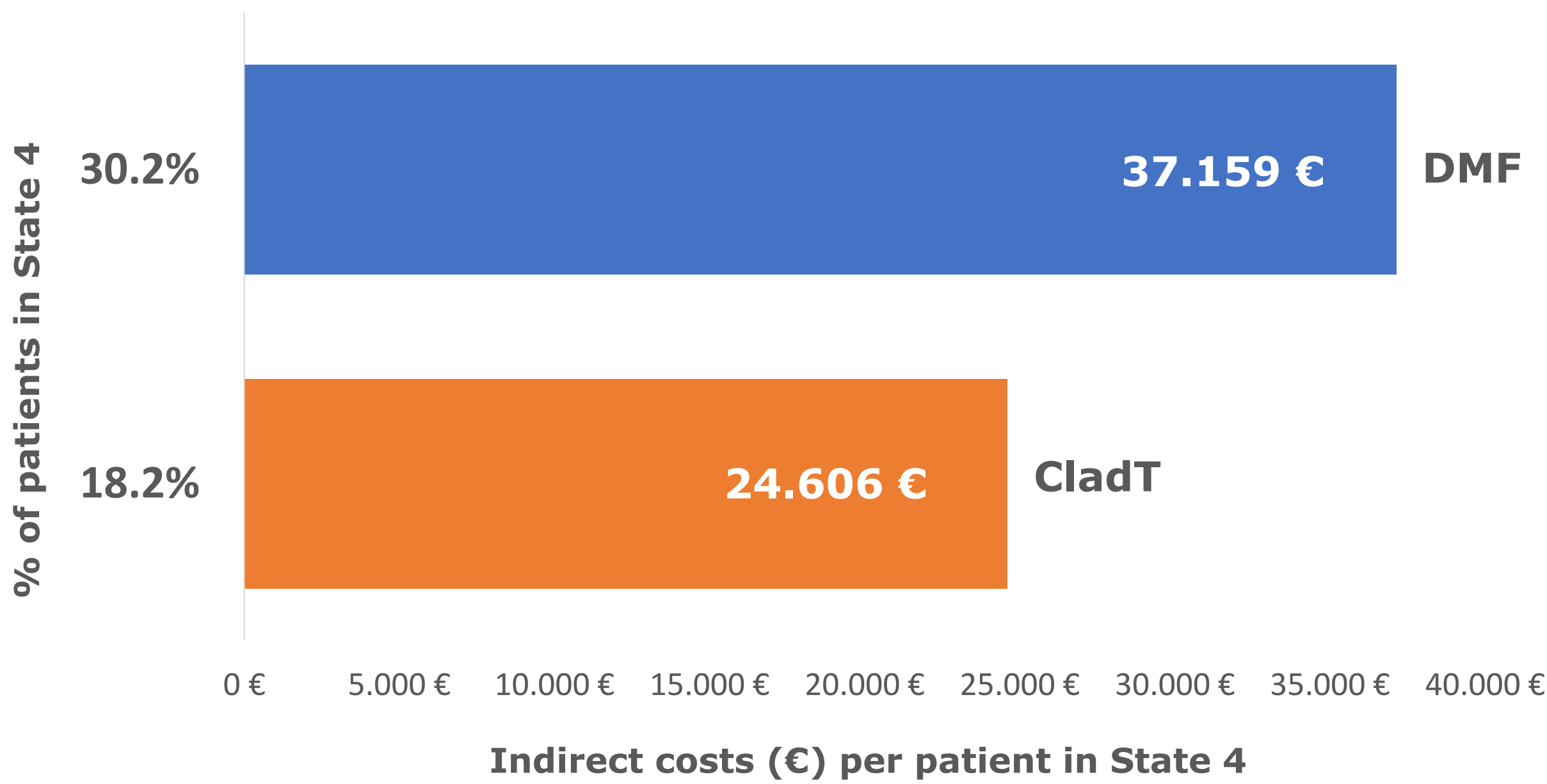
- CladT had a 94.4% probability of being cost-effective for a willingness to pay of €25,000 per QALY gained (Table 2). The results under this perspective were consistent with the results obtained from the perspective of the National Health System (13) and in the sensitivity analyses performed.

Table 2. Base case results

Treatment	Total cost per patient, mean (95% CI)	QALY per patient, mean (95% CI)	Cost difference	QALY difference	Probability of cost-effectiveness CladT vs DMF
CladT	306,700 € (283,777; 330,419 €)	6.1883 (1.3961; 7.4440)	-81,637 € (-77,452; -88,549 €)	0.1399 (-0.2379; 0.2067)	94.4%
DMF	388,337 € (361,229; 418,968 €)	6.0484 (1.6340; 7.2373)			

- Difference in costs can be explained by the innovative mechanism of action of CladT, which is based on the concept that the early depletion of autoreactive immune cells will have a long-term efficacy (12) and therefore has the potential to protect against relapses for years following the discontinuation of the treatment.

Figure 4. Indirect costs (€) per patient and % of patients in State 4 with CladT vs DMF.



- Indirect costs, related to losses in productivity, were lower in the CladT arm (24,606 €) than in the DMF arm (37,159 €) in Stage 4 due to a slower disability progression. In fact, at the end of the 10-year horizon, the % of patients in the health state 4 was 18.2% and 30.2% with CladT and DMF respectively (Figure 4).
- The difference of 0.1399 QALYs in favour of CladT was clinically relevant, since it is generally considered that the minimum clinically relevant utility difference (i.e., that which the patient is able to detect) between two interventions would be between 0.030 and 0.074 QALYs (14).
- In the absence of troublesome side effects and excessive cost, this result would recommend a change in the patient's management, prioritizing an early use in terms of efficiency CladT vs DMF.

1. Gil-González I, Martín-Rodríguez A, Conrad R, Pérez-San-Gregorio MÁ. Quality of life in adults with multiple sclerosis: a systematic review. *BMJ Open*. 2020; 10: e041249.
2. Chalmers TA, Baggesen LM, Norgaard M, Koch-Henriksen N, Mayani M, Sørensen PS, Danish Multiple Sclerosis Group. Early versus later treatment start in multiple sclerosis: a register-based cohort study. *Eur J Neurol*. 2018; 25: 1262-e110.
3. Sicras-Mainar A, Ruiz-Beato E, Navarro-Artieda R, Maurino J. Impact on healthcare resource utilization of multiple sclerosis in Spain. *BMC Health Serv Res*. 2017; 17: 854.
4. Canadian Agency for Drugs and Technologies in Health. CADTH therapeutic review. Comparative clinical and cost-effectiveness of drug therapies for relapsing-remitting multiple sclerosis [Internet]. Ottawa: The Agency; 2013 Oct. (CADTH Therapeutic Review vol.1, no. 2b). Available from: http://www.cadth.ca/media/pdf/TR0004_RRMS_ScienceReport_e.pdf.
5. Siddiqui MK, Khurana IS, Budhia S, et al. Systematic literature review and network meta-analysis of cladribine tablets versus alternative disease-modifying treatments for relapsing-remitting multiple sclerosis. *Curr Med Res Opin*. 2017; 34: 1361-71.
6. Su W, Kansal A, Vicente C, Deniz B, Sarda S. The cost-effectiveness of delayed-release dimethyl fumarate for the treatment of relapsing-remitting multiple sclerosis in Canada. *J Med Econ*. 2016; 19: 718-27.
7. Signorini A, Sacca F, Lanzillo R, Maniscalco GT, Signorilelo E, Repice AM. Cladribine vs other drugs in MS: Merging randomized trial with real-life data. *Neurol Neuroimmunol Neuroinflamm*. 2020; 7: e878.
8. Casado V, Martínez-Yélamos S, Martínez-Yélamos A, Carmona O, Alonso L, Romero L, Moral E, Gubieras L, Arbizu T. Direct and indirect costs of Multiple Sclerosis in Baix Llobregat (Catalonia, Spain), according to disability. *BMC Health Serv Res*. 2006; 6: 143.
9. Casado V, Bonaventura I, Brieval L, Martínez-Yélamos S, Martín G, Presas-Rodríguez S, et al. Direct costs of relapses in patients with Relapsing-remitting Multiple Sclerosis. *Neurol Persp*. 2021; DOI: <https://doi.org/10.1016/j.neurop.2021.05.003>.
10. Poveda JL, Trillo JL, Rubio-Terrés C, Rubio-Rodríguez D, Polanco A, Torres C. Cost-effectiveness of Cladribine T ablets and fingolimod in the treatment of relapsing multiple sclerosis with high disease activity in Spain. *Expert Rev Pharmacoecon Outcomes Res*. 2020; 20: 295-303.
11. BotPlus 2.0. Consejo General de Colegios Oficiales de Farmacéuticos (CGCOF). 2021. Available at URL: www.portalfarma.com (Accessed on: 18/06/2021).
12. Cladribine tablets : Oral immunotherapy of relapsing-remitting multiple sclerosis with short yearly treatment periods]. *Nervenarzt*. 2018; 89: 895-907. Article in German.
13. Ginestal R, Durán O, Rubio Terrés C, Rubio-Rodríguez D, De Los Santos H, Ordoñez C, et al. Cost-Effectiveness of Cladribine Tablets and Dimethyl Fumarate in the Treatment of Relapsing Remitting Multiple Sclerosis in Spain (EE149). Presented at the ISPOR Europe 2022 | 6-9 November 2022 | Vienna, Austria.
14. Wee H-L, Machin D, Luke W-C, Li S-C, Cheung Y-B, Luo N, et al. Assessing differences in utility scores: a comparison of four widely used preference-based instruments. *Value Health*. 2007; 10: 256-65.

ACKNOWLEDGEMENTS: Health Value provided editorial assistance, which was funded by Merck, S.L.U., Madrid, Spain, an affiliate of Merck KGaA