

Cost-Effectiveness of Dimethyl Fumarate Compared to Teriflunomide for Relapsing Remitting Multiple Sclerosis Patients in Italy: Results of an Updated Analysis

Lorenzo Giovanni Mantovani¹, Paolo Angelo Cortesi¹, Michela Molina², Laura Santoni², Luca Prosperini³

¹ Research Centre on Public Health (CESP), University of Milan—Bicocca, Monza, Italy

² Biogen Italia, Milan, Italy

³ Department of Neurosciences, S. Camillo-Forlanini Hospital, Rome, Italy

Dear Editor,

With regards to the article published in the journal *Farmeconomia, Health Economics and Therapeutic Pathways* in 2022; entitled “*Cost-Effectiveness of Dimethyl Fumarate Compared to Teriflunomide for Relapsing Remitting Multiple Sclerosis Patients in Italy*”, we would like to inform you that we reviewed and updated the following cost input data, with a specific focus on: i) disability-related annual costs, expressed in Euro and inflated from December 2015 to July 2023 (inflation coefficient 1.188) (Table I) [1]; ii) annual treatment costs with disease-modifying treatments (DMTs) (dimethyl fumarate and teriflunomide) were recalculated using the ex-factory prices per pack, iii) cost of relapse management (cost per episode) for Italian National Healthcare Service (NHS) and societal perspective that was obtained from Battaglia et al., 2017 [2], by inflating it with consumer price index from December 2015 to July 2023 [1]; iv) treatment-related adverse event costs were updated, as shown in Table II. In addition, the mortality tables of the general Italian population were aligned with the most recent evidence [3]. Finally, a threshold analysis was conducted to identify up to what level of discount applicable to teriflunomide price, dimethyl fumarate remains dominant or cost effective considering a willingness to pay (WTP) of € 50,000 per quality-adjusted life years (QALY) gained.

RESULTS OF THE UPDATED ANALYSIS

The results of the updated analysis confirm and strengthen those published in 2022, showing that in the base-case analysis (societal perspective and lifetime horizon), dimethyl fuma-

Corresponding author

Lorenzo Giovanni Mantovani
lorenzo.mantovani@unimib.it

Received 5 December 2024
Accepted 9 December 2024
Published 17 December 2024

Costs (€) ¹		EDSS level									
		0	1	2	3	4	5	6	7	8	9
Societal perspective	RRMS	5,337	5,337	5,337	5,337	24,280	24,280	24,280	45,124	45,124	45,124
	SPMS	11,660	11,660	11,660	11,660	53,044	53,044	53,044	98,579	98,579	98,579
NHS perspective	RRMS	2,758	2,758	2,758	2,758	8,841	8,841	8,841	9,996	9,996	9,996
	SPMS	6,026	6,026	6,026	6,026	19,315	19,315	19,315	21,839	21,839	21,839

Table I. Annual disability-related costs, by MS form and perspective [2,4]

¹ To avoid double counting DMT costs, disease management costs (e.g. monitoring, etc.) were subtracted from this calculation and considered in other calculation sections of the model

EDSS: expanded disability status scale; NHS: National Healthcare Service; RRMS: relapsing remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis

Description of cost	Value (€)	Source/Note
Acquisition per pack, dimethyl fumarate	1,153.00 (56 capsules, 240 mg)	Ex-factory price ¹ (Official Journal 122, 2022 [5])
Acquisition per pack, teriflunomide	1,027.75 (28 tablets, 14 mg)	Ex-factory price ¹ (Official Journal 256, 2021 [6])
Annual administration cost, dimethyl fumarate	0.00	Assumption, as both drugs are administered orally
Annual administration cost, teriflunomide	0.00	
Monitoring cost, dimethyl fumarate (Year 1)	892	[7,8]
Monitoring cost, teriflunomide (Year 1)	922	[7–9]
Monitoring cost, dimethyl fumarate (Year 2)	334	[7,8]
Monitoring cost, teriflunomide (Year 2)	350	[7–9]
Annual adverse events cost, dimethyl fumarate	32	Mild to moderate: GP [10] or the specialist [11] visit; Severe: DH or hospital admission [12,13]
Annual adverse events cost, teriflunomide	12	
Relapse management cost—cost per episode, societal perspective	3,089	Battaglia et al. 2017 [2], expressed in Euro (July 2023) [1]
Relapse management cost—cost per episode, NHS perspective	1,778	

Table II. Economic data included in the analysis

¹ It does not include temporary law reductions, and any discounts applied to structures of Italian NHS. The economic analysis included the discounts to the Italian National Healthcare Service (NHS);
 DH: day hospital; GP: general practitioner

Item	Dimethyl fumarate (A)	Teriflunomide (B)	Difference (A-B)
Outcome			
LYs	19.631	19.545	0.086
QALYs	6.530	5.956	0.573
Costs (€)			
Treatment costs ²	78,186 (6.9%)	69,794 (5.9%)	8,392
Adverse events	265 (0.0%)	89 (0.0%)	177
Relapse ³	50,873 (4.5%)	56,777 (4.8%)	-5,904
EDSS ³	1,008,389 (88.6%)	1,051,805 (89.2%)	-43,417
• Inpatient care	157,857 (13.9%)	164,546 (14.0%)	-6,689
• Day admission	39,948 (3.5%)	40,856 (3.5%)	-908
• Consultations	27,730 (2.4%)	28,702 (2.4%)	-972
• Tests	14,850 (1.3%)	14,788 (1.3%)	62
• Medication	24,095 (2.1%)	24,842 (2.1%)	-747
• Community service	96,831 (8.5%)	101,863 (8.6%)	-5,031
• Investments	33,589 (3.0%)	35,126 (3.0%)	-1,537
• Informal care	241,209 (21.2%)	252,348 (21.4%)	-11,139
• Absence, invalidity and early retirement	372,280 (32.7%)	388,735 (33.0%)	-16,455
Total social costs (€)	1,137,714 (100%)	1,178,465 (100%)	-40,752
ICER (€/QALY gained)	Dimethyl fumarate dominant		

Table III. Results of the incremental cost-effectiveness analysis (base-case: societal perspective and lifetime horizon)—Discounted (3.5% discount rate¹)

¹ National Institute for Health and Care Excellence (NICE). Guide to the methods of technology appraisal 2013. Available at: <http://www.nice.org.uk/article/pmg9/chapter/foreword>. (last accessed November 2024).

² Including monitoring costs

³ Including direct and indirect costs

EDSS: expanded disability status scale; ICER: incremental cost-effectiveness ratio; LYs: life-years; QALYs: quality-adjusted life years

rate is a dominant strategy (i.e. more effective and less costly) compared with teriflunomide, both in terms of survival (19.631 and 19.545 life years, LYs, respectively), and quality-of-life-adjusted survival (6.530 and 5.956 QALYs, respectively). The total lifetime cost per patient treated with dimethyl fumarate (€ 1,137,714) was lower than the cost per patient treated with teriflunomide (€ 1,178,465). Table III illustrates the results of the cost-effectiveness analysis.

The cost saving for patients treated with dimethyl fumarate vs teriflunomide was € 40,752. The saving is mainly evident on cost of community service (–€ 5,031), relapses (–€ 5,904), inpatient care (–€ 6,689), informal care (–€ 11,139) and long-term absence/early retirement (–€ 16,455).

In addition, the results of the base case analysis are also confirmed by the sensitivity analyses (deterministic and probabilistic). The one-way deterministic sensitivity analysis showed that dimethyl fumarate remains dominant compared with teriflunomide in all tested alternative scenarios. Five additional deterministic scenarios were conducted. In the first, Italian NHS perspective was adopted with lifetime horizon. In the second and third analyses, a shorter time horizon was used (15 years) to run both the Italian societal perspective and the Italian NHS perspective analyses. In the fourth and fifth analyses a shorter time horizon was used (5 years) to run both the Italian societal perspective and the Italian NHS perspective analyses (Table IV). The results of the probabilistic analysis are shown in Figure 1 (*scatter plot*) and Figure 2 (acceptability curve of the cost-effectiveness analysis—CEAC) which shows that when the willingness to pay (WTP) was € 50,000 per QALY gained, dimethyl fumarate had 84% probability of being cost-effective compared to teriflunomide. In 83.5% of the probabilistic simulations, dimethyl fumarate was dominant over teriflunomide.

Finally, a threshold analysis was conducted starting from the base-case analysis (Societal perspective and lifetime horizon) and shows that 1) dimethyl fumarate would remain dominant over teriflunomide, up to 61% discount in the acquisition cost of the latter; 2) dimethyl fumarate could be cost-effective compared with teriflunomide with a 98% discount to the acquisition cost of the latter, below a WTP of € 50,000 per QALY gained (Table V).

Alternative Scenario	Perspective	Time horizon	ICER (€/QALY gained)
#1	Italian NHS perspective	Lifetime	Dimethyl fumarate dominant
#2	Societal perspective	15 years	
#3	Italian NHS perspective	15 years	
#4	Societal perspective	5 years	
#5	Italian NHS perspective	5 years	

Table IV. Sensitivity analysis: results of alternative scenarios

ICER: incremental cost-effectiveness ratio; NHS: National Health Service; QALY: quality-adjusted life years

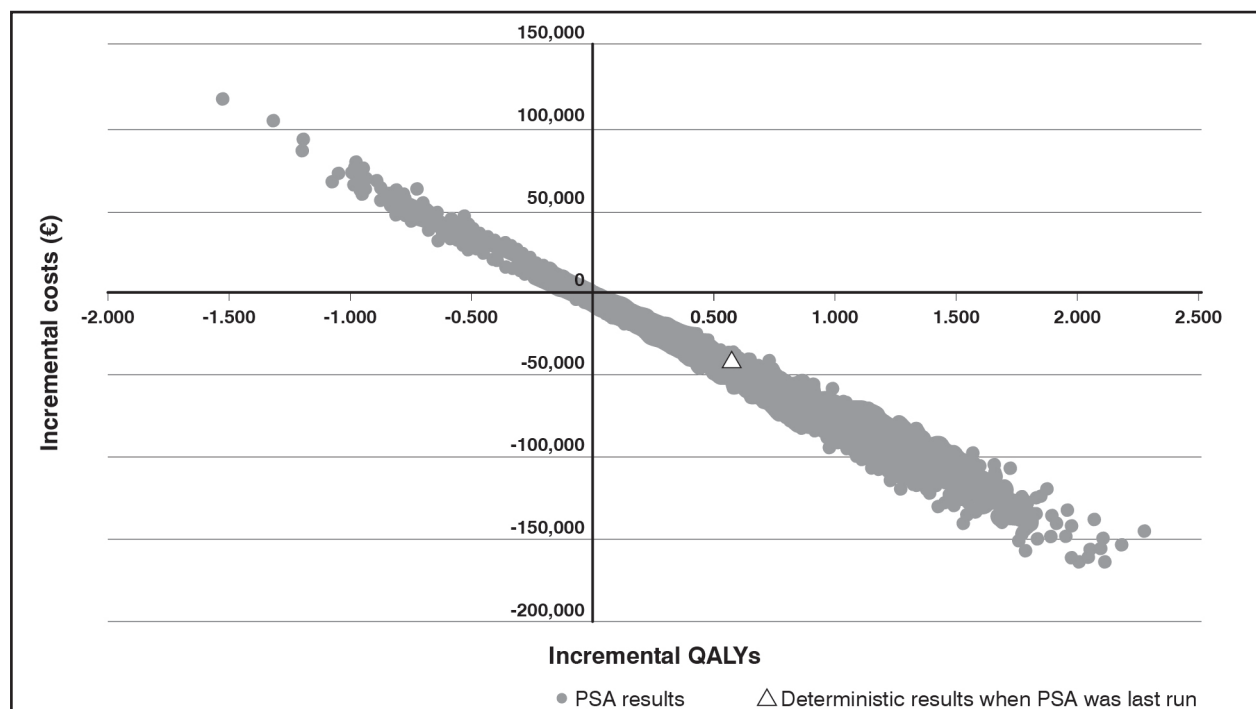


Figure 1. Probabilistic sensitivity analysis: scatter plot of dimethyl fumarate vs. teriflunomide (base-case: societal perspective and lifetime horizon)

PSA: probabilistic sensitivity analysis; QALY: quality-adjusted life years

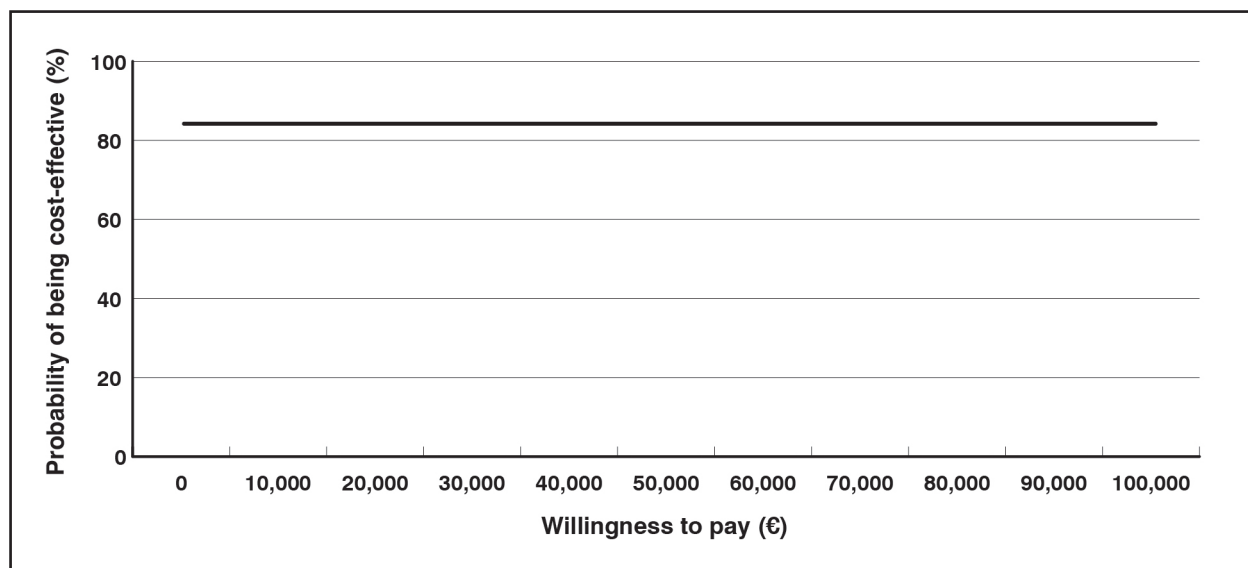


Figure 2. Probabilistic sensitivity analysis: acceptability curve of the cost-effectiveness analysis (CEAC) of dimethyl fumarate vs. teriflunomide (base-case: societal perspective and lifetime horizon)

Perspective	Time horizon	Teriflunomide % discount	ICER (€/QALY gained)
Societal	Lifetime	61,2	Dimethyl-fumarate dominates
		98	Dimethyl-fumarate is cost effective vs teriflunomide considering WTP threshold of € 50,000 per QALY gained

Table V. Threshold Analysis Results

ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life years; WTP: willingness to pay

CONCLUSION

The model used to perform the cost-effectiveness analysis of dimethyl fumarate compared to teriflunomide for patients with relapsing remitting multiple sclerosis (RRMS) in Italy published in 2022 was modified with updated economic data and references (i.e., tables of mortality of the general Italian population). No changes were made to the structure and design of the model, or to the clinical parameters used as inputs. The results of the updated analysis confirm and strengthen those published in 2022, showing that dimethyl fumarate is a dominant strategy in the treatment of RRMS as compared to teriflunomide included in the model from the perspective of both the Italian NHS and the Italian society in all tested scenarios. Finally, dimethyl fumarate would remain dominant over teriflunomide, up to 61% discount in the acquisition cost of the latter and cost-effective compared with teriflunomide with a 98% discount to the acquisition cost of the latter, below a WTP of 50,000 euros per QALY gained.

Acknowledgement

The authors are grateful to Rossella Bitonti, Carolina Moreno, Emanuele Colalillo (PharmaLex Italy S.p.A) for supporting the development of the economic evaluation and the drafting of the manuscript.

Funding

Biogen Italia (Milan, Italy) provided funding for pharmacoeconomic support on the development of the analysis and drafting of the manuscript.

Conflicts of interest

LGM declares research grant from Biogen, Ammirall, Roche, Bayer. Speaker’s fee from Ammirall, Roche, Biogen, Bayer.

PAC declares research grant from Angelini. Speaker’s fee from Pfizer, Roche.

MM and LS are employees of and may hold stock in Biogen.

LP declares personal fees and non-financial support from Biogen, Bristol-Mayer Squibb, Merck, Novartis, Roche, Sanofi and Viatrix.

REFERENCES

1. National Institute of Statistics of Italy (ISTAT). Inflation rates. Available: <https://rivaluta.istat.it/> (last accessed September 2023)
2. Battaglia M, Kobelt G, Ponzio M, Berg J, Capsa D, Dalén J. New insights into the burden and costs of multiple sclerosis in Europe: Results for Italy. *Mult Scler.* 2017;23: 104–116; <https://doi.org/10.1177/1352458517708176>
3. National Institute of Statistics of Italy (ISTAT). Mortality rates, 2022. [cited 6 Oct 2023]. Available: <https://demo.istat.it/app/?i=TVM&l=it> (last accessed October 2023)
4. Karampampa K, Gustavsson A, Miltenburger C, Eckert B. Treatment experience, burden and unmet needs (TRIBUNE) in MS study: results from five European countries. *Mult Scler.* 2012;18: 7–15. <https://doi.org/10.1177/1352458512441566>
5. Italian Medicines Agency (AIFA). Renegotiation of the medicinal product for human use «Tecfidera». Official Journal n. 122 of the Italian Republic of May 26, 2022.
6. Italian Medicines Agency (AIFA). Renegotiation of the medicinal product for human use «Aubagio». Official Journal n. 256 of the Italian Republic of October 26, 2021.
7. De Angelis F, John NA, Brownlee WJ. Disease-modifying therapies for multiple sclerosis. *BMJ.* 2018;363. <https://doi.org/10.1136/BMJ.K4674>
8. Clinical expert opinion to determine monitoring costs associated to multiple sclerosis disease modifying therapies. Data on file. 2020
9. Italian Medicines Agency (AIFA). Aubagio. Summary Of Product Characteristics. Document made available by AIFA on 03/08/2022
10. Garattini L, Castelnuovo E, Lanzeni D, Viscarra C, DYSCO VISITE Gruppo di studio DYSCO VISITE. Durata e costo delle visite in medicina generale: il progetto DYSCO. *Farmeconomia Heal Econ Ther pathways.* 2003;4: 109–114. <https://doi.org/10.7175/FE.V4I2.773>
11. Italian Ministry of Health (2013). Outpatient intervention tariffs. Italian Republic Official Gazette. Chapter n. 23; Supplement n. 8; 28 January 2013
12. Italian Ministry of Health, Department of Planning of the National Healthcare Service. Hospital activity and analysis of hospital discharge forms in 2020 (Report)
13. Italian Ministry of Health (2013). Inpatient intervention tariffs. Italian Republic Official Gazette. Chapter n. 23; Supplement n. 8; 28 January 2013