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-
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.

Table II. Economic data included in the analysis

1It 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

| Description of cost                           | Value (€) | Source/Note                                      |
|-----------------------------------------------|-----------|--------------------------------------------------|
| Acquisition per pack, dimethyl fumarate       | 1,153.00  | Ex-factory price1 (Official Journal 122, 2022 [5]) |
| Acquisition per pack, teriflunomide           | 1,027.75  | Ex-factory price1 (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 III. Results of the incremental cost-effectiveness analysis (base-case: societal perspective and lifetime horizon)—Discounted (3.5% discount rate1)

1National Institute for Health and Care Excellence (NICE). Guide to the methods of technology appraisal 2013. Available at: http://www.nice.org.uk/article/ pgmg9/chapter/foreword. (last accessed November 2024)

| Outcome                  | Dimethyl fumarate (A) | Teriflunomide (B) | Difference (A-B) |
|--------------------------|-----------------------|-------------------|------------------|
| **LYs**                  | 19.631                | 19.545            | 0.086            |
| **QALYs**                | 6.530                 | 5.966             | 0.573            |
| **Costs (€)**            |                       |                   |                  |
| Treatment costs2         | 78,186 (6.9%)         | 69,794 (5.9%)     | 8,392            |
| Adverse events           | 265 (0.0%)            | 89 (0.0%)         | 177              |
| Relapse3                 | 50,873 (4.5%)         | 56,777 (4.8%)     | −5,904           |
| EDSS4                    | 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
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).

Table IV. Sensitivity analysis: results of alternative scenarios
ICER: incremental cost-effectiveness ratio; NHS: National Health Service; QALY: quality-adjusted life years

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

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Conflicts of interest

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