Neurol Ther
https://doi.org/10.1007/s40120-026-01042-7

ORIGINAL RESEARCH

Horizon Scanning of Multiple Sclerosis Expenditure in Italy (2025–2029): Updated Insights from the Oracle Model

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Received: June 15, 2026 / Accepted: September 11, 2026
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ABSTRACT

Introduction: Multiple sclerosis (MS) is a chronic and progressively disabling neurological disease associated with a substantial clinical and socioeconomic burden. The introduction of an increasing number of new innovative therapies has further intensified concerns regarding the long-term sustainability for the Italian National Healthcare Service (NHS). Despite substantial therapeutic progress in MS management, with several treatments available for most MS patient populations, no definitive cure is currently available, and a critical therapeutic gap persists for non-relapsing secondary progressive MS (NR-SPMS), for which no approved treatments are specifically indicated. The objective of the present research is to estimate the Italian NHS expenditure for MS disease-modifying therapies (DMTs) between 2025 and 2029.

Methods: Building on a published horizon-scanning model (i.e., Oracle), this study updates

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40120-026-01042-7.

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Published online: 03 October 2026

projections of expenditure and treatment patterns for MS DMTs through 2029, integrating clinical inputs (i.e., treated patients, patient shares for each reimbursed therapy) with economic inputs (i.e., annual therapy costs). Assumptions and input data were derived from IQVIA® proprietary databases and informed by clinical and pharmacoeconomic expert inputs. Results were validated in a multi-stakeholder roundtable.

Results: This study shows that the number of treated patients is projected to rise to about 77,000 by 2029, i.e., approximately +10% from 2024. Traditional platform therapies are projected to decrease by more than ten percentage points between 2024 and 2029, reflecting a shift toward high-efficacy and innovative therapies. New options include Bruton's tyrosine kinase (BTK) inhibitors (e.g., tolebrutinib, fenebrutinib, remibrutinib), projected to reach approximately 16% patient share within 3 years of first launch.

Conclusion: Despite higher patient volumes and new launches, total DMT expenditure is expected to decline from €784 million in 2024 to €622 million in 2029, mainly driven by losses of exclusivity and price renegotiations. Results support the sustainability of the NHS and the reallocation of resources toward innovation, including innovative therapies for currently underserved populations such as NR-SPMS.

Keywords: Multiple sclerosis; Horizon scanning model; Forecast; Italian National Healthcare Service expenditure; BTKi; NR-SPMS; DMTs

Key Summary Points

Why carry out this study?

MS is a chronic, disabling disease with significant burden and a persistent unmet need, particularly in NR-SPMS with no approved therapies.

The growing availability of innovative treatments raises concerns about long-term sustainability for the Italian NHS.

This study aimed to estimate Italian NHS expenditure for MS DMTs in Italy from 2025 to 2029.

What was learned from the study?

Numbers of treated patients are projected to increase (i.e., by about +10%) with a shift toward high-efficacy and innovative therapies, including BTK inhibitors.

Despite more patients treated and new treatments, overall DMT expenditure in Italy is expected to decrease because of loss of exclusivity and price renegotiations, supporting NHS sustainability and resource reallocation.

INTRODUCTION

Multiple sclerosis (MS) is a chronic and progressively disabling neurological disease that causes substantial disability, profoundly impairs quality of life, and increases the risk of serious complications that ultimately affect life expectancy [1–3]. Italy is among the European countries with the highest MS prevalence, and epidemiological trends show a continuous rise in both prevalence and incidence [4]. Current assessments indicate that by 2025 the MS population will exceed 140,000 individuals, with approximately 3650 new cases diagnosed annually [5]. The steady upward trend is partly attributable to advances in diagnostic accuracy and earlier detection, but environmental and genetic factors may also contribute [6].

MS manifests along a spectrum comprising relapsing-remitting MS (RRMS), primary progressive MS (PPMS), and secondary progressive MS (SPMS), which can be further classified into active (aSPMS) and non-relapsing (NR-SPMS) [7]. RRMS and aSPMS are collectively referred to as relapsing forms of multiple sclerosis (RMS) [8, 9]. These phenotypic categories correspond to the traditional clinical classification of MS and continue to be used to regulatory guidance for the development and evaluation of disease-modifying therapies (DMTs) [10, 11]. Currently, DMTs include traditional platform therapies, namely

first-generation treatments with established safety profiles and moderate efficacy in reducing relapse activity, and more innovative high-efficacy therapies that include agents associated with a greater reduction in relapsing activity but a more complex safety and monitoring profile [12–14]. Despite substantial therapeutic progress in the management of MS, with several treatments available for most MS patient populations (i.e., RRMS, aSPMS, PPMS), no definitive cure is available, and disability progression, which represents a central feature of the disease course, remains insufficiently addressed [15, 16]. Moreover, a critical therapeutic gap persists for NR-SPMS, for which no treatment options are currently approved [17–21].

Beyond its impact on functional abilities and health-related quality of life, MS imposes a substantial social and economic burden, generating significant costs for patients, caregivers, and healthcare systems such as hospital admissions, specialist visits, diagnostic procedures, and DMTs [1, 5, 22–25]. As a result, MS is considered one of the most resource-intensive chronic neurological conditions worldwide [25–27].

The pharmaceutical landscape expected in the coming years adds further complexity for policymakers and payers, as several innovative therapies are anticipated to enter the Italian MS market by 2029, including Bruton's tyrosine kinase inhibitors (BTKis), tyrosine kinase inhibitors (TKis), and anti-CD40L antibodies [28–31]. Notably, the class of BTKis is expected to be the first among new therapies to reach the market for the treatment of NR-SPMS, thereby addressing a key unmet need in this patient population [32]. Table 1 provides an overview of the molecules expected to launch by 2029, taking into account the ongoing phase III registrational clinical trials [33–41].

While advancements in pharmaceutical research offer promising avenues to improve clinical outcomes, they also raise questions about affordability and the overall impact of pharmaceutical expenditure, especially within universal healthcare systems such as the Italian National Healthcare Service (NHS) [42, 43]. However, these cost pressures may be partially mitigated by the concurrent occurrence of several loss-of-exclusivity (LoE) events and by periodic price renegotiations with the Italian Medicines

Table 1 Overview of phase III clinical trials of foreseen future launches up to 2029 (as of December 2025)

Molecule	Drug class	Clinical trial ID	Indication	Phase	Sponsor	Primary completion date
Tolebrutinib	BTK inhibitors	NCT04411641	NR-SPMS	III	Sanofi	08/2024
Masitinib	TK inhibitors	NCT05441488	NR-SPMS PPMS	III	AB science	12/2028
Fenebrutinib	BTK inhibitors	NCT04586023	RMS	III	Roche	09/2025
		NCT04586010				01/2026
		NCT04544449	PPMS			09/2025
Remibrutinib	BTK inhibitors	NCT05147220 NCT05156281	RMS	III	Novartis	04/2026
Frexalimab	Anti-CD40L antibodies	NCT06141473	RMS	III	Sanofi	05/2027
		NCT06141486	NR-SPMS			03/2028

BTK Bruton's tyrosine kinase, *TK* tyrosine kinase, *CD* cluster of differentiation, *NCT* National Clinical Trial, *NR-SPMS* non-relapsing secondary progressive multiple sclerosis, *PPMS* primary progressive multiple sclerosis, *RMS* relapsing forms of multiple sclerosis

Agency (AIFA), which foster competition and tender-based procurement mechanisms, helping to balance access to innovation with long-term system sustainability [44, 45].

In this scenario, to ensure an efficient allocation of clinical and economic resources amid growing demand for MS care, it is important to generate evidence-based insights to support planning and policy decisions that guarantee equitable access to innovation while ensuring long-term sustainability for people living with MS [46, 47].

In light of this, the objective of this study is to estimate the Italian NHS expenditure for MS DMTs between 2025 and 2029, taking into account three key drivers: (i) the introduction of new therapies, (ii) loss of exclusivity events, and (iii) price renegotiations with AIFA for products already on the market [48].

METHODS

Study design

This analysis is based on a previously published Microsoft Excel®-based horizon-scanning model estimating Italian NHS expenditure for MS disease-modifying therapies, updated to extend the time horizon to 2025–2029 and to reflect changes in the Italian MS landscape, such as future launches and loss of exclusivity [48].

Annual NHS expenditure is calculated by multiplying the number of patients receiving each treatment (i.e., clinical inputs) by the estimation of the annual cost of therapy sustained by NHS (i.e., estimation of the price net of overall discount including discount negotiated with AIFA, tender and commercial discount) of each available therapy (i.e., economic inputs). Figure 1 summarizes the methodological

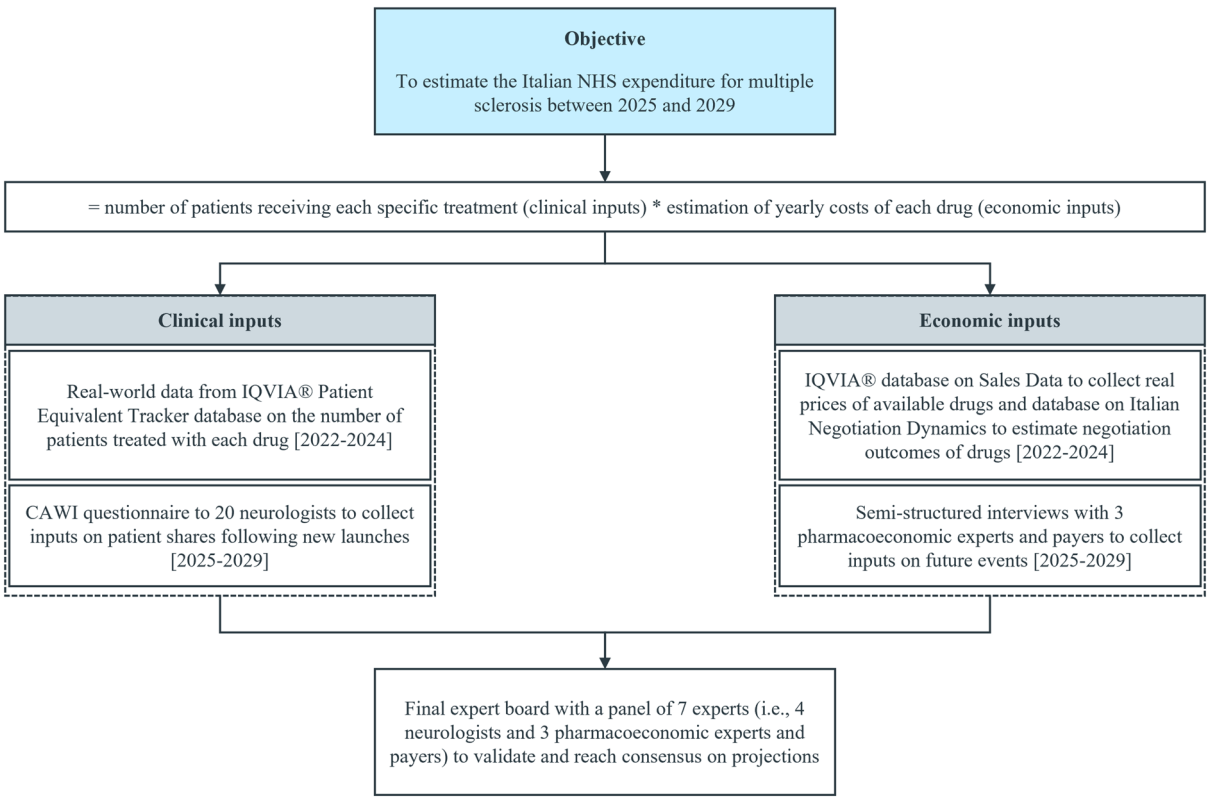


Fig. 1 Methodology and sources used to define and validate inputs of the model. *NHS* National Healthcare System, *CAWI* computer-assisted web interviewing

framework, the clinical and economic inputs used in the model. Additional information regarding the different data sources is reported in next paragraphs.

The previously published methodology and assumptions were reviewed by an expanded expert panel including 20 neurologist key opinion leaders (KOLs), among which four chair KOLs were identified, and three pharmacoeconomic experts and payers.

For both clinical and economic inputs, the analysis comprised two distinct phases: a baseline input collection covering the period 2022–2024, and a forecast input collection spanning 2025–2029. Baseline inputs were derived from the integration of IQVIA® proprietary databases (i.e., database on Sales Data, database on Italian Negotiation Dynamics, and Patient Equivalent Tracker), updated as of December 2024. Forecast estimates were informed by a computer-assisted web interviewing (CAWI) survey involving 20 clinicians and by semi-structured interviews with three pharmacoeconomic experts and payers, conducted between June and September 2025 [49–51].

The neurologists involved were selected on the basis of their (i) substantial clinical experience in the management of MS, (ii) active roles within MS specialist centers, (iii) contributions to scientific publications or national guidelines, and (iv) representation from different regions of Italy to ensure coverage of diverse local healthcare contexts. The final sample included clinicians resulting in broad geographical representation (i.e., eight from Northern Italy, five from Central Italy, seven from Southern Italy and the Islands). For pharmacoeconomic experts and payers, the selection focused on individuals with proven expertise in both national and regional access dynamics. The selection of economic experts was intended to ensure a comprehensive perspective, including one expert with a national-level overview, and two experts also providing regionally focused insights.

No ethical committee approval was required for this study. All the databases used in the study are property of IQVIA® and are accessible by its employees at any time.

Clinical Inputs

To inform the model baseline (i.e., the 2022–2024 period), the number of individuals with MS receiving each marketed DMT in Italy from 2022 to 2024 was obtained through the IQVIA® Patient Equivalent Tracker (PET) database, updated as of December 2024. The PET database estimates the number of treated patients by converting sales and consumption data into patient equivalents, using product-specific dosing schemes, correction coefficients, and primary market research. In particular, patient estimates are generated by integrating monthly volume data across distribution channels with validated pack-level dosing information from official European Medicines Agency (EMA) and AIFA sources, complemented where needed by demographic data, published evidence, and primary market research.

The projected number of patients receiving MS treatment over the 2025–2029 horizon was calculated by applying the compound annual growth rate (CAGR) derived from the baseline period (2022–2024) to future years. Additional adjustments were introduced on the basis of neurologist insights, particularly regarding the expected impact of new therapies specifically indicated for NR-SPMS. Through structured expert elicitation, clinicians assessed the proportion of patients with NR-SPMS who are currently untreated and the potential increase in treatment eligibility and access following the availability of dedicated therapeutic options. These assessments were subsequently incorporated into the model to estimate the expected variation in the treated MS population over the study horizon.

Using baseline data, the model assumes that patient shares for existing treatments remain stable over time, unless affected by competitive dynamics following the access to new products.

These competitive effects were estimated to inform the 2025–2029 forecast inputs through KOL interviews, focusing on (i) estimation of MS patient population variation, (ii) therapy switch dynamics, and (iii) impact of LoE events in terms of patient shares (Table 2).

Table 2 Overview of clinical assumptions considered to develop the model

Event type	Assumption	Source [48]
Patient population variation	The increase in the number of patients with MS treated in 2022–2024 has been applied to future patient projections	IQVIA® Patient Equivalent Tracker database
	Specific evaluation has been considered for increased numbers of patients with NR-SPMS following future launches for this subgroup	Expert interviews
Therapy switch	Horizontal switching is possible, so new launches affect both treatment-naïve patients and those carried over from existing treatments	Expert interviews
Generic and biosimilar drugs penetration	Generics: penetration of generic drug is equal to 74% of the total originator small molecule market	Analog analysis Expert interviews
	Biosimilars: penetration of biosimilar drug is equal to 65% of the total originator biologic market	

MS multiple sclerosis, *NR-SPMS* non-relapsing secondary progressive multiple sclerosis

After the assumptions were validated, a computer-assisted web interview survey was administered to the 20 neurologists to gather quantitative insights and complement the preliminary projections. Specifically, the survey explored upcoming launches in terms of (i) expected peak patient shares of newly introduced therapies, (ii) projected uptake rates, (iii) time to peak uptake, and (iv) anticipated treatment-switching dynamics following their introduction. Responses were collected through predefined quantitative response fields, including percentage allocations, time estimates expressed in quarters, and ordinal classifications of adoption speed (i.e., slow, linear, or fast), complemented by optional qualitative comments [52]. In addition, a dedicated section examined NR-SPMS, focusing on estimating the size of this patient population and its potential growth following the introduction of new treatments. The survey was delivered through the Decipher® platform. Questionnaire responses were collected independently, aggregated using descriptive statistics, and subsequently reviewed through a structured validation process based on anonymized and aggregated outputs, consistent with established approaches for expert elicitation in healthcare decision-making [52–54].

Economic Inputs

Current (i.e., 2022–2024) annual treatment costs for DMTs available on the Italian market were estimated using the IQVIA® database on Sales Data, updated as of December 2024, containing real-world consumption and sales information. This source enables the statistical processing of expenditure data collected from a representative hospital panel, allowing the estimation of costs incurred by the National Healthcare Service for each marketed product. The resulting net prices are estimated by incorporating all relevant reductions, including mandatory statutory discounts, negotiated commercial discounts, and tender-related price adjustments applied to ex-factory list prices. Dosing regimens used for cost calculations were obtained from the Summary of Product Characteristics for each therapy, as published on the European Medicines Agency (EMA) website [55].

To develop the 2025–2029 forecast inputs, assumptions regarding the costs of emerging treatments, the renegotiation of prices for marketed products, and the cost effects associated with the market entry of generics and biosimilars were aligned with those adopted in a previously published study (Table 3) [48]. These

Table 3 Overview of economic assumptions considered to develop the model

Event type	Assumption	Source [48]
Loss of exclusivity	Branded small molecules: application of a maximum discount of 70% vs. ex-factory price, reached 2 years after LoE Generics: application of a maximum discount of 89% vs. originator ex-factory price, reached 1 year after LoE Biologics: application of a maximum discount of 41% vs. ex-factory price, reached 3 years after LoE Biosimilars: application of a maximum discount of 72% vs. originator ex-factory price, reached 3 years after LoE	IQVIA® database on Sales Data Expert interviews
New launch	New launches: annual net cost of therapy aligned with average annual net cost of the treatment line (i.e., according to the AIFA classification) at the time of launch Tolebrutinib: it is expected to be launched in NR-SPMS with a premium price	IQVIA® database on Sales Data Expert interviews
Renegotiation	5% additional discount will be applied on top of the discount obtained at previous negotiation Renegotiations are assumed to happen every 3 years No renegotiations are foreseen for drugs that have not undergone renegotiation since 2018	Italian Official Gazette IQVIA® database on Italian Negotiation Dynamics Expert interviews

LoE loss of exclusivity, *AIFA* Italian Medicines Agency, *NR-SPMS* non-relapsing secondary progressive multiple sclerosis

assumptions reflect average trends observed in recent Italian tenders, acknowledging regional variability.

Overall, assumptions are based on an analog analysis from IQVIA®'s proprietary database on Italian Negotiation Dynamics and were validated by three pharmacoeconomic experts and payers ensuring consistency with real-world negotiation practices and regulatory expectations [44, 45, 48, 56]. Additional details on the analog selection and characteristics are provided in Table S1 in the electronic supplementary material. The assumptions regarding LoE events are consistent with preliminary evidence from generics and biosimilars recently introduced to the market (e.g., teriflunomide and natalizumab). Early real-world observations suggest that both discount trends and the time required for price stabilization are evolving in line with the assumed patterns. Further details on the modelled scenario and the alternative scenarios explored are provided in Table S2 in the electronic supplementary material.

Data Analysis and Validation

Aggregated clinical and economic inputs were analyzed using descriptive statistics. The final multi-stakeholder roundtable, including the four clinical chair KOLs and three pharmacoeconomic experts and payers, reviewed the results, validated the coherence of the projections, and reached consensus on the final estimates [57].

In line with methodological recommendations for models based on predominantly linear and additive calculations, uncertainty was assessed through deterministic sensitivity analyses, as well as complementary scenario analyses (see Table S2 in the electronic supplementary material for details) [58, 59]. One-way sensitivity analysis was conducted on key parameters to evaluate the robustness of the annual expenditure estimates [60, 61]. Variables assessed included discount levels, uptake rates, and time to peak for future launches; the

expected increase in treated patients for NR-SPMS; renegotiation timelines, and dynamics linked to LoE events (e.g., price reductions and market penetration of generics and biosimilars). For each parameter, a ± 20% variability range around its baseline value was applied [62–64]. The baseline reference used for this analysis corresponds to the estimated expenditure reduction observed between 2024 and 2029.

RESULTS

Clinical Results

Results show that the number of patients receiving treatment for MS in Italy will continue to rise, increasing from approximately 60,500 individuals in 2022 to an estimated 77,000 in 2029. This upward trend reflects both the continuation of underlying baseline dynamics and the expected expansion of treatment eligibility for progressive forms of the disease, particularly NR-SPMS. Insights collected from clinical experts indicate that the introduction of targeted therapies for NR-SPMS could lead to an additional 4% increase in the treated MS population. Since many of these individuals progress from relapsing forms of MS and are already under treatment (e.g., mainly ocrelizumab and siponimod), the resulting population growth remains modest and may reflect continued use of currently available therapies. Moreover, a proportion of patients with NR-SPMS are expected to remain untreated, primarily as a result of advanced age or severe disability, which may limit the appropriateness or feasibility of initiating disease-modifying treatment.

Results on patient share evolution indicate a marked decline of traditional platform therapies, whose use is expected to decrease to about 33% by 2029 (from 43% in 2024), reflecting the progressive shift toward more effective options. Among these, anti-CD20 treatments are anticipated to reach a peak patient share of 27% in 2026, supported by the uptake of recently introduced agents such as ublituximab, then stabilize at 22% patient share by 2029 as a portion of patients transition to more innovative treatments. BTK inhibitors (e.g., tolebrutinib, fenebrutinib, remibrutinib) are projected to reach nearly 16% of patient share within 3 years from the first launch in late 2026, with tolebrutinib expected to be the first molecule introduced in this class, and first for NR-SPMS. Regarding other therapeutic classes, sphingosine-1-phosphate modulators are projected to continue their slight decline, from 15% in 2024 to 10% in 2029. Conversely, anti-α4 integrin therapies are forecast to remain relatively stable, showing only a minimal reduction from 10% to 9% over the same period with most of this share expected to be captured by the biosimilars first introduced in 2024.

Economic Results

The economic results overall confirmed the assumptions related to the events considered (i.e., LoEs, new launches, and renegotiations).

Regarding future launches, a specific consideration applies to tolebrutinib, for which a premium price may be justified given its potential to address an unmet need in NR-SPMS [15]. Moreover, evidence suggests a reduced risk of disability progression and its oral administration may offer additional indirect and organizational advantages compared with infusion-based regimens, producing organizational benefits (e.g., reduction in necessary space, staff) [24].

Overall Expenditure Estimation

Combining clinical and economic inputs, the total NHS expenditure for MS is projected to decrease from €784 million in 2024 to €622 million in 2029, corresponding to an overall reduction of approximately €160 million over the period. This reduction is expected despite an increase in the number of treated patients with MS, reflecting the substantial budgetary impact of loss of exclusivity events and scheduled renegotiations with AIFA, which collectively drive a progressive decrease in treatment expenditure. Figures 2 and 3 illustrate the evolution of MS market expenditure, segmented by therapy class

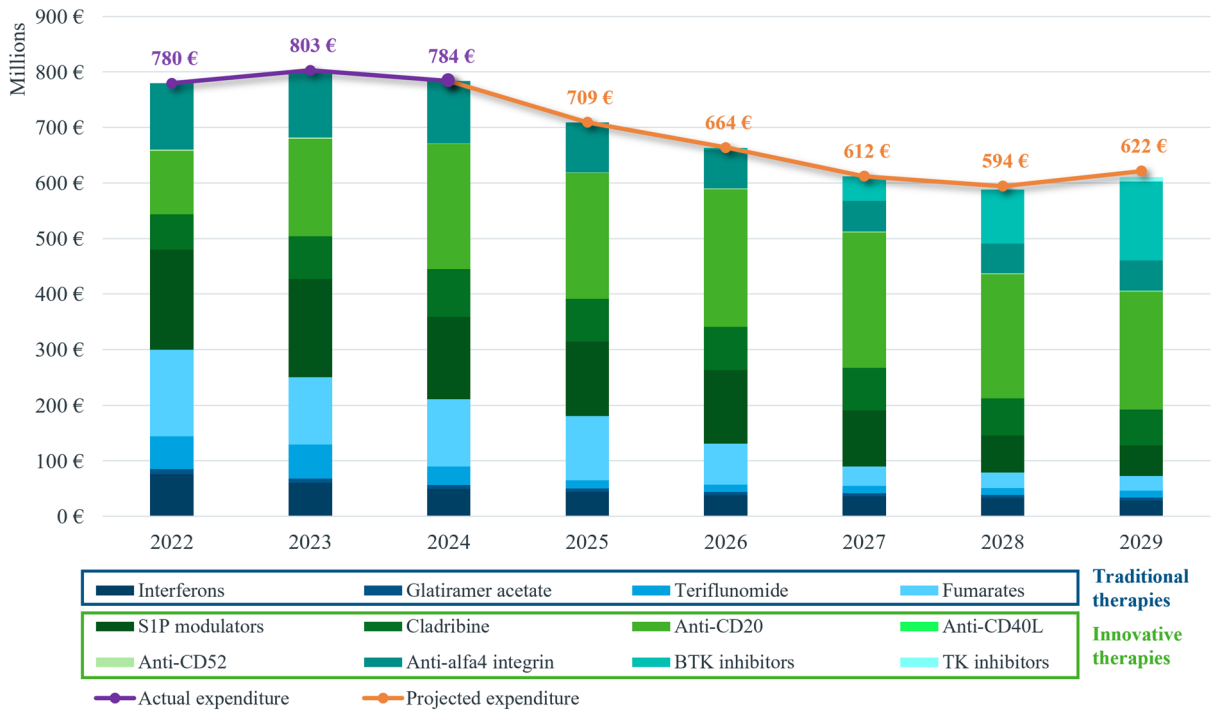


Fig. 2 Multiple sclerosis market expenditure (M€) and share (%) evolutions. *M* millions, *S1P* sphingosine-1-phosphate, *CD* cluster of differentiation, *BTK* Bruton's tyrosine kinase, *TK* tyrosine kinase



Fig. 3 Multiple sclerosis market expenditure (M€) and treated patient (k) evolutions. *M* millions, *MS* multiple sclerosis, *NHS* National Healthcare System, *k* thousands

share and by the number of patients treated, respectively.

Overall, the sensitivity analysis confirms the model's stability and robustness, as all evaluated parameters showed an impact below 10% under alternative assumptions. The largest influence on total costs is variations in the discount applied at launch for new molecules, which can shift expenditure outcomes by +9.0% to −8.3% (Fig. 4). Conversely, the parameter related to the

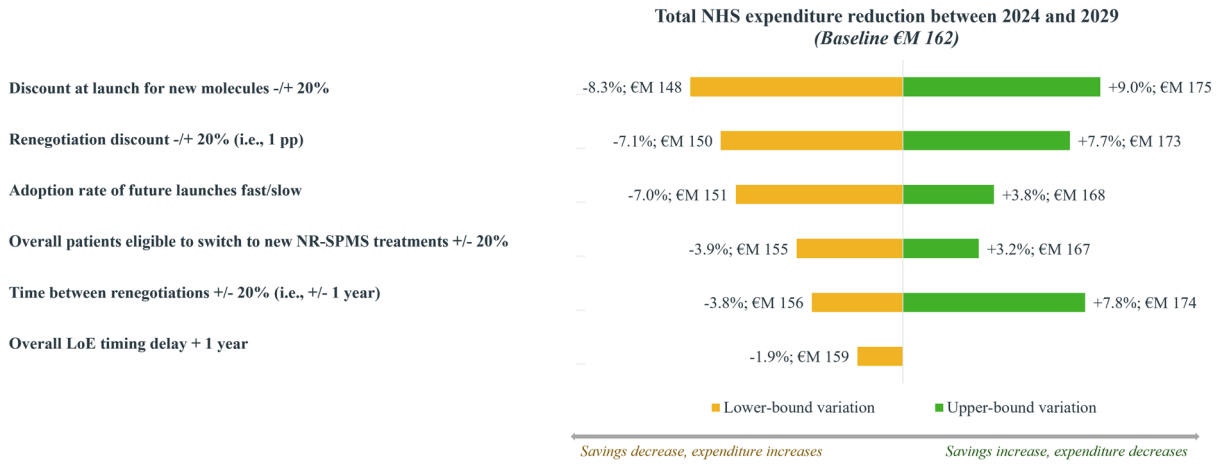


Fig. 4 Deterministic one-way sensitivity analysis. *NHS* National Healthcare System, *M* millions, *pp* percentage point, *NR-SPMS* non-relapsing secondary progressive multiple sclerosis, *LoE* loss of exclusivity

number of patients eligible to switch to newly introduced NR-SPMS treatments produces a more moderate impact on results (i.e., between +3.2% and −3.9%), as well as future LoE delay (i.e., −1.9%).

DISCUSSION

Multiple sclerosis is a chronic and increasingly prevalent neurological disorder for which no curative therapy exists although several innovative advancements are approaching [65]. Indeed, the therapeutic landscape for MS is entering a phase of rapid transformation, driven by strong expectations for innovation and by a clinical mindset increasingly oriented toward early use of high-efficacy therapies [66]. Neurologists are prioritizing treatments capable of delaying disability progression from the outset, while the convenience of administration, particularly the shift toward oral agents, is becoming an important factor in treatment selection [67–69]. Focusing on clinical aspects, this shift is reflected in the findings of this horizon scanning model, which shows a switch toward broader adoption of high-efficacy therapies, accompanied by a gradual decline in the use of traditional platform options (i.e., interferons, glatiramer acetates, teriflunomide, fumarates). At the same time, anti-CD20 therapies have consolidated their position as the most frequently prescribed treatments, while the introduction of innovative molecules (i.e., BTKis, TKis, anti-CD40L) marks a significant step forward in expanding the therapeutic possibilities. Indeed, new therapies are anticipated to address unmet needs such as NR-SPMS and disability progression, complementing current high-efficacy therapies that primarily target relapse activity but have shown limited impact on the progression of disability [15, 16, 70].

Beyond the general expectations surrounding upcoming launches, those for NR-SPMS are particularly high. In this setting, new therapies are anticipated to include the first reimbursed treatment option and to address a long-standing therapeutic gap, potentially improving outcomes for a previously underserved patient population. The new reimbursed treatment for NR-SPMS is projected to reach about 10% of the patient share out of the estimated 15% NR-SPMS population, including currently untreated patients (i.e., about 3% of patients with MS) and patients already on therapy (i.e., about 7% of patients with MS). More specifically, collected data suggest that approximately half of patients with NR-SPMS who are currently untreated may become eligible for treatment with new therapeutic options. On the other, since MS is increasingly viewed as a disease continuum,

a proportion of patients already on therapy remain treated after entering the progressive phase, mainly with therapies such as ocrelizumab and siponimod [7, 8, 71]. In this case, switching decisions will likely be driven by considerations of safety and ease of use, as well as the potential to delay disability progression, which is currently unaddressed by available therapies.

Despite the introduction of innovative therapies and a growing patient population, overall pharmaceutical expenditure is projected to decline in the coming years. This trend is primarily driven by the expiration of market exclusivity for a number of marketed drugs and the subsequent increase in competitive pressure, which substantially reduces the costs of established treatments. Periodic price renegotiations with AIFA further contribute to helping lower overall spending. Potential indirect savings may also amplify the impact on direct costs. For instance, the oral administration of newly available therapeutic options, compared with the subcutaneous- and infusion-based regimens required for several platform treatments, may generate organizational efficiencies, such as reduced demand for dedicated clinical space and staff time, with the potential for additional indirect cost optimization. Moreover, the introduction of the first treatment capable of reducing disability progression may generate additional cost savings, while improving quality of life [15, 24, 72, 73]. Indeed, as disability progression is associated with marked increases in non-healthcare direct costs (i.e., from +2% of total expenses in mild disability to +19% in severe cases) and indirect costs due to productivity loss (i.e., from + 29% to + 42%), limiting progression may contribute to mitigating the broader economic impact on patients and society [24, 73]. In this context, a qualitative focus on disability-related outcomes remains particularly relevant when considering indirect costs, especially in light of emerging treatments targeting disability progression [73–75].

Overall, from a policy perspective, the findings suggest that savings generated by LoE events and price renegotiations may facilitate the introduction of innovative therapies while contributing to the efficient management of pharmaceutical expenditure in MS over the study horizon. Altogether, these elements provide a coherent foundation for informed long-term planning and efficient allocation of healthcare resources within the evolving MS treatment landscape, thereby creating the financial conditions needed to accommodate new therapies while taking current budget constraints into account. In this context, the integration of innovation could be effectively pursued (and provide clinical benefits) without compromising the long-term sustainability of the healthcare system.

Limitations and Future Research

The analysis relies on a structured expert panel that was selected to ensure clinical and economic expertise and adequate geographic representation. Nevertheless, future research could further strengthen the evidence base by expanding the panel in terms of size and diversity, as well as by including additional stakeholder perspectives across care settings to broaden the scope (e.g., patients, caregivers) and capture indirect costs or other healthcare resource use. Future research could also assess the organizational and healthcare resource implications associated with different treatment administration modalities, providing a more comprehensive understanding of how therapeutic innovation may affect both pharmaceutical expenditure and care delivery. Hence, future work could integrate updated real-world evidence, including real-world data on the utilization, effectiveness, and safety of newly available therapies, to better understand their overall impact. An additional valuable avenue for future investigation would be the assessment of the net budget impact of innovation, integrating both the costs of newly introduced therapies and the savings generated through market competition and renegotiation mechanisms.

In conclusion, the findings should be regarded as robust within the scope of the assumptions considered in this study, which integrates data from interviews, a survey, IQVIA® databases (updated as of December 2024), and publicly available sources (updated as of December 2025).

Nonetheless, the projections remain subject to clinical and economic developments that may fall outside the parameters applied in this study. Continued refinement through updated real-world evidence will be essential to further strengthen future analyses.

CONCLUSION

This study suggests that total pharmaceutical expenditure for MS in Italy is projected to decline by 2029, despite the introduction of new therapies, including options for non-relapsing secondary progressive MS. The expected reduction is mainly driven by loss of exclusivity effects which offset the impact of innovation. These savings may sustain innovation to enhance patient management and facilitate access to more effective therapies. In this scenario, there is strong anticipation for innovative therapies such as BTK inhibitors and anti-CD40L, which are expected to be important in addressing the persistent unmet need in NR-SPMS, potentially improving outcomes in previously underserved patients while maintaining system sustainability.

ACKNOWLEDGEMENTS

We thank all the participants of the study.

The Oracle 3.0 study group is: Pietro Osvaldo Annovazzi, Marco Capobianco, Paola Cavalla, Elena Colombo, Antonella Conte, Cinzia Cordioli, Diana Ferraro, Matilde Inglese, Giorgia Teresa Maniscalco, Girolama Alessandra Marfia, Marcello Moccia, Damiano Paolicelli, Emilio Portaccio, Paolo Ragonese, Rocco Totaro, Ignazio Roberto Zarbo.

Author Contributions. All authors contributed to the study conception and design, and to the material presented in this manuscript. Data collection and analysis were performed by Francesca Donnaloja, Alessandro Carrera, and Maria Vittoria Azzi; Massimiliano Calabrese, Diego Centonze, Eleonora Cocco, Roberta Di Turi, Andrea Marcellusi, Andrea Marinozzi and Francesco Patti provided insights during the qualitative interviews; the survey was designed by Francesca Donnaloja and Alessandro Carrera and revised by Maria Vittoria Azzi, Massimiliano Calabrese, Diego Centonze, Eleonora Cocco, and Francesco Patti; Massimiliano Calabrese, Diego Centonze, Eleonora Cocco, Francesco Patti filled in the survey; Massimiliano Calabrese, Diego Centonze, Eleonora Cocco, Roberta Di Turi, Andrea Marcellusi, Andrea Marinozzi, and Francesco Patti participated in the final expert board. All authors had equal opportunity to review and edit the manuscript and give approval prior to submission.

Funding. This study was funded by Sanofi S.r.l., Milan, Italy, which also funded the journal's Rapid Service Fee.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of Interest. Diego Centonze acted as an advisory board member and received honoraria for speaking or consultation fees from Alexion, Almirall, Amicus, Bayer, Biogen, BMS, Celgene, Chiesi, GW Pharmaceuticals, Horizon, Janssen, Lundbeck, Merck, Novartis, Roche, Sandoz, Sanofi-Genzyme, Viatris, and Teva. He is also the principal investigator in clinical trials of Biogen, BMS, Merck, Mitsubishi, Novartis, Roche, Sanofi-Genzyme, Actelion. His preclinical and clinical research was supported by grants from Almirall, Bayer Schering, BMS, Biogen, Celgene, Lundbeck, Merck Serono, Novartis, Roche, Sanofi-Genzyme, and Teva. Massimiliano Calabrese received speaker honoraria or consultation fees from Biogen, Bristol Myers Squibb, Merck Serono, Novartis, Amgen and Roche and received research support from the Progressive MS Alliance and Italian Minister of Health and Biogen, Bristol Myers Squibb, Merck Serono, Novartis, and Roche. Eleonora Cocco received compensation for travel grants, participation

in advisory boards, and/or speaking activities from Alexion, Almirall, Amgen, Biogen, Neuraxpharm, Merck Serono, Sanofi, Roche, BMS Celgene, Janssen, Sandoz, and Novartis; and serves as PI in clinical trials for Roche, Sanofi-Genzyme, and BMS. Roberta di Turi received honoraria for participation in advisory boards from Sanofi. Pietro Osvaldo Annovazzi received honoraria for lecturing and participation in advisory boards, and/or travel expenses for attending congresses and meetings from Alexion, Almirall, Amgen, Biogen, BMS-Celgene, Janssen, Juvisé, Lundbeck, Merck, Neuraxpharm, Novartis, Roche, Sanofi-Genzyme, Viatris. Paola Cavalla received compensation for travel grants, participation in advisory boards, and/or speaking activities from Alexion, Biogen, BMS Celgene, Merck-Serono, Neuraxpharm, Sanofi-Genzyme, Novartis and Roche; and serves as principal investigator in clinical trials for Merck Serono, Novartis, Roche and Sanofi-Genzyme. Elena Colombo reports travel expenses, speaker honoraria, and advisory board work from Sanofi, Biogen, Novartis, Merck, Roche, Bristol Myers Squibb, Juvisé, Alexion, Amgen, Neuraxpharm. Antonella Conte acted as an Advisory Board member and received honoraria for speaking or consultation fees from Alexion, Almirall, Biogen, BMS, Lundbeck, Merck, Novartis, Roche, Sandoz, Sanofi-Genzyme. She is also the principal investigator in clinical trials of Biogen, BMS, Merck, Roche, Sanofi. Cinzia Cordioli received personal compensation for speaking and advisory board and travel grants from Merck, Biogen, Roche, Novartis. Diana Ferraro has received honoraria for speaking and/or advisory boards and/or for travel from Alexion, Amgen, Binding Site, Biogen, Bristol-Myers-Squibb, Merck, Neuraxpharm, Novartis, Roche, Sanofi. Matilde Inglese received honoraria for speaking or consultation fees from Alexion, Amgen, Biogen, BMS, Merck, Novartis, Roche, Sandoz, Sanofi-Genzyme. She serves as ECTRIMS executive committee General Secretary. Giorgia Teresa Maniscalco received compensation for travel grants, participation in advisory boards, and/or speaking activities from Alexion, Amgen, Biogen, Merck Serono, Sanofi, Roche, and Novartis. Girolama Alessandra Marfia received compensation for travel grants, participation in advisory boards, and/or speaking activities from Alexion, Almirall, Amgen, Biogen, Neuraxpharm, Merck Serono, Sanofi, Roche, BMS Celgene, Janssen, and Novartis; and serves as principal investigator in clinical trials for Merck Serono, Novartis, Roche, Sanofi-Genzyme, and BMS. Marcello Moccia has received research support from the MUR PNRR Extended Partnership (MNESYS no. PE00000006, and DHEAL-COM no. PNC-E3-2022-23683267) and by Campania Region. NeuroDiaTE Project (CUP E65E24002260002); and honoraria from Alexion, Biogen, BMS, Ipsen, Janssen, Juvisé, Merck, Novartis, Neuraxpharm, Roche, Sandoz, and Sanofi-Genzyme. Damiano Paolicelli has received honoraria for advisory board membership and speaking activities, travel support, research grants, consulting fees, or clinical trial support from Alexion, Amgen, Biogen, BMS-Celgene, Sanofi-Genzyme, Merck, Novartis, Neuraxpharm and Roche. Paolo Ragonese acted as an advisory board member and received honoraria for speaking or consultation fees from Alexion, Almirall, Biogen, BMS, Celgene, Horizon, Janssen, Merck, Novartis, Roche, Sandoz, Sanofi. Emilio Portaccio received compensation for travel grants, participation in advisory boards, and/or speaking activities from Biogen, Merck Serono, Sanofi, Teva, Roche, BMS Celgene, Janssen, and Novartis; and serves on the editorial board of *Frontiers in Neurology* and *Brain Sciences*. Rocco Totaro acted as an advisory board member and received honoraria for speaking or consultation fees from Alexion, Almirall, Amgen, Biogen, BMS, Merck, Novartis, Roche, Sanofi-Genzyme. Principal investigator in clinical trials of Biogen, BMS, Merck, Roche, Sanofi. Ignazio Roberto Zarbo reports travel expenses, speaker honoraria, and advisory board work from Biogen, Novartis, Roche, Sanofi, Merck, Bristol Myers Squibb, Juvisé, Teva Pharmaceuticals, Alexion, Amgen, Almirall, Coloplast. Maria Vittoria Azzi is an employee of Sanofi and may hold shares and/or stock options in the company. Francesco Patti has received personal compensation for speaking activities or serving on advisory boards for Almirall, Alexion, Amgen, Biogen, Bristol Myers Squibb, Janssen, Merck, Neuraxpharm, Novartis, Roche and Sanofi; has received research grants from Alexion, Almirall, Biogen, Bristol Myers Squibb, Merck, Novartis, Roche, Sanofi FISM,

Reload Association (Onlus), Italian Health Ministry and University of Catania.

Ethical Approval. No ethical committee approval was required for this study. All the databases used in the study are property of IQVIA® and are accessible by its employees at any time.

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