INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

Tolebrutinib for Secondary Progressive Multiple Sclerosis

Draft Evidence Report

April 15, 2025

Prepared for

CALIFORNIA TECHNOLOGY ASSESSMENT FORUM

ICER Staff and Consultants	The University of Colorado Modeling Team
Grace A. Lin, MD Medical Director for Health Technology Assessment Institute for Clinical and Economic Review **Shahariar Mohammed Fahim, PhD, MSc** Senior Research Lead Institute for Clinical and Economic Review **Marina Richardson, PhD, MSc** Associate Director, HTA Methods and Health Economics Institute for Clinical and Economic Review **Foluso Agboola, MBBS, MPH** Senior Vice President of Research Institute for Clinical and Economic Review	**Brett McQueen, PhD** Associate Professor, Department of Clinical Pharmacy University of Colorado Anschutz Medical Campus **Antal Zemplenyi, PhD** Visiting Research Associate, University of Colorado Anschutz Medical Campus *The role of the University of Colorado is limited to the development of the cost-effectiveness model, and the resulting ICER report does not necessarily represent the view of the University of Colorado.*

ICER's value assessments are free from financial conflicts of interest from health care companies. As an organization, we value transparency and hold ourselves, and our collaborators, to high standards for conducting our work. Our full policy to manage potential conflicts of interest can be found here. You can find ICER's Code of Ethics here. Any conflicts reported by the authors of this report, contributing staff members, or expert reviewers can be found on page V.

DATE OF PUBLICATION: April 15, 2025

How to cite this document: Lin GA, McQueen B, Fahim SM, Richardson M, Zemplenyi A, Raymond F, Agboola F. Tolebrutinib for Secondary Progressive Multiple Sclerosis: Effectiveness and Value; Draft Evidence Report. Institute for Clinical and Economic Review, April 15, 2025. https://icer.org/assessment/multiple-sclerosis-2025/

Grace Lin served as the lead author for the report. Shahariar Mohammed Fahim led the systematic review and authorship of the comparative clinical effectiveness section of this report with the assistance from Finn Raymond. Brett McQueen and Antal Zemplenyi developed the cost-effectiveness model and authored corresponding sections of the report. Marina Richardson conducted analysis for the budget impact model. Foluso Agboola provided methodologic guidance on the clinical and economic evaluations. We would also like to thank Becca Piltch, Anna Geiger, and Marie Phillips for their contributions to this report.

About ICER

The Institute for Clinical and Economic Review (ICER) is an independent, non-profit research institute that conducts evidence-based reviews of health care interventions, including prescription drugs, other treatments, and diagnostic tests. In collaboration with patients, clinical experts, and other key stakeholders, ICER analyzes the available evidence on the benefits and risks of these interventions to measure their value and suggest fair prices. ICER also regularly reports on the barriers to care for patients and recommends solutions to ensure fair access to prescription drugs. For more information about ICER, please visit www.icer.org.

The funding for this report comes from non-profit foundations, with the largest single funder being the Arnold Ventures. No funding for this work comes from health insurers, pharmacy benefit managers (PBMs), or life science companies. ICER receives approximately 21% of its overall revenue from these health industry organizations to run a separate Policy Summit program, with funding approximately equally split between insurers/PBMs and life science companies. Life science companies relevant to this review who participate in this program include: Sanofi. For a complete list of funders and for more information on ICER's support, please visit https://icer.org/who-we-are/independent-funding/.

For drug topics, in addition to receiving recommendations from the public, ICER scans publicly available information and also benefits from a collaboration with IPD Analytics, an independent organization that performs analyses of the emerging drug pipeline for a diverse group of industry stakeholders, including payers, pharmaceutical manufacturers, providers, and wholesalers. IPD provides a tailored report on the drug pipeline on a courtesy basis to ICER but does not prioritize topics for specific ICER assessments.

About CTAF

The California Technology Assessment Forum (CTAF) – a core program of ICER – provides a public venue in which the evidence on the effectiveness and value of health care services can be discussed with the input of all stakeholders. CTAF seeks to help patients, clinicians, insurers, and policymakers interpret and use evidence to improve the quality and value of health care.

The CTAF Panel is an independent committee of medical evidence experts from across California, with a mix of practicing clinicians, methodologists, and leaders in patient engagement and advocacy. All Panel members meet strict conflict of interest guidelines and are convened to discuss the evidence summarized in ICER reports and vote on the comparative clinical effectiveness and value of medical interventions. More information about CTAF is available at https://icer.org/who-we-are/people/independent-appraisal-committees/ctaf.

The findings contained within this report are current as of the date of publication. Readers should be aware that new evidence may emerge following the publication of this report that could potentially influence the results. ICER may revisit its analyses in a formal update to this report in the future.

The economic models used in ICER reports are intended to compare the clinical outcomes, expected costs, and cost-effectiveness of different care pathways for broad groups of patients. Model results therefore represent average findings across patients and should not be presumed to represent the clinical or cost outcomes for any specific patient. In addition, data inputs to ICER models often come from clinical trials; patients in these trials may differ in real-world practice settings.

In the development of this report, ICER's researchers consulted with clinical experts, patients, manufacturers, and other stakeholders. The following individuals served as external reviewers of the draft evidence report:

Expert Reviewers

Bruce A. Cohen, MD
Professor of Neurology
Northwestern University, Feinberg School of Medicine, Davee Department of Neurology

Simone Huygens, PhD
Health Economist
Huygens & Versteegh

Kavita V. Nair, PhD
Professor of Neurology and Pharmacy
University of Colorado Anschutz Medical Campus

Hollie Schmidt, MS, MBA
Vice President of Scientific Operations
Accelerated Cure Project for MS

Matthijs Versteegh, PhD, MA, BSc
HTA Specialist
Huygens & Versteegh; Dutch Health Care Institute

None of the external reviewers or other experts we spoke to are responsible for the final contents of this report, nor should it be assumed that they support any part of it. Furthermore, it is possible that external reviewers may not have had the opportunity to review all portions of the draft report. The report should be viewed as attributable solely to the ICER team and its affiliated researchers.

To protect patient confidentiality, ICER does not routinely name individual patients or care partners who provided us with input and feedback.

For a list of stakeholders from who we requested input from, or who have submitted public comments so far, please visit: https://icer.org/wp-content/uploads/2025/04/ICER_Stakeholder-List_Working-Version_041525.pdf

Conflict of Interest Disclosures for the Report

Table 1. ICER Staff and External Collaborators Conflict of Interest Disclosures

ICER Staff and External Collaborators	Conflict of Interest
Foluso Agboola, MBBS, MPH	No conflicts to disclose.
Anna Geiger, BS	No conflicts to disclose.
Shahariar Mohammed Fahim, PhD	No conflicts to disclose.
Grace Ham, MSc	No Conflicts to disclose.
Grace Lin, MD	No conflicts to disclose.
Brett McQueen, PhD	R. Brett McQueen reports compensation from Sanofi for a special speaker series in April 2024 related to type 1 diabetes and fees for reviewing a project attempting to improve early diagnosis of type 1 diabetes. He has not received any funding directly related to a product or directly related to multiple sclerosis.
Marie Phillips, BA	No conflicts to disclose.
Becca Piltch, MPP	No conflicts to disclose.
Finn Raymond, BS	No conflicts to disclose.
Marina Richardson, PhD, MSc	No conflicts to disclose.
Antal Zemplenyi, PhD	No conflicts to disclose.

Table 2. Expert Reviewers of the Draft Evidence Report Conflict of Interest Disclosures

Expert Reviewer	Conflict of Interest
Bruce A. Cohen, MD	Dr. Bruce Cohen has equity interests in excess of $10,000 in Abbott Laboratories, AbbVie, and CVS Health.
Simone Huygens, PhD	Dr. Simone Huygens received monetary value in excess of $5,000 for services from Merck KGgA, Pfizer, Santen, Takeda, Beigene, Dutch Health Care Institute. She also is >25% shareholder of Huygens & Versteegh which provides health economic services to life science companies.
Kavita V. Nair, PhD	Dr. Kavita Nair received monetary value for services in excess of $5,000 from Esai.
Hollie Schmidt, MS, MBA	No conflicts to disclose.
Matthijs Versteegh, PhD, MA, BSc	Dr. Matthijs Versteegh received monetary value in excess of $5,000 for services from Merck KGgA, Pfizer, Santen, Takeda, Beigene, Dutch Health Care Institute. He also is >25% shareholder of Huygens & Versteegh which provides health economic services to life science companies.

Table of Contents

List of Acronyms and Abbreviations Used in this Report

%	Percent
9HPT	9-hole peg test
AE	Adverse event
AHRQ	Agency for Healthcare Research and Quality
ALT	Alanine transaminase
BILI	Bilirubin
BTKIs	Bruton’s tyrosine kinase inhibitors
CDI	Confirmed disability improvement
CDP	Confirmed disability progression
CDR	Clinical trial diversity rating
CE	Cost effectiveness
CI	Confidence interval
Cm	Centimeter
CPT	Current procedural terminology
DMT	Disease-modifying-treatment
EDSS	Expanded Disability Status Scale
EQ-5D	EuroQol-5 Dimension mapping tool
evLYs	Equal value life years
FDA	Food and Drug Administration
Gd	Gadolinium
GDP	Gross domestic product
HIDI	Health Improvement Distribution Index
HR	Hazard ratio
HRQoL	Health-related quality of life
IQR	Interquartile range
LSM	Least squares mean
LY	Life year
Mg	Milligrams
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
N	Number
NA	Not applicable
NC	Not calculated
NDA	New drug application
NE	Not estimated
NICE	National Institute for Health Care and Excellence
PDDS	Patient determined disease steps
PDRR	Participant to disease-prevalence representation ratio
PIRA	Progression independent of relapse activity
PPMS	Primary progressive multiple sclerosis
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRLs	Paramagnetic rim lesions
PT	Physical therapy
QALY	Quality-adjusted life year
RAW	Relapse-associated worsening
RCT	Randomized controlled trial
RRMS	Relapsing-remitting multiple sclerosis
SD	Standard deviation
SPMS	Secondary-progressive multiple sclerosis
T25FW	Timed 25-foot walk test

TEAEs	Treatment-emergent adverse events
UK	United Kingdom
ULN	Upper limit of normal
US	United States
UTI	Urinary tract infection

Executive Summary

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system, affecting nearly a million people in the United States, with the disease more prevalent in women and persons 45 to 65 years old.[1,2] Symptoms of MS, including weakness, fatigue, vision changes, memory and concentration problems, and pain, can cause physical, emotional, and cognitive impairment.[3] MS is a costly disease, with an estimated annual economic burden in the US over $85 billion.[4]

While the majority of persons are initially diagnosed with relapsing-remitting MS (RRMS), most eventually transition to secondary progressive MS (SPMS), which is marked by progressive worsening of disability without symptomatic relapses. SPMS can be classified into active disease (with relapses and/or new MRI changes) or non-active disease, with or without progression of disability. Active SPMS with MRI activity only (no clinical relapses) and non-active SPMS are classified into the larger category of non-relapsing forms of SPMS (nrSPMS).

The symptoms of MS typically emerge in young adulthood and thus the disease has a large impact not only on physical health, but also on work and educational productivity, family planning, and social and leisure activities. Challenges shared by persons living with SPMS include a delays in diagnosis, difficulty accessing care with MS specialists, high out-of-pockets costs of drugs, and managing symptoms such as fatigue, urinary symptoms, and pain that may not respond to disease-modifying therapies. A recent survey of MS patients reflected the high burden of SPMS, with respondents reporting a loss of independence and identity, as well as a negative impact on career and relationships.[5] Finally, there is also a high caregiver burden associated with SPMS, with caregivers noting that they need to plan their lives around the needs of the patient.

Although there are many highly efficacious disease-modifying therapies (DMTs) available to treat both RRMS and active SPMS, once a person has transitioned to non-active SPMS, treatment options are very limited. Tolebrutinib (Sanofi) is an oral, once-daily, Bruton's Tyrosine Kinase Inhibitor that is under U.S. Food and Drug Administration (FDA) review for the treatment of nrSPMS, with a decision expected by September 2025.[6]

Tolebrutinib was tested against placebo in the HERCULES trial, a Phase III randomized, controlled trial of 1,131 participants with nrSPMS who had not had a clinical relapse within the last 24 months. The participants, who had a mean age of 49 years old, were predominately female (62%), White (92%), and had a high degree of disability, with a median EDSS score of 6. The trial met the primary endpoint of confirmed disability progression sustained for ≥ 6 months, with fewer participants in the tolebrutinib group reaching that endpoint than in the placebo group (hazard ratio (HR) 0.69, 95% confidence interval (CI) 0.55 to 0.88) at 24 months, a difference that was maintained at trial end (45 months). Results from additional clinical outcomes were mixed; while there appeared to be benefit from tolebrutinib on the 25-foot walk test (HR 0.77, 95% CI 0.64 to 0.92) and confirmed disability improvement (HR 1.88, 95% CI 1.10 to 3.21) at 24 months, other outcomes such as change in 9-hole peg test did not show a statistically significant difference (HR 0.97, 95% CI 0.74 to 1.29). There was a similarly mixed picture for MRI outcomes, with the tolebrutinib group having fewer new or enlarging lesions on T2-weighted MRI but no change in measures of brain atrophy.

Overall adverse events were similar in the tolebrutinib and placebo groups, although the tolebrutinib group had a higher proportion of participants who had a serious adverse event compared to the placebo group (15.0% vs. 10.4%). Elevation of liver enzymes >3 times the upper limit of normal (ULN) occurred in 4% of participants in the tolebrutinib group, with 4 participants (0.5%) having an increase in liver enzymes of >20 times ULN. One participant in the tolebrutinib group died from complications from liver transplant attributed to tolebrutinib toxicity. After the institution of weekly liver monitoring tests, all elevations in liver enzymes resolved without sequelae.

The data available from the HERCULES trial demonstrates that tolebrutinib slows progression in nrSPMS. However, the significance of the lack of improvement in outcomes such as the 9HPT and brain atrophy remains unclear. Additionally, there is a small but non-trivial risk of severe liver toxicity; though this risk may be mitigated by weekly monitoring of liver function tests, such intensive monitoring may not be a realistic expectation in practice. Thus, we rate the overall net health benefit for tolebrutinib compared with best supportive care as **promising but inconclusive (P/I)**.

Table ES1. Evidence Ratings

Treatment	Comparator	Evidence Rating
Non-Relapsing SPMS		
Tolebrutinib	Best supportive care	P/I

In the cost-effectiveness analyses, treatment with tolebrutinib increases QALYs, evLYs, life years, and years without a wheelchair compared with best supportive care. At the placeholder price of $115,000 per year, the incremental cost-effectiveness ratios for tolebrutinib are $2.5 million per QALY gained, $1.6 million per evLY gained, $3 million per life year gained, and $800,000 per year without a wheelchair. The cost-effectiveness findings are primarily driven by the placeholder acquisition costs for tolebrutinib. The actual cost-effectiveness of tolebrutinib will depend on its price.

1. Background

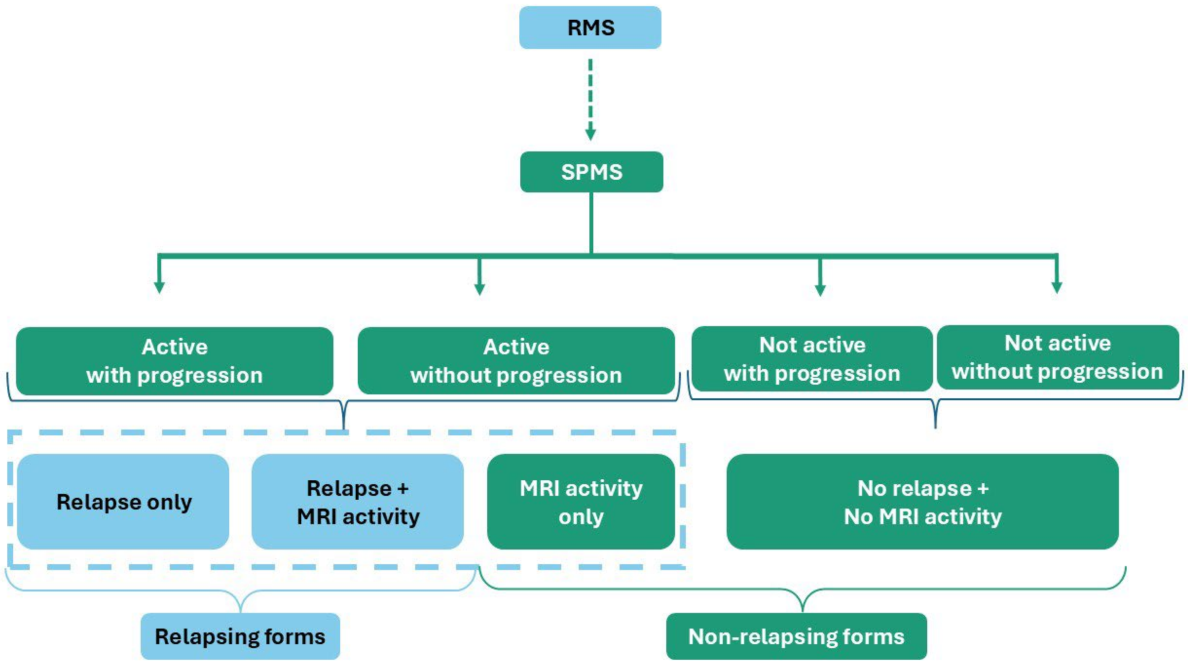
Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system affecting nearly a million people in the United States.[1,2] MS causes damage to the myelin sheath (a protective covering that surrounds nerve fibers), which eventually leads to degeneration of axons (long threadlike part of a nerve cell) and results in physical and cognitive symptoms such as weakness, fatigue, vision changes, memory and concentration problems, and pain.[3] In the United States (US), the disease is more prevalent in women and individuals between 45 and 65 years old. There also appear to be racial and ethnic differences in prevalence, with the disease being more prevalent in White Americans compared with Black and Hispanic Americans. However, Blacks have a higher risk of both developing MS and having poorer outcomes compared with White Americans, and Hispanics born in the US appear to develop MS earlier in life.[1,7] MS is a disease that is debilitating, progressive, and costly, with an estimated annual economic burden in the US being over $85 billion.[4]

Diagnosis of MS relies on a combination of clinical signs and symptoms, imaging, and laboratory criteria known as the 2017 McDonald Criteria[8]; these criteria are currently in the process of being updated.[9] Relapsing-remitting MS (RRMS) is the most common form of MS at disease-onset (85% of patients) and is marked by periods of symptom flares (relapses) followed by recovery; a minority of patients present with primary progressive MS (PPMS), which is characterized by a steady worsening of symptoms and disability from disease onset.[3]

The majority of patients with RRMS eventually transition to a non-relapsing form of MS, called secondary progressive MS (SPMS). Although progression independent of relapses can happen from the onset of MS,[10] SPMS is marked by progressive worsening of disability without symptomatic relapses. The median time to transition from RRMS to SPMS is 32.4 years from disease onset. [11] Risk factors associated with progression include older age at MS onset, early high relapse frequency, longer disease duration, male sex, and higher baseline Expanded Disability Status Scale (EDSS) score.[12] SPMS is a retrospective diagnosis; no imaging findings or biomarkers demarcate the transition between RRMS and SPMS in real-time.[11] Thus, diagnosis is challenging and often delayed. For example, the main measure of disability, the EDSS, does not capture visual, cognitive, bowel, or bladder function well, and thus, patients may appear clinically stable by EDSS while still having deterioration in other domains.[13] Magnetic resonance imaging (MRI) markers (e.g., brain atrophy, volume of T2 lesions, paramagnetic rim lesions) may correlate with progression;[11] however, persons living with SPMS report that symptoms and disability progression may not necessarily correlate with MRI findings. Persons living with SPMS may have active disease (with relapses and/or new MRI changes) or non-active disease, with or without progression during their disease course (Figure 1); however, since those with non-active disease are less likely to have a recent MRI, defining whether a person has active or non-active disease can be difficult.[11,14]

Figure 1 shows the categories of active and non-active SPMS, and their definitions based on relapses and MRI activity. Non-relapsing forms of MS include both active SPMS with MRI activity only (no clinical relapses) and non-active disease.

Figure 1. Phenotypes of SPMS



Note: The green areas highlight the SPMS disease course and subtypes.

Treatment for MS involves a comprehensive approach focusing on preventing relapses, delaying progression and worsening of disability, as well as symptom control, psychological support, rehabilitation, and lifestyle interventions. For RRMS, there are a variety of disease-modifying treatments (DMTs), including monoclonal antibodies, interferons, fumarates, and S1P receptor modulators approved to treat MS. In particular, monoclonal antibodies show high efficacy in preventing relapse and slowing down disease progression; some also carry an increased risk of infections due to B-cell depletion. Monoclonal antibodies and siponimod can be used to treat active SPMS, although the use of siponimod may be limited by the presence of cardiovascular disease and cytochrome P450 genotype.[15] However, once a person has transitioned to non-active SPMS, there are no DMTs currently approved for treatment in this population. While some patients and clinicians may opt to continue DMT with non-active SPMS, 2018 American Academy of Neurology guidelines deem it reasonable to trial stopping DMT therapy in persons with non-active disease who are not ambulatory (EDSS >7 for at least two years),[16] as clinical and subclinical disease activity may decrease due to the aging immune system.[17]

Bruton's Tyrosine Kinase Inhibitors (BTKIs) are being investigated as potential treatments for all forms of MS as they decrease acute and chronic neuroinflammation and target remyelination, repair, and recovery. This ICER report will focus on tolebrutinib (Sanofi), an oral, once-daily, BTKI that crosses the blood-brain barrier and modulates persistent activation of BTK enzyme within the central nervous system. It is being studied for the treatment of various forms of MS. However, the scope of this report is for the treatment of non-relapsing forms of SPMS (see Figure 1 for definition). A new drug application (NDA) for tolebrutinib for non-relapsing forms of SPMS has been submitted to the U.S. Food and Drug Administration with a "breakthrough therapy" designation,[18] with a decision expected by September 28, 2025.[6]

Table 1.1. Interventions of Interest

Intervention	Mechanism of Action	Delivery Route	Prescribing Information
Tolebrutinib	Bruton's Tyrosine Kinase Inhibitor	Oral	60 mg tablet once daily

mg: milligrams

2. Patient Community Insights

This section was developed with input from patients and caregivers, as well as patient advocacy groups, clinicians, researchers, and the manufacturer of tolebrutinib. We talked with patients living with SPMS and caregivers, as well as seven clinicians, and one patient advocacy coalition composed of nine different patient organizations. In addition, we obtained data from a survey conducted by the MS Coalition to learn from people with MS about their experiences with the disease. This document incorporates feedback gathered during calls with stakeholders, open input submissions from the public, the survey conducted by the MS Coalition, and information from prior ICER reviews focused on MS.[19] ICER looks forward to continued engagement with stakeholders throughout its review and encourages comments to refine our understanding of the clinical effectiveness and value of preventive treatments.

Because the symptoms of MS typically emerge in young adulthood, the disease has a large impact not only on physical health, but also on mental health, work and educational productivity, family planning, and social and leisure activities. Since the primary goal for people living with MS is to maintain independence and the ability to perform normal activities, early diagnosis and comprehensive treatment with DMTs are critical. We heard from persons living with SPMS that initial diagnosis of MS is often delayed – most had symptoms for years prior to getting a diagnosis. We also heard that although DMTs are very effective at preventing relapses, some symptoms are not adequately treated by existing DMTs. For example, persons living with SPMS noted that pain, fatigue, numbness, urinary incontinence, and cognitive difficulties often persist despite DMT treatment, and often cause the need to take additional medications outside of the DMT. Persons living with SPMS also noted that some symptoms, such as fatigue, are unpredictable, causing difficulty with planning work and other activities, and that medications may exacerbate fatigue. We also heard that urinary symptoms have a large impact on quality of life, since urinary urgency and incontinence may limit the ability to leave the house for long periods of time or limit excursions to places with ready access to the toilet. Cognitive symptoms were also noted to have a substantial impact on quality of life and the ability to perform at work. Some people living with SPMS have had to retire from the workforce prematurely due to the disease. Finally, at the late stages of the disease, limitations in arm and hand mobility place substantial limitations on activities of daily living.

Access to specialist care and coordination of care are two additional issues that affect persons living with MS. For example, those living in more rural areas did not have easy access to MS specialists and sometimes traveled great distances to get the level of care they desired. Furthermore, many people living with MS see multiple specialists, and people living with SPMS we spoke with were frustrated with the lack of coordination of care and the self-advocacy needed to manage their condition adequately.

MS is associated with a high caregiver burden, though the specific caregiving duties depend on the patient's disabilities. For example, for persons living with SPMS who have limited leg mobility, caregivers need to help with transfers to and from a wheelchair. For those with limitations in arm and/or hand mobility, the assistance needed increases to include dressing and feeding. The time burden of caregiving limits outside activities; one caregiver noted that he planned his days around his partner's illness. Finally, once a person living with SPMS needs a full-time caregiver, the caregivers face a decision of whether they will leave the workforce to become a full-time caregiver.

Insurance coverage can be a substantial barrier to receiving DMTs. Persons living with SPMS described ongoing anxiety about whether their insurance plan will cover their DMT. The high co-pays and co-insurance for treatment often lead to a reliance on grants and patient assistance programs to help cover costs. Additionally, access to ancillary services such as physical therapy (PT) can be limited due to the current PT model emphasizing improvement as a goal and for continued coverage; in persons living with SPMS, PT is important for maintenance of mobility and improvement may not be a reasonable goal. Furthermore, physical therapists with specialized training in neurological diseases can also be difficult to find.

Persons living with SPMS conveyed that since disability progression is not linear and symptoms may not correspond with MRI lesions, disability progression can occur even in the face of "stable" MRI findings. Thus, they would like more researchers to focus on the concept of "smoldering MS," particularly for future treatments. Finally, research into treatments that re-myelinate nerves and/or improve disability should be a high priority.

Health Equity Considerations

Because SPMS occurs after progression from RRMS, people with SPMS are, on average, older than those with RRMS. However, there are few data about treatment outcomes in patients ≥ 60 years old, as these patients are typically excluded from MS trials. Additionally, older persons and those who are no longer ambulatory often feel as though clinicians do not offer more aggressive treatment options, particularly since 2018 American Academy of Neurology guidelines state that it is reasonable to consider stopping DMT in older patients with stable disease. Finally, for persons living with MS who live in more rural areas, access to MS specialists is difficult and thus may affect the quality of care they receive.

Survey of MS Patient Experience

In December 2022 and January 2023, the MS Coalition fielded a cross-sectional survey of MS patients to learn about the interactions and experiences with the health care system of people with multiple sclerosis.[5] Of the 1412 respondents, 210 reported being diagnosed with SPMS. Those with SPMS tended to have higher mobility impairment, with 62% of respondents having a disability score of 5-7. One-third of respondents were not currently on a DMT, and the average number of DMTs tried in the past was around three. Slowing progression, preventing relapses, and the doctor's recommendation were the most important reasons when deciding whether to start a DMT. The majority of respondents with SPMS reported no current barrier to receiving a DMT in terms of treatment logistics; however, financial barriers could be substantial. Around 15% respondents reported that out-of-pocket costs caused them to delay, pause, or stop a DMT, and 41% of respondents reported receiving copay assistance or financial support to cover the cost of DMT. Of those receiving financial assistance, 70% reported that they would not be able to afford their DMT without assistance. Finally, comments from respondents reflected the high burden of SPMS, with respondents reporting a loss of independence and identity, as well as a negative impact on career and relationships.

3. Comparative Clinical Effectiveness

3.1. Methods Overview

The methods for the systematic literature review are described in Supplement Section D1. We published the research protocol for the systematic literature review on Open Science Framework and registered it with PROSPERO (CRD42025617271).

Scope of Review

We reviewed the clinical effectiveness of tolebrutinib for the treatment of non-relapsing SPMS compared to best supportive care, defined as pharmacological and non-pharmacological treatments to alleviate the symptoms of MS. We searched for evidence on patient-important outcomes, including disability progression or improvement as measured by expanded disability status score (EDSS), timed 25-foot walk test (T25FW), 9-hole peg test (9HPT), mobility, cognitive function, fatigue, health-related quality of life (HRQoL), MRI outcomes, and harms of tolebrutinib. The full scope of this review is provided in Supplement Section D1.

Evidence Base

Evidence informing this review comes primarily from HERCULES, a Phase III randomized controlled trial (RCT) comparing tolebrutinib to placebo in non-relapsing forms of SPMS.[20] This review included data from a recent publication and a conference presentation, in addition to limited data submitted by the manufacturer as academic in confidence.[21-23] We sought additional data on harms of tolebrutinib from two Phase III (GEMINI 1 and 2) and two Phase II trials (NCT03889639 and NCT03996291) conducted in the RRMS population.[20,24-27]

HERCULES was a Phase III, randomized, placebo-controlled trial that evaluated the efficacy and safety of tolebrutinib (60 mg orally once daily) in adults aged 18-60 years old with a confirmed diagnosis of SPMS and no clinical relapses in the two years prior to screening. Additional inclusion criteria were an EDSS score of 3.0-6.5 and documented evidence of disability progression in the last 12 months. The study excluded participants taking certain medications for MS within a prespecified time, depending on the expected washout period. Participants were randomized 2:1 into the tolebrutinib and placebo groups. The primary endpoint was time to onset of disability progression, confirmed over ≥6 months.[20] The investigators tested six secondary outcomes in a prespecified hierarchical sequence, meaning they evaluated each outcome individually and proceeded to the next only if statistical significance was achieved with the primary outcome and the preceding secondary outcome. Additional details about this trial and four clinical trials assessing tolebrutinib for the treatment of RRMS are available in Supplement Section D2.

Baseline characteristics were similar across both arms in this trial (Table 3.1). Overall, participants were mostly female (62%), White (92%), treatment-experienced (74%), had a mean age of 49 years old, and a median EDSS score of six. At baseline, the mean time since SPMS diagnosis was around 8 years, and the mean time since the most recent clinical relapse was around 7.5 years. Around 13% of the trial participants had at least one gadolinium (Gd)-enhancing T1 lesion at baseline, meaning these participants showed MRI disease activity even without clinical relapse. The median follow-up was 133 weeks.[22] Additional baseline characteristics are presented in Supplement Table D3.2.

Table. 3.1. Baseline Characteristics of Key SPMS Trial: HERCULES[21,22]

		Tolebrutinib (N=754)	Placebo (N=377)
Age, years ± SD		48.9 ± 8.0	48.9 ± 8.0
Female, n (%)		454 (60.2)	242 (64.2)
Race, n (%)	**White**	703 (93.2)	348 (92.3)
	Black	6 (0.8)	4 (1.1)
	Asian	36 (4.8)	19 (5.0)
	Other	9 (1.2)	6 (1.6)
EDSS Score	**Mean ± SD**	5.5 ± 1.0	5.6 ± 0.9
	Median (Range)	6 (4.8, 6.3)	6 (5.0, 6.3)
Time since RRMS symptom onset, mean years ± SD		17.1 ± 8.3	17.6 ± 8.4
Time since diagnosis of SPMS, mean years ± SD		7.9 ± 7.3	8.4 ± 7.8
Time since most recent clinical relapse, mean years ± SD		7.4 ± 5.3	7.6 ± 5.5
Participants with ≥1 Gd-enhancing T1 lesions, n (%)		93 (12.5)	49 (13.1)
Number of T2 lesions, median (IQR)		50 (35, 73)	49 (33, 75)
Participants with ≥1 prior DMTs, n (%)		549 (72.8)	288 (76.4)

DMT: disease-modifying therapy, EDSS: Expanded Disability Status Scale, Gd: Gadolinium; IQR: interquartile range, N: number, RRMS: relapsing remitting multiple sclerosis, SD: standard deviation

Evaluation of Clinical Trial Diversity

We rated the demographic diversity (race/ethnicity, sex, age) of the participants in the trials using the ICER-developed Clinical trial Diversity Rating (CDR) Tool.[28] Around 10% of the trial populations were from the US. Because the US-based baseline characteristics were not publicly available, the HERCULES trial was rated using the full sample. The trial achieved "fair" diversity rating for race/ethnicity, driven mostly by the underrepresentation of those who identify as Black or African American and Hispanic. The trial received a "poor" rating for age because participants aged 65 years or older were underrepresented compared to the overall population. This is particularly important as there has been an increase in the prevalence of MS among older adults.[29] Due to adequate representation of males and females, the trial received a "good" rating for diversity for sex. See Supplement D1 for full details of CDR methods and results.

3.2. Results

Clinical Benefits

As mentioned earlier, the evidence for this review comes primarily from the Phase III HERCULES trial. The primary endpoint was six-month confirmed disability progression (CDP), defined as an increase of ≥1 point from the baseline EDSS score if the baseline score was ≤5.0 or an increase of ≥0.5 point if the baseline EDSS score was >5, that was sustained for at least 6 months. Other measures of disease progression, disease improvement, and disease activity were evaluated as secondary outcomes.

Disability Progression

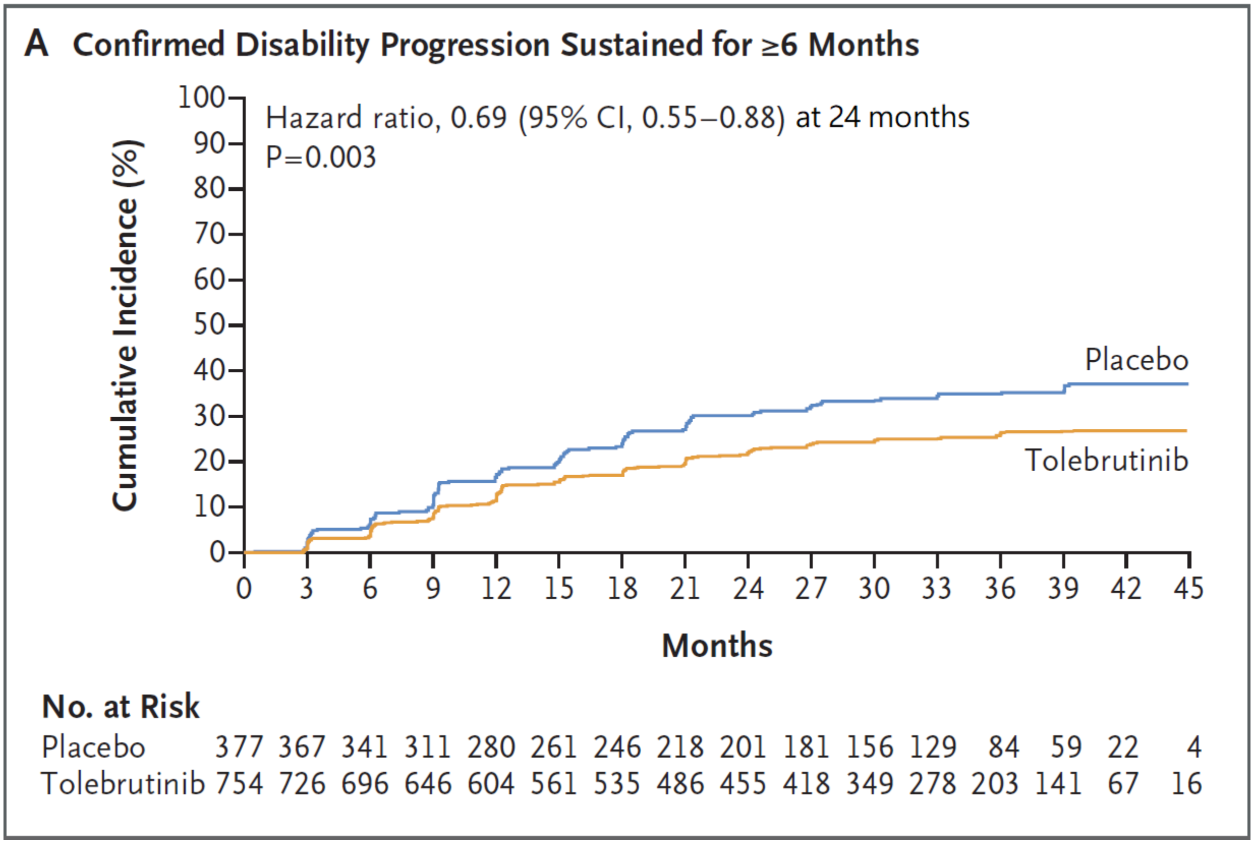
As noted above, HERCULES trial evaluated the six-month CDP, as its primary outcome. At 24 months of follow-up, there was a statistically significant reduction in participants showing sustained 6-month CDP in the tolebrutinib arm compared with the placebo arm (22.6% vs. 30.7%, hazard ratio 0.69; 95% CI 0.55 to 0.88, p=0.003).[22] This difference slightly increased by the end of the trial, with 26.9% of the tolebrutinib group having reached the primary endpoint compared with 37.2% in the placebo group at 45 months.[21] However, only 20 patients (16 in the tolebrutinib group and 4 in the placebo group) had made it to 45 months of follow-up.[22] See Figure 3.1. Data submitted as academic in confidence showed that the reductions in six-month CDP appeared to be greater in lower EDSS subgroups (e.g., ≤4.5 or ≤5.5) compared to their respective higher EDDS subgroups (>4.5 or >5.5).[23] See Table 3.2.

Table 3.2. Disability Progression and Improvement-Related Outcomes from HERCULES Trial[22]

	Tolebrutinib (N=754)	Placebo (N=377)	Between Group Difference at 24 Months; HR (95% CI)	P Value
Proportion of Patients Achieving 6-month CDP	22.6%	30.7%	0.69 (0.55 to 0.88)	P = 0.003
Proportion of Patients Achieving >20% Increase in 9HPT Scores	19%	19.6%	0.97 (0.74 to 1.29)	P = 0.84
Proportion of Patients Achieving >20% Increase in T25FW Scores	41.1%	49.6%	0.77 (0.64 to 0.92)	NR
Proportion of Patients Achieving 6-month CDI	8.6%	4.5%	1.88 (1.10 to 3.21)	NR

CI: confidence interval, CDI: confirmed disability improvement, CDP: confirmed disability progression, HR: hazard ratio, NR: significance testing not reported due to prespecified hierarchical sequence, 9HPT: 9 hole peg test, T25FW: timed 25-foot walk test

Figure 3.1: Primary Endpoint: Time to 6-Month CDP from HERCULES Trial[22]



CDP: confirmed disability progression, CI: confidence interval, HR: hazard ratio
Source: Data from Fox et al 2025

The HERCULES trial also evaluated other disease progression endpoints including the 9HPT and the T25FW.

9HPT is a standardized test of upper extremity function where patients repeatedly place and then remove nine pegs into nine holes arranged in a square pattern. An increase of >20% from baseline is considered to be clinically meaningful worsening.[30,31] After 24 months of follow-up, there was no statistically significant difference in the proportion of patients who achieved a >20% increase in 9HPT that was sustained over at least 3 months. (19.0% vs 19.6%, HR 0.97, 95% CI 0.74 to 1.29; p = NS).[22] See Table 3.2.

T25FW test is a measure of gait velocity where patients complete two 25-foot walks and a change of ≥20% is considered to be clinically meaningful worsening.[31] Although fewer participants experienced worsening on this outcome in the tolebrutinib group compared to placebo at 24 months (41.1% to 49.6%, hazard ratio 0.77, 95% CI 0.64 to 0.92), formal significance testing was not done because a preceding outcome (9HPT) lacked statistical significance.[22] See Table 3.2.

Disability Improvement

The HERCULES trial also evaluated confirmed disability improvement (CDI), which was defined as a decrease of at least one point from the baseline EDSS score. Overall, few patients in the trial achieved a sustained 6-month improvement in this endpoint. At 24 months, a higher proportion of the participants receiving tolebrutinib showed improvement compared to the placebo group (8.6% vs. 4.5%, hazard ratio 1.88; 95% CI 1.10 to 3.21).[22] Formal significance testing for this outcome was not done because a preceding outcome (9HPT) lacked statistical significance. See Table 3.3.

Disease Activity, Including Relapse and MRI-Related Outcomes

The investigators evaluated the annualized relapse rate as a part of the exploratory analyses and found similar rates after adjustment and adjudication across both arms (0.033 in the tolebrutinib group and 0.032 in the placebo group).[22] See Table 3.3.

In terms of MRI-related outcomes, the annualized rate of new or enlarging T2 lesions was significantly lower in the tolebrutinib arm compared to placebo (1.84 vs. 2.95, RR 0.62; 95% CI 0.43, 0.90; p=0.01).[22] Data related to T1 lesions was not measured in this trial. See Table 3.3.

Brain volume loss was first measured in the HERCULES trial at six months to avoid any confounding effects of volume loss due to the reduction of inflammation that occurred with the initiation of treatment, and was subsequently measured every six months until the end of the study. Both groups demonstrated similar mean percentage change in brain volume at the end of the study (-0.69% for the tolebrutinib arm vs. -0.78% for the placebo arm, least-squares mean difference 0.08 (-0.03 to 0.29) compared to baseline.[22] Formal significance testing for this outcome was not done because a preceding outcome (9HPT) lacked statistical significance. See Table 3.3.

Table 3.3. Disease Activity-Related Outcomes from HERCULES Trial[22]

	Tolebrutinib	Placebo	Between Group Difference (95% CI)	P Value
Annualized Adjusted Adjudicated Relapse Rate (95% CI)	0.033 (0.024 to 0.045)	0.032 (0.021 to 0.049)	NA	NR
Annualized New or Enlarging T2 Lesions Rate: Mean estimate (95% CI)	1.84 (1.44 to 2.34)	2.95 (2.24 to 3.88)	RR: 0.62 (0.43 to 0.90)	0.01
Percentage Change in Brain Volume Loss: Mean Change (SE)	-0.69% (0.03)	-0.78% (0.05)	MD: 0.08 (-0.03 to 0.29)	NR

CI: confidence interval, MD: mean difference; NR: significance testing not reported due to prespecified hierarchical sequence; RR: relative risk, SE: standard error

Other Patient-Important Outcomes of Interest

At the time of report publication, data on HRQoL (Multiple Sclerosis Quality of Life-54 and EuroQol 5-dimension 5-level) and cognitive function (Symbol Digit Modalities Test and California Verbal Learning Test-II) from the HERCULES trial have not been reported, though the trial protocol indicates that these outcomes were measured during the trial.[20,22]

We also sought data on the paced auditory serial addition test (PASAT-3), a measure of cognitive function, mobility, pain, fatigue, bladder and bowel dysfunction, and depression, but none appeared to be evaluated in the HERCULES trial. Additionally, the trial did not assess caregiver-related outcomes such as their health, quality of life, and productivity.

Harms

In the HERCULES trial, both treatment arms experienced high rates of discontinuation (23%), primarily caused by participant decisions. Adverse events-related discontinuations were marginally higher in the tolebrutinib arm compared to placebo (4% versus 3%).[22]

Table 3.4 summarizes key harms recorded during the trial. Overall, a similar proportion of patients in the tolebrutinib and placebo groups were reported to have suffered an adverse event during the trial. However, more participants in the tolebrutinib arm experienced serious adverse events compared to placebo (15% versus 10%). Two patients died in the tolebrutinib arm, including one due to post-operative complications after liver transplant deemed related to tolebrutinib. This death occurred prior to a protocol change, increasing the monitoring of liver function tests to weekly liver function tests. The most frequent adverse event with a higher proportion of participants in the tolebrutinib arm than in placebo was COVID-19 infections.[22]

Liver toxicity is a prominent safety concern for tolebrutinib. A higher proportion of the participants receiving tolebrutinib had liver enzyme elevations (alanine transaminase [ALT] >3 times the upper limit of normal) compared to placebo (4% versus 1.6%). Four patients (0.5%) in the tolebrutinib arm experienced severe liver injury, defined as peak ALT increases of 20 times the upper limit of normal, compared to none in the placebo. All cases of severe liver injury occurred within the first 90 days of treatment with tolebrutinib. Except for one, all cases of severe liver injury took place prior to the protocol update.[22] After the protocol change requiring increased liver function test monitoring, all instances of elevated liver-enzyme tests resolved without the need for medical interventions. Liver toxicity data from the two Phase III RMS trials (GEMINI 1 and 2) was consistent with the experience reported for the HERCULES trial.[24] See Table 3.4 and Supplement Table D3.6.

Infections represent a notable threat to patients with MS. Although higher proportions of participants in the tolebrutinib arm experienced COVID-19, influenza, and nasopharyngitis, both urinary tract infections and respiratory infections were more frequent in the placebo arm.[22]

Overall, harms from trials involving RMS patients reported similar types of adverse events mentioned in the HERCULES trial.[22,32-37] See Supplement Table D3.6.

Table 3.4. Key Harms from HERCULES Trial[22]

Arms	Tolebrutinib	Placebo
	N=752	N=375
Any Adverse Events, n (%)	613 (81.5)	293 (78.1)
Discontinuations due to Adverse Events	29 (3.9)	11 (2.9)
Serious Adverse Events, n (%)	113 (15.0)	39 (10.4)
Death, n (%)	2 (0.3)	1 (0.3)
Infections and Infestations	409 (54.4)	185 (49.3)
COVID-19 Infection, n (%)	192 (25.5)	85 (22.7)
Influenza	42 (5.6)	13 (3.5)
Nasopharyngitis, n (%)	70 (9.3)	26 (6.9)
Upper RTI, n (%)	31 (4.1)	18 (4.8)
UTI, n (%)	85 (11.3)	49 (13.1)
Liver Safety	**N=741**	**N=372**
ALT >3 x ULN (%)	30 (4.0)	6 (1.6)
ALT >20 x ULN (%)	4 (0.5)	0

ULN: upper limit of normal, UTI: urinary tract infection, RTI: respiratory tract infection

Subgroup Analyses and Heterogeneity

There is no data available at this time on any subgroups of interest, including race/ethnicity, age, disease duration, disease activity (active versus non-active), and level of disability.

Uncertainty and Controversies

While currently available data from the HERCULES trial show promising results in terms of reducing disease progression in persons with nrSPMS, some additional outcomes, such as the 9-HPT and measures of brain atrophy, were not consistent with six-month CDP data. Clinical experts and patient groups were concerned about the lack of difference in brain atrophy between the tolebrutinib and placebo groups, since brain atrophy is a marker for progression independent of relapses.[38] Clinical experts also suggested that the higher rate of new T2 lesions on MRI observed in patients on tolebrutinib in the two Phase III GEMINI trials conducted in the RRMS patients versus teriflunomide tempered their enthusiasm.[24] Finally, there have been no data reported on other patient-important outcomes, such as health-related quality of life and cognitive function, though those appeared to have been collected during the trial.[39]

Improvement of disability was mentioned by persons living with MS as an important outcome. Although more patients in the tolebrutinib group achieved six-month confirmed disability improvement (CDI) compared with the placebo group (10% to 5%), few patients overall achieved this outcome. Thus, clinical experts were guarded about the significance of the six-month CDI findings.

The incidence and severity of liver toxicity due to tolebrutinib treatment remains a concern, as there appears to be a small but significant risk of severe liver toxicity, with one case of liver injury that lead to liver transplant and subsequently death from post-transplant complications. Trials of tolebrutinib were halted temporarily due to these concerns.[40] Changes to the trial protocols were made to increase monitoring of liver function tests, which appears to mitigate the risk of severe liver injury. However, the increase in liver monitoring may have resulted in unblinding given the intensity of testing. In clinical practice, it may also be a substantial burden for patients, particularly those with high levels of disability, for whom leaving the house for frequent testing may be difficult. Furthermore, we do not have long-term safety data on tolebrutinib in MS, so as with any drug with a new mechanism of action, additional harms may surface with longer-term use.

The HERCULES trial included both patients with active and non-active forms of SPMS. We do not have data on whether there are differences in efficacy based on subgroup. Since there are DMTs that can be used for active SPMS, when to use tolebrutinib in clinical practice, particularly in patients who are currently doing well on other DMTs, is not yet clear. Additionally, since tolebrutinib was not better at preventing relapses in patients with RRMS compared with teriflunomide in the GEMINI trials, and the annualized relapse rate in the HERCULES trial also did not differ between groups, clinicians may be somewhat reluctant to use tolebrutinib in patients who may still be having relapses.

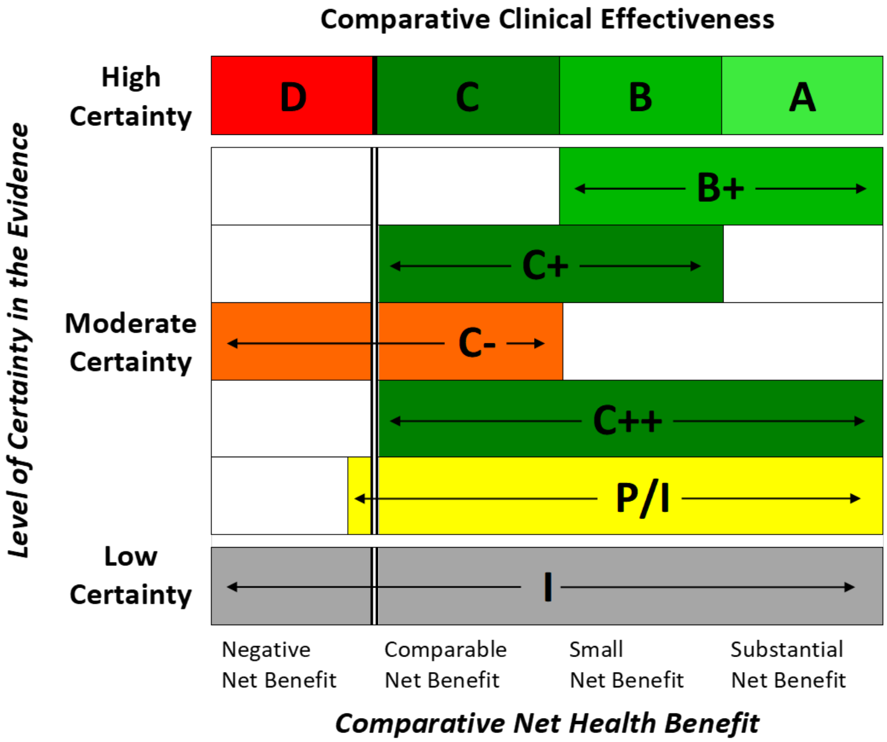
Additional Stakeholder Insights

Clinical experts emphasized that the diagnosis of SPMS is difficult. Some clinicians felt that some of their colleagues may not give a definitive diagnosis of SPMS, particularly non-relapsing forms of SPMS, due to the fact that there are currently no approved DMTs for this population; they also felt that the availability of an effective treatment may drive earlier diagnosis. Clinical experts also discussed that decisions to continue or stop DMTs depend on individual patient factors and preferences.

3.3. Summary and Comment

An explanation of the ICER Evidence Rating Matrix (Figure 3.2) is provided here.

Figure 3.2. ICER Evidence Rating Matrix



__A = "Superior"__ - High certainty of a substantial (moderate-large) net health benefit
__B = "Incremental"__ - High certainty of a small net health benefit
__C = "Comparable"__- High certainty of a comparable net health benefit
__D= "Negative"__- High certainty of an inferior net health benefit
__B+= "Incremental or Better" –__ Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit
__C+ = "Comparable or Incremental"__ - Moderate certainty of a comparable or small net health benefit, with high certainty of at least a comparable net health benefit
__C- = "Comparable or Inferior"__ – Moderate certainty that the net health benefit is either comparable or inferior with high certainty of at best a comparable net health benefit
__C++ = "Comparable or Better"__ - Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit
__P/I = "Promising but Inconclusive"__ - Moderate certainty of a small or substantial net health benefit, small (but nonzero) likelihood of a negative net health benefit
__I = "Insufficient"__ – Any situation in which the level of certainty in the evidence is low

Persons with non-relapsing SPMS, particularly with the non-active type, have limited treatment options to slow the progression of disability. The data available from the HERCULES trial demonstrates that tolebrutinib slows progression of disease and, in a small number of people, may also lead to disability improvement. However, some other outcome results were not as expected given the overall decrease in progression of disability; the significance of the inconsistencies in the direction of outcomes is not clear. Additionally, there is a small but non-trivial risk of severe liver toxicity (defined as liver function tests ≥20 times the upper limit of normal), though this risk appeared to be mitigated by intensive weekly monitoring of liver function tests. Full adherence to weekly monitoring may not be possible in clinical practice, as it imposes a substantial burden on a population that already has mobility challenges, and thus, those who are not able to be monitored closely may face an increased risk of severe liver toxicity. Finally, long-term data on the persistence of slowing of disease progression, along with more data on whether improvement occurs, are needed to confirm the overall net health benefits of tolebrutinib.

Thus, for persons with non-relapsing forms of SPMS, we rate the evidence for tolebrutinib compared with best supportive care as **promising but inconclusive (P/I)**.

Table 3.3. Evidence Ratings

Population	Treatment	Comparator	Evidence Rating
Non-Relapsing SPMS	Tolebrutinib	Best supportive care	P/I

P/I: promising but inconclusive

4. Long-Term Cost Effectiveness

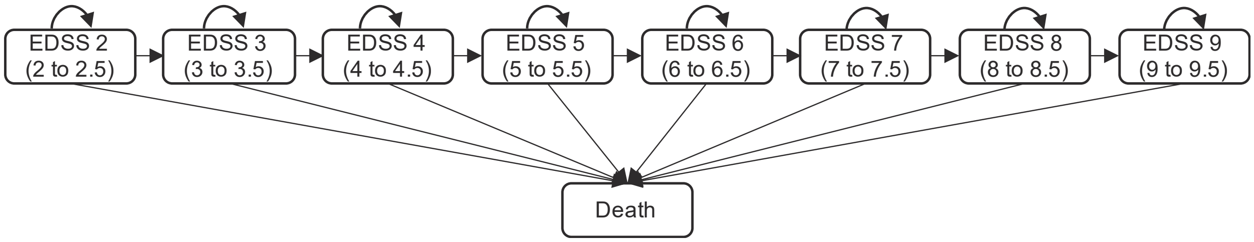
4.1. Methods Overview

The primary aim of this analysis was to estimate the cost-effectiveness of tolebrutinib for non-relapsing SPMS using a decision analytic model. The lifetime model compared tolebrutinib to best supportive care, defined as pharmacological and non-pharmacological treatments to alleviate the symptoms of MS. Analyses were conducted from the health care system perspective and the modified societal perspective. The base-case analysis took a health care sector perspective (i.e., focus on direct medical care costs only), and patient and caregiver productivity impacts and other indirect costs and effects were considered in the modified societal perspective analysis. The model was developed in Microsoft Excel.

We developed a *de novo* decision analytic model for this evaluation, informed by key clinical trials and prior relevant economic models. Costs and outcomes were discounted at 3% per year. The model focused on an intention-to-treat analysis, with a hypothetical cohort of patients with non-relapsing SPMS being treated with tolebrutinib or best supportive care entering the model. A Markov model with annual cycle length was used to account for SPMS disease progression over a lifetime. This approach builds on insights gained from previously published economic models and clinical data from HERCULES.[41] While few economic models specifically target SPMS,[19,42-44] several models for relapsing-remitting multiple sclerosis (RRMS) have incorporated the progression and clinical course of SPMS, often employing a Markov cohort structure with a similar cycle length.[45-47]

The model encompassed health states defined by the Expanded Disability Status Scale (EDSS) and was informed by baseline EDSS and six-month confirmed disability progression from the natural history of SPMS from the London, Ontario Cohort and clinical trial comparisons between tolebrutinib and placebo (see Figure 4.1).[41,48] The model consisted of nine health states: eight EDSS states (2–9) and death. Patients started at EDSS scores of 3.0 or higher based on the baseline EDSS scores of patients in the HERCULES trial.[41] Additional data can be found in the Supplement.

Figure 4.1. Model Schematic*



EDSS: Expanded Disability Status Scale

*Individuals can remain at the same EDSS rating, transition from their current EDSS level to more severe health states (higher EDSS score), or move to MS-related or all-cause death. While the model schematic only shows arrows moving between individual units (e.g., EDSS 3 to EDSS 4) states, it's possible for patients to advance more than one EDSS state each cycle (e.g., EDSS 3 to EDSS 6). E2.4 in this document show the probabilities of these transitions, with some transitions having a probability of zero. The health states are categorized into whole unit increments based on the EDSS. Transitions occur annually.

4.2. Key Model Assumptions and Inputs

The model includes several assumptions stated in Table 4.1. The full list of assumptions can be found in the Supplement.

Table 4.1. Key Model Assumptions

Assumption	Rationale
Transitions between EDSS states for tolebrutinib and best supportive care were based on the minimum change required to meet the confirmed disability progression (CDP) criteria defined in the HERCULES trial (i.e., an increase of 1.0 EDSS point when baseline EDSS is ≤5.0 or an increase of 0.5 EDSS points when baseline EDSS is >5.0). To estimate transition probabilities, the 0.5-unit increase observed within the trial follow-up was extrapolated to a one-unit equivalent.	CDP may capture changes larger than these thresholds, however no data was provided on the exact magnitude of these changes. The model assumes the minimum required change for progression—that is, a 1-point increase for baseline EDSS ≤5.0 or a 0.5-point increase for baseline EDSS >5.0—as the basis for estimating progression through EDSS states. This assumption reflects the trial endpoint in HERCULES and allowed for consistency in modeling movement across EDSS levels.
The model applied relative effect estimates from the HERCULES trial to natural history data to quantify the treatment effect.	Treatment effectiveness was modeled using the relative effect estimate from the HERCULES trial, which reported CDP for tolebrutinib and placebo. The treatment effect was assumed to slow disease progression, which has an indirect effect of reducing related complications and improving long-term survival outcomes.
6-month confirmed disability improvement (CDI) was not considered in the base-case model as it does not necessarily represent a true reversal of disease progression.	The 6-month CDI endpoint does not provide sufficient evidence to determine whether an observed improvement reflects actual disease reversal or merely a temporary slowing of progression. Longer follow-up data would be required to establish true regression. The potential impact of 6 month CDI was explored through a scenario analysis incorporating a one-time improvement.
Patients who progress on tolebrutinib (meet the criteria of 6-month CDP) continued treatment and progressed at the same rate until death.	Although clinical practice guidelines, including from the American Academy of Neurology (AAN), suggest that clinicians may consider discontinuation of disease-modifying therapies in patients with SPMS who are non-ambulatory (EDSS score ≥7),[49] consensus was not reached among clinicians on stopping rules. Additionally, AAN guidelines were published prior to the availability of disease-modifying therapies for SPMS. Therefore, treatment effectiveness was considered as long as patients use tolebrutinib up until death. Scenario analyses explored the implications of stopping treatment at EDSS levels 7 or 8.
The risk reduction in progression was consistent across EDSS states in the tolebrutinib group.	We received no data on specific risk reductions for different EDSS levels. In the absence of stratified data, the model assumes a uniform risk reduction across all EDSS states.
Mortality was calculated using U.S. life tables, applying relative risk based on EDSS health states. Treatments indirectly affect mortality by delaying progression to worse EDSS states, where the risk of mortality is higher.	No mortality benefit was observed in the tolebrutinib trial; however, a significantly increased risk of mortality has been demonstrated with increasing MS severity.

Assumption	Rationale
The discontinuation rate was based on data from the HERCULES trial.	Currently, there is no data to inform real-world treatment patterns associated with tolebrutinib. Therefore, the model reflected the adverse event discontinuation rate observed in the HERCULES trial and applied in the model only during a period of time consistent with the trial.

CDI: Confirmed Disability Improvement, CDP: Confirmed Disability Progression, EDSS: Expanded Disability Status Scale, SPMS: Secondary Progressive Multiple Sclerosis

Table 4.2 presents the key model inputs. A comprehensive list and description of all model inputs, along with their respective sources, can be found in the Supplement.

Table 4.2. Key Model Inputs

Parameter	Input	Source
Hazard Ratio for 6-Month Disability Progression (CI), Tolebrutinib vs. Placebo	0.69 (0.55 to 0.88)	ECTRIMS 2024[21]
Natural History Annual Transition Probabilities	A matrix including transitions from EDSS 2-9 to EDSS 2-9 states.	London, Ontario MS dataset[19,45,48,50]
Tolebrutinib Discontinuation Rate	3.9%	HERCULES trial and calculation to reach discontinuation rate by end of trial[41]
Initial EDSS State Distributions		Academic in confidence
EDSS 2	[redacted]	
EDSS 3		
EDSS 4		
EDSS 5		
EDSS 6		
Standardized mortality ratios		Pokorski 1997[51]
EDSS 2	1.6 (1.28-1.92)	
EDSS 3	1.64 (1.31-1.96)	
EDSS 4	1.67 (1.34-2.01)	
EDSS 5	1.84 (1.47-2.21)	
EDSS 6	2.27 (1.82-2.73)	
EDSS 7	3.1 (2.48-3.72)	
EDSS 8	4.45 (3.56-5.34)	
EDSS 9	6.45 (5.16-7.74)	
Health State Utilities		Mauskopf 2016 and ICER MS Review 2023[19,45]
EDSS 2	0.7365	
EDSS 3	0.6509	
EDSS 4	0.5816	
EDSS 5	0.5005	
EDSS 6	0.4118	
EDSS 7	0.3000	
EDSS 8	0.2095	

Parameter	Input	Source
EDSS 9	0.1034	
Annual Background Non-Drug Health Care Costs		Hernandez (2016) interpolation of ICER 2020 Review[19]
EDSS 2	$15,330	
EDSS 3	$19,848	
EDSS 4	$24,367	
EDSS 5	$28,889	
EDSS 6	$33,410	
EDSS 7	$37,929	
EDSS 8	$42,448	
EDSS 9	$46,969	
Annual Acquisition Cost of Tolebrutinib	$115,000	Placeholder price; projection from IPD Analytics

EDSS: Expanded Disability Status Scale

Clinical Inputs

Clinical inputs were derived using both the natural history of SPMS and treatment effects from the Phase III trials for tolebrutinib. Key clinical inputs include disease progression, adverse events, discontinuation, and mortality. Treatment effectiveness, as measured by disease progression, was defined using the tolebrutinib arm hazard ratio for disability progression to higher EDSS states, while the comparator arm followed the natural history of disease progression (Table 4.2 and Table E2.2). We applied the hazard ratio in the transition matrix to reduce the individual progression-moving (e.g., EDSS 5 to 6) transitions that move patients to higher EDSS states. Initial state distributions for EDSS were provided in confidence from the manufacturer and are redacted from this report. In a scenario analysis, if relevant data become available, we will model a subset of disability improvement (Table E2.3) by adjusting EDSS state distributions after the first cycle of the model.

Transition Probabilities

Transition probabilities between EDSS states for patients with SPMS in the absence of treatment are provided in Table E2.4. These values were used in the prior ICER MS reviews and were based on a previous study that calculated the transition probabilities among patients with SPMS using data from the London, Ontario MS dataset.[19,45,48,50]

Discontinuation

The rate of trial discontinuation was similar for both tolebrutinib and placebo in the HERCULES trial. For up to 45 months, representing the maximum observation time reported in the trial results, the model assumed that patients would adhere to the treatment and only accounted for treatment-emergent adverse events (TEAEs) leading to discontinuation. In this study, 3.9% of patients in the tolebrutinib group discontinued due to serious TEAEs (Table 4.2). We apply a cycle-specific transition probability that reaches 3.9% by cycle 3 in the model. After 45 months, we assume no long-term discontinuation given a lack of data on disease-modifying use in this population.

Mortality

All-cause mortality based on age- and sex-adjusted United States life tables was multiplied by MS-specific mortality using a standardized mortality ratio that increases with EDSS (Table 4.2). These standardized mortality ratios were used in previous MS ICER reviews[19] and were calculated using the following equation from a prior study:[51]

$$\text{Mortality Multiplier} = 0.0219*EDSS^3 - 0.1972*EDSS^2 + 0.6069*EDSS + 1.$$

This prior study was the most commonly used source for mortality estimates in MS cost-effectiveness analyses as reported by a recently published systematic literature review.[50]

Adverse Events

Publicly available data indicate that 15.0% of participants in the tolebrutinib group experienced serious treatment-emergent adverse events (TEAEs), compared to 10.4% in the control group. However, specific types of adverse events were not detailed. In the model, we used the difference (4.6%) to represent the excess serious TEAEs associated with tolebrutinib.

Liver enzyme elevations exceeding three times the upper limit of normal (ULN) were reported in 4.1% of participants receiving tolebrutinib, compared to 1.6% in the placebo group. The difference may explain the higher rate of serious adverse events in the tolebrutinib group.

To estimate the impact of TEAEs, we applied a global annualized disutility value. Specifically, we used a disutility of 0.01, which represents the higher end of the range observed in the 2017 ICER report for disease-modifying therapies in RRMS.[52] This disutility value was multiplied by the proportion of patients experiencing serious adverse events in both groups. The disutility for managing adverse events was included in the first cycle of the model with any remaining serious adverse events management through discontinuation after the first cycle. Specific TEAEs were not reported by frequency of interaction with the health care system. Without specific information on TEAEs and management in a specific setting (e.g., emergency department or inpatient hospital stay), we did not include the costs associated with TEAEs. We specifically requested this information from the manufacturer to include in a future update for the final evidence report.

Health State Utilities

Health state utility values were applied similarly to the 2023 ICER report on MS,[19] which derived these values from publicly available literature (Table 4.2). For EDSS scores from 0 to 7, utility estimates were based on a prior published study that utilized patient responses to the EuroQol-5 Dimension mapping tool (EQ-5D) from the DEFINE and CONFIRM trials for relapsing-remitting MS and a United Kingdom (UK) survey for SPMS.[45] This study reported a steep decline in utility scores after EDSS 7, with a more gradual decline observed for EDSS 0 to 7. To estimate utility scores for EDSS 8 and 9, the 2023 ICER report on MS made an adjustment due to potential limitations in the sample size for these higher EDSS states. We adopted their methodology, which involved fitting a non-linear model between EDSS 0 (or EDSS 1 for SPMS) and EDSS 7, and applying the resulting estimates for EDSS 8 and 9 separately for relapsing-remitting and SPMS.

Economic Inputs

All costs used in the model were updated to 2024 US dollars.

Drug Acquisition Costs

Tolebrutinib (Sanofi) is an oral drug taken 60 mg daily. For tolebrutinib, we will be using an annual placeholder price of $115,000, which is the mid-point of the range anticipated by IPD Analytics ($110,000-$120,000).[53] IPD Analytics indicated that this pricing is consistent with the pricing of other branded oral drugs.

Health Care Utilization Costs

Annual health care costs based on EDSS state are presented in Table 4.2. Annual costs reflect MS care including inpatient and outpatient visits, medical equipment, and other pharmaceutical interventions not related directly to DMTs. Hernandez used an extrapolation approach based on the data from Kobelt et al. to estimate average management costs by each level of EDSS ($1115xEDSS + $4593; R^2=0.995).[54,55] This results in an increasing cost by EDSS, reflecting higher management of MS including the use of additional durable medical equipment, among other resources. For the modified societal perspective, we included cost components of lost productivity (both reduced time at work and lost work time) and reduced earnings from early retirement.

4.3. Results

Base-Case Results

The average per person total discounted costs, life years (LYs), quality-adjusted life years (QALYs), and equal value of life years (evLYs) gained are detailed in Table 4.3. Over a lifetime, tolebrutinib, at the placeholder price, had a total discounted cost of $2,219,000 with discounted QALYs, LYs, and evLYs of 4.30, 13.98, and 4.63, respectively. Undiscounted years without a wheelchair (EDSS <7) was 6.27 in the tolebrutinib arm. Over a lifetime, best supportive care had a total discounted cost of $657,000 with discounted QALYs, LYs, and evLYs of 3.66, 13.46, and 3.66, respectively. Undiscounted years without a wheelchair (EDSS <7) was 4.28 for best supportive care.

Table 4.3. Results for the Base-Case for Tolebrutinib Compared to Best Supportive Care

Treatment	Intervention Acquisition Costs*	Intervention-Related Costs†	Non-Intervention Related Costs‡	Total Costs*	Years Without a Wheelchair (EDSS <7)	QALYs	evLYs	Life Years
Tolebrutinib	$1,550,000	$10,000	$660,000	$2,219,000	6.27	4.30	4.63	13.98
Best Supportive Care	$0	$0	$657,000	$657,000	4.28	3.66	3.66	13.46

evLYs: equal value of life years gained, QALY: quality-adjusted life year

*Based on placeholder price

†Intervention-related costs include costs of monitoring required for the intervention, as specified in clinical trials, guidelines, or package label

‡Non-intervention related costs include health state costs related and unrelated to SPMS and cost of death

Table 4.4 presents the discounted lifetime incremental results, including cost per QALY gained, cost per evLY gained, cost per life year gained, and undiscounted results for cost per additional year able to walk without a wheelchair. At the placeholder price, total discounted costs for tolebrutinib were approximately $1,563,000 higher than best supportive care; gains in QALYs, LYs, and evLYs were 0.63, 0.53, and 0.97, respectively, in relation to best supportive care. Gains in years without a wheelchair were 1.99 in relation to best supportive care.

Table 4.4. Incremental Cost-Effectiveness Ratios for the Base Case

Treatment	Comparator	Cost per QALY Gained*	Cost per evLY Gained*	Cost per Life Year Gained*	Cost per Additional Year Without a Wheelchair (EDSS <7)*
Tolebrutinib	Best supportive care	$2,500,000	$1,600,000	$3,000,000	$800,000

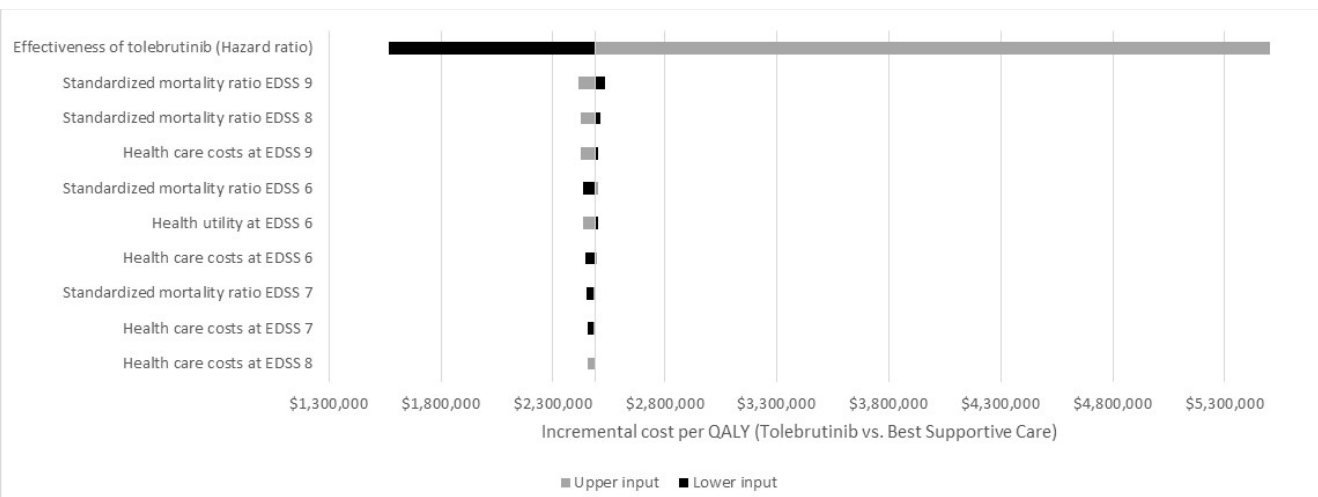
evLYs: equal value of life years gained, QALY: quality-adjusted life year
*Based on placeholder price

Sensitivity Analyses

To demonstrate the effects of uncertainty on both costs and health outcomes, we varied input parameters using available estimates of parameter uncertainty (e.g., standard errors or plausible parameter ranges). Figure 4.2 demonstrates the impact of varying individual inputs on the incremental cost-effectiveness ratios with QALYs and evLYs as the outcome, respectively. Key drivers of cost-effectiveness estimates include the effectiveness of tolebrutinib, mortality, and health-related quality of life.

Probabilistic sensitivity analyses were also performed by jointly varying multiple model parameters over 1,000 simulations. Tables 4.5 and 4.6 present the probability of reaching certain cost-effectiveness thresholds for tolebrutinib. At the placeholder price, a total of 0% of simulations reached any of the thresholds when including QALYs or evLYs as the outcome.

Figure 4.2. Tornado Diagram (Tolebrutinib versus Best Supportive Care)*



EDSS: expanded disability status scale
*Based on placeholder price

Table 4.5. Probabilistic Sensitivity Analysis Cost per QALY Gained Results: Tolebrutinib versus Best Supportive Care

	Cost Effective at $50,000 per QALY Gained*	Cost Effective at $100,000 per QALY Gained*	Cost Effective at $150,000 per QALY Gained*	Cost Effective at $200,000 per QALY Gained*
Tolebrutinib	0%	0%	0%	0%

QALY: quality-adjusted life year

*Based on placeholder price

Table 4.6. Probabilistic Sensitivity Analysis Cost Per evLY Gained Results: Tolebrutinib versus Best Supportive Care

	Cost Effective at $50,000 per evLY Gained*	Cost Effective at $100,000 per evLY Gained*	Cost Effective at $150,000 per evLY Gained*	Cost Effective at $200,000 per evLY Gained*
Tolebrutinib	0%	0%	0%	0%

evLYs: equal value of life years gained

*Based on placeholder price

Scenario Analyses

We performed the following scenario analyses:

1. Modified societal perspective that includes components such as patient productivity impacts (e.g., lost productivity, reduced working time, early retirement, etc.), impacts on caregivers, and other inputs as applicable. See Table E5.1 for more information on alternative approaches for including caregiver disutility.

2. Alternative stopping rule for tolebrutinib (i.e., once a patient reaches an EDSS score of 7).

3. Pending data from the manufacturer, we plan to include disability improvement in EDSS health states for the tolebrutinib arm. Specifically, we requested post-trial EDSS state distributions to include this improvement in the modeling analysis.

See additional scenario analysis in Supplement E5

Table 4.7. Scenario Analysis Results

Treatment	Base-Case Results*	Scenario Analysis 1*	Scenario Analysis 2*	Scenario Analysis 3*
Tolebrutinib	$2,500,000 per QALY and $1,600,000 per evLY	$2,900,000 per QALY and $1,700,000 per evLY	$1,100,000 per QALY and $800,000 per evLY	Pending manufacturer data submission

*Based on a placeholder price

Threshold Analyses

Threshold analyses were conducted for tolebrutinib to calculate the annual price needed to meet commonly accepted cost-effectiveness thresholds for QALYs and evLYs and are shown in Table 4.8 and 4.9.

Table 4.8. QALY-Based Threshold Analysis Results

	Anticipated Intervention Acquisition Cost*	Annual Price to Achieve $50,000 per QALY Gained	Annual Price to Achieve $100,000 per QALY Gained	Annual Price to Achieve $150,000 per QALY Gained	Annual Price to Achieve $200,000 per QALY Gained
Tolebrutinib	$115,000	$1,300	$3,600	$6,000	$8,300

QALY: quality-adjusted life year

*Based on placeholder price

Table 4.9. evLY-Based Threshold Analysis Results

	Anticipated Intervention Acquisition Cost*	Annual Price to Achieve $50,000 per evLY Gained	Annual Price to Achieve $100,000 per evLY Gained	Annual Price to Achieve $150,000 per evLY Gained	Annual Price to Achieve $200,000 per evLY Gained
Tolebrutinib	$115,000	$2,500	$6,100	$9,700	$13,300

evLY: equal value of life years

*Based on placeholder price

Model Validation

We used several approaches to validate model findings. First, we had two different model experts review the model structure, assumptions, and inputs. Second, we performed internal model validation by varying inputs to identify any errors or illogical results. Third, we replicated a previous SPMS ICER review (2019) and identified model inputs that can be consistently compared (e.g., life years gained and years able to walk without a wheelchair in best supportive care arm) and results were within a relative 10% of findings between both models. Finally, as part of ICER's efforts in acknowledging modeling transparency, we offered to share the model with the manufacturer for external validation.

Uncertainty and Controversies

While we used the best available evidence from the literature and recent HERCULES trial, the primary endpoints do not necessarily reflect transitions between EDSS health states. For example, the endpoint confirmed disability progression was defined as an increase in EDSS of 1.0 when baseline EDSS was less than or equal to five but an increase of 0.5 EDSS points when baseline EDSS was greater than five. The model structure, like other MS-specific model structures, relies on whole unit increment changes in EDSS irrespective of starting EDSS states. Therefore, we assumed the treatment effect for tolebrutinib would be consistent across EDSS movement regardless of baseline EDSS in addition to assuming the treatment effect would persist over a lifetime in the base-case analysis. While not directly addressing these limitations, the one-way sensitivity analysis provides a range of possible incremental cost-effectiveness ratios by tolebrutinib's treatment effect.

Other data gaps that influenced model decisions include a lack of information on disability improvement, long-term discontinuation, detailed costs across EDSS, and variability in literature-based health-related quality of life values. In the HERCULES trial, there was a statistically significant change in confirmed disability improvement that impacted about 5% of patients when comparing tolebrutinib to placebo. While we requested this data from the manufacturer, we did not receive detailed information on the distribution of EDSS post-trial, and therefore were unable to model this improvement. Conceptually, improvement would improve health outcomes for patients by moving them backward in EDSS over time. While there is longitudinal evidence on discontinuing disease-modifying therapies, we found no evidence on long-run discontinuation in a non-relapsing SPMS population. To address part of this limitation, we ran a scenario analysis on a stopping rule for tolebrutinib at EDSS seven and above. The model structure is built to include future evidence on discontinuation of tolebrutinib. There is variation in quality of life values across EDSS that is reflected in the literature. We spoke with clinical experts who suggested EDSS as an instrument may not fully capture the average person's progression on any given day. The variation in health-related quality of life utility scores we found in the literature may reflect both EDSS as an instrument and the variation in quality of life for persons with SPMS. Because health state costs by EDSS were based on an extrapolated relationship, costs at certain levels above EDSS 7 may not represent the resources used to treat and manage the complications associated with those EDSS levels. For example, a proportion of patients at higher EDSS levels may be cared for in specialized centers where costs may exceed the average inputs used in the model. We varied these inputs in sensitivity analyses and found that health state costs at higher EDSS levels (e.g., EDSS > 7) were bigger drivers of uncertainty in the results compared with health state costs at lower EDSS levels (e.g., EDSS < 7).

Related to quality of life inputs, we acknowledge that other outcomes not currently included in this review are important to the MS community. Additional outcomes may include cognition (Symbol Digit Modalities Test), fatigue (Modified Fatigue Impact 5-Item Scale), and upper and lower limb function (9HPT).[56] There is currently no evidence to inform the impact of tolebrutinib against best supportive care on cognition and fatigue, and recently published data from HERCULES found no significant difference in the effect of tolebrutinib on the Nine-Hole Peg Test score as compared to placebo.[22] Although there was a statistically significant difference in the Timed 25FWT between tolebrutinib and placebo, the high correlation between the Timed 25FWT and EDSS will double count the health-related quality of life effects already included in the model through a slowing of progression through EDSS. The high correlation between these outcomes was demonstrated in a study by Kalinowski et al. 2022 which found that there was no additional health related quality of life benefits achieved with improvements in Timed 25FWT beyond those captured by changes in EDSS.[57]

Finally, when including the impact on caregiver quality of life in the modified societal perspective analysis, the data used in the model had variation in utility scores across disease severity that was not always consistent with utility scores experienced by patients. For example, utility scores at higher levels of EDSS (e.g., seven and eight) were lower than utility scores at lower EDSS levels (e.g., five and six). [58] The published article (Acaster et al. 2013) acknowledged the small samples and cross-sectional design of the study as potential limitations of the data.[58] When included in the model, we found the incremental cost-effectiveness ratios increased. By slowing disease progression, the intervention prolonged the time patients spent in lower EDSS states (EDSS <7), which—despite being less severe—was associated with greater caregiver burden and higher QALY losses for caregivers. Additionally, extended survival resulted in a larger proportion of patients requiring long-term care compared to those receiving best supportive care, further amplifying the caregiver burden and increasing the incremental cost-effectiveness ratio. This effect is also known as the 'carer QALY trap' To address any limitations around the carer QALY trap, we conducted a variety of scenarios, including the additive QALY approach where the denominator is the sum of the patient and one caregiver (see Table E5.1 in the Supplement).[59,60] Given the uncertainty in the source we used for the caregiver disutilities, we also conducted a separate analysis with a constant disutility value across all EDSS states. None of these scenarios reached near or below commonly cited cost-effectiveness thresholds.

4.4 Summary and Comment

Our analyses showed that the use of tolebrutinib for the treatment of SPMS is more effective than best supportive care. However, at the placeholder price of $115,000 per year, tolebrutinib is expected to exceed standard cost-effectiveness thresholds in the US health care system. The cost-effectiveness findings are primarily driven by the placeholder acquisition costs for tolebrutinib. The model is most sensitive to the treatment effect of slowing progression to higher EDSS states. Scenario and sensitivity analyses were consistent with base-case findings.

5. Benefits Beyond Health and Special Ethical Priorities

Our reviews seek to provide information on benefits beyond health and special ethical priorities offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that was not available in the evidence base nor could be adequately estimated within the cost-effectiveness model. These elements are listed in the table below, with related information gathered from patients and other stakeholders. Following the public deliberation on this report the appraisal committee will vote on the degree to which each of these factors should affect overall judgments of long-term value for money of the intervention(s) in this review.

Table 5.1. Benefits Beyond Health and Special Ethical Priorities

Benefits Beyond Health and Special Ethical Priorities	Relevant Information
There is substantial unmet need despite currently available treatments.	There are no currently approved treatment for non-active forms of SPMS. Thus, there is substantial unmet need for a treatment that slows disability in this population. To inform unmet need as a benefit beyond health, the results for the evLY and QALY absolute and proportional shortfalls have been reported below. evLY shortfalls: • Absolute shortfall: 23.8 • Proportional shortfall: 83.6% QALY shortfalls: • Absolute shortfall: 22.7 • Proportional shortfall: 82.9% The absolute and proportional shortfalls represent the total and proportional health units of remaining quality adjusted life expectancy, respectively, that would be lost due to un- or under-treated illness. Please refer to the ICER Reference Case – Section 2. Quantifying Unmet Need (QALY and evLY Shortfalls) for the shortfalls of other conditions assessed in prior ICER reviews.
This condition is of substantial relevance for people from a racial/ethnic group that have not been equitably served by the health care system.	There are a lack of data regarding potential racial/ethnic differences in the prevalence of SPMS; however, in studies of persons with MS as a whole, Black people have a higher incidence than White, Hispanic, and Asian subgroups. Black persons with MS may also have more rapid disease progression and greater disability relative to other racial/ethnic groups.
The treatment is likely to produce substantial improvement in caregivers' quality of life and/or ability to pursue their own education, work, and family life.	Slowing of progression and potential improvement in disability may improve caregiver quality of life if persons with MS require less caregiving.
The treatment offers a substantial opportunity to improve access to effective treatment by means of its mechanism of action or method of delivery.	Tolebrutinib is orally administered; the majority of currently available DMTs to treat SPMS are injectables or infusions. Therefore, tolebrutinib may improve access for patients who do not have easy access to infusion centers.

ICER did not calculate the Health Improvement Distribution Index (HIDI) because of sparse data regarding prevalence of SPMS by race and ethnicity.

6. Health Benefit Price Benchmark

ICER does not provide a health benefit price benchmark as part of draft reports because results may change with revision following receipt of public comments. We therefore caution readers against assuming that the values provided in the Threshold Prices section of this draft report will match the health benefit price benchmark that will be presented in the next version of this Report.

7. Potential Budget Impact

7.1. Overview of Key Assumptions

Results from the cost-effectiveness model were used to estimate the potential total budgetary impact of tolebrutinib for the non-relapsing SPMS population. Potential budget impact is defined as the total differential cost of using the new therapy rather than relevant existing therapy for the treated population, calculated as differential health care costs (including drug costs) minus any offsets in these costs from averted health care events. All costs were undiscounted and estimated over a five-year time horizon. We used the placeholder price for tolebrutinib of $115,000 annually and the three threshold prices (at $50,000, $100,000, and $150,000 per evLYG) in our estimates of budget impact.

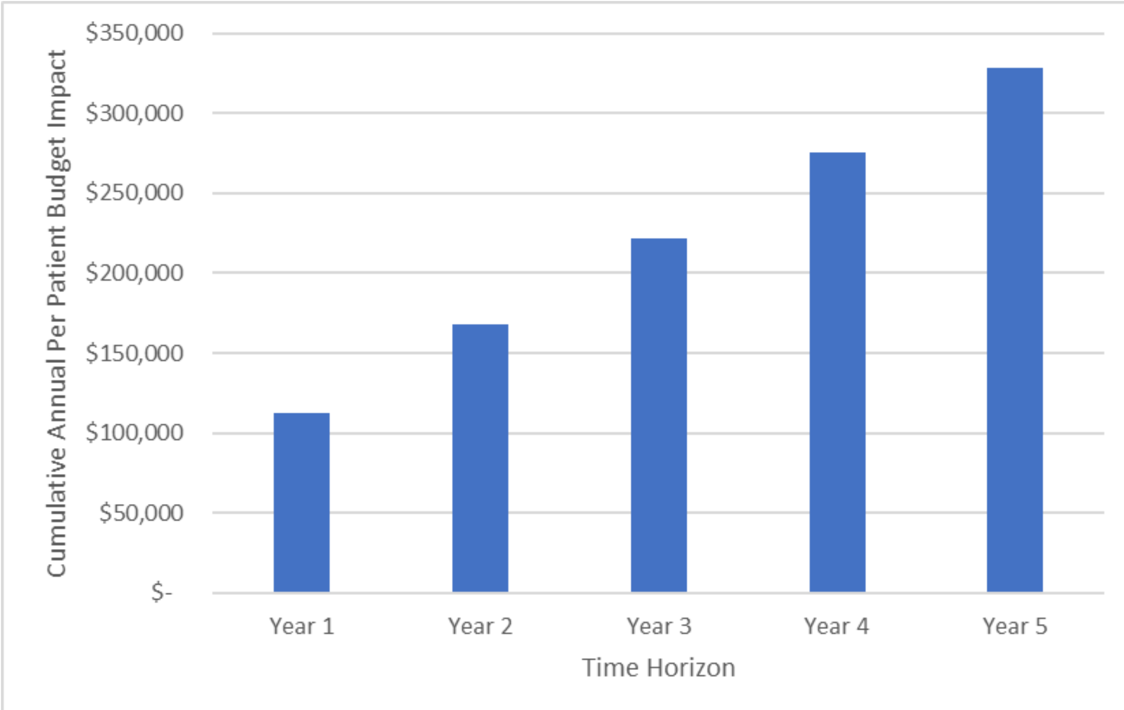
This potential budget impact analysis included the estimated number of individuals in the US who would be eligible for tolebrutinib. To estimate the size of the potential candidate population for treatment, we used inputs for the prevalence of MS in the US (0.32%),[1] and the percentage of patients with non-relapsing SPMS (20.5%).[61] Applying these sources to the average total US adult population projected over the next five years (269,395,454) results in estimates of 177,994 eligible patients in the US.[62] For the purposes of this analysis, we will assume that 20% of these patients would initiate treatment in each of the five years, or 35,599 patients per year.

7.2. Results

Figure 7.1 illustrates the cumulative annual per patient treated population budget impact for tolebrutinib compared to best supportive care. The cumulative per patient annual budget impact represents the incremental costs of tolebrutinib compared to best supportive care across all patients treated within a time horizon (including those who initiated tolebrutinib in previous years), assuming tolebrutinib is used with 20% uptake each year over five years.

At tolebrutinib's placeholder price of $115,000 annually, the average annual budget impact per patient was $112,801 in year one, with cumulative annual budget impact per patient increasing to $328,104 by year five.

Figure 7.1. Cumulative Per Patient Budget Impact for Tolebrutinib Compared to Best Supportive Care using a Placeholder Price



Assuming a 20% uptake of tolebrutinib each year, 8% of patients could be treated over five years at the placeholder price of $115,000 before reaching the ICER potential budget impact threshold of $880 million per year. 93% of patients could be treated at the $150,000 per evLYG threshold price ($9,700), and all eligible patients could be treated at the $100,000 and $50,000 per evLYG threshold prices ($6,100 and $2,500 respectively) before reaching the ICER potential budget impact threshold.

References

1. Hittle M, Culpepper WJ, Langer-Gould A, et al. Population-Based Estimates for the Prevalence of Multiple Sclerosis in the United States by Race, Ethnicity, Age, Sex, and Geographic Region. *JAMA Neurology.* 2023;80(7):693-701.
2. Wallin MT, Culpepper WJ, Campbell JD, et al. The prevalence of MS in the United States. *Neurology.* 2019;92(10):e1029-e1040.
3. Olek MJ. Multiple Sclerosis. *Annals of Internal Medicine.* 2021;174(6):ITC81-ITC96.
4. Bebo B, Cintina I, LaRocca N, et al. The Economic Burden of Multiple Sclerosis in the United States. *Neurology.* 2022;98(18):e1810-e1817.
5. Talente B, Finseth LT, Blake N, et al. Patient Experiences with the Impacts of Multiple Sclerosis & Disease-Modifying Therapies. *Clinicoecon Outcomes Res.* 2025;17:199-215.
6. Tolebrutinib regulatory submission accepted for priority review in the US for patients with multiple sclerosis [press release]. March 25, 2025 2025.
7. Langer-Gould A, Brara SM, Beaber BE, Zhang JL. Incidence of multiple sclerosis in multiple racial and ethnic groups. *Neurology.* 2013;80(19):1734-1739.
8. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol.* 2018;17(2):162-173.
9. Montalban X. 2024 Revisions of the McDonald Criteria. ECTRIMS Congress; September 18-20, 2024, 2024; Copenhagen, Denmark.
10. Kappos L, Wolinsky JS, Giovannoni G, et al. Contribution of Relapse-Independent Progression vs Relapse-Associated Worsening to Overall Confirmed Disability Accumulation in Typical Relapsing Multiple Sclerosis in a Pooled Analysis of 2 Randomized Clinical Trials. *JAMA Neurol.* 2020;77(9):1132-1140.
11. Ziemssen T, Bhan V, Chataway J, et al. Secondary Progressive Multiple Sclerosis. *Neurology Neuroimmunology & Neuroinflammation.* 2023;10(1):e200064.
12. Iaffaldano P, Lucisano G, Patti F, et al. Transition to secondary progression in relapsing-onset multiple sclerosis: Definitions and risk factors. *Mult Scler.* 2021;27(3):430-438.
13. Cree BAC, Arnold DL, Chataway J, et al. Secondary Progressive Multiple Sclerosis: New Insights. *Neurology.* 2021;97(8):378-388.
14. Pontieri L, Greene N, Wandall-Holm MF, et al. Patterns and predictors of multiple sclerosis phenotype transition. *Brain Communications.* 2024;6(6).
15. Food and Drug Administration. MAYZENT Prescribing Information. In:2024.
16. Rae-Grant A, Day GS, Marrie RA, et al. Practice guideline recommendations summary: Disease-modifying therapies for adults with multiple sclerosis. *Neurology.* 2018;90(17):777-788.
17. Zeydan B, Kantarci OH. Impact of Age on Multiple Sclerosis Disease Activity and Progression. *Curr Neurol Neurosci Rep.* 2020;20(7):24.
18. Breakthrough Therapy by the FDA for non-relapsing secondary progressive multiple sclerosis [press release]. December 13, 2024 2024.
19. Lin GA WM, Nikitin D, Agboola F, McKenna A, Herron-Smith S, Pearson SD, Campbell J. *Treatments for Relapsing Forms of Multiple Sclerosis; Final Evidence Report. Institute for Clinical and Economic Review.*: Institute for Clinical and Economic Review;2023.
20. Clinicaltrials.gov. Long Term Safety and Efficacy Study of Tolebrutinib (SAR442168) in Participants With Relapsing Multiple Sclerosis. https://clinicaltrials.gov/study/NCT03996291. Published 2024. Accessed.

21. Fox RJ, Bar-Or A, Traboulsee A, et al. Efficacy and Safety of Tolebrutinib Versus Placebo in Non-Relapsing Secondary Progressive Multiple Sclerosis: Results From the Phase 3 HERCULES Trial. Paper presented at: 40th Congress of the European Committee for Treatment and Research in Multiple Sclerosis2024; Copenhagen, Denmark.
22. Fox RJ, Bar-Or A, Traboulsee A, et al. Tolebrutinib in Nonrelapsing Secondary Progressive Multiple Sclerosis. *New England Journal of Medicine.* 2025;0(0).
23. Sanofi. Sanofi Data Submission. *Data on file.* 2025.
24. Oh J, Arnold DL, Cree BAC, et al. Tolebrutinib versus Teriflunomide in Relapsing Multiple Sclerosis. *New England Journal of Medicine.* 2025;0(0).
25. Clinicaltrials.gov. Relapsing Forms of Multiple Sclerosis (RMS) Study of Bruton's Tyrosine Kinase (BTK) Inhibitor Tolebrutinib (SAR442168) (GEMINI 1). https://clinicaltrials.gov/study/NCT04410978. Published 2024. Accessed 03/05/2025.
26. Clinicaltrials.gov. Relapsing Forms of Multiple Sclerosis (RMS) Study of Bruton's Tyrosine Kinase (BTK) Inhibitor Tolebrutinib (SAR442168) (GEMINI 2). https://clinicaltrials.gov/study/NCT04410991. Published 2024. Accessed 03/05/2025.
27. Clinicaltrials.gov. Dose-finding Study for SAR442168 in Relapsing Multiple Sclerosis. https://clinicaltrials.gov/study/NCT03889639. Published 2020. Accessed.
28. Agboola FW, AC. A Framework for Evaluating the Diversity of Clinical Trials. *Journal of Clinical Epidemiology.* 2024:111299.
29. Fernandez O, Sorensen PS, Comi G, et al. Managing multiple sclerosis in individuals aged 55 and above: a comprehensive review. *Front Immunol.* 2024;15:1379538.
30. Feys P, Lamers I, Francis G, et al. The Nine-Hole Peg Test as a manual dexterity performance measure for multiple sclerosis. *Mult Scler.* 2017;23(5):711-720.
31. Schwid SR, Goodman AD, McDermott MP, Bever CF, Cook SD. Quantitative functional measures in MS: what is a reliable change? *Neurology.* 2002;58(8):1294-1296.
32. Oh J, Arnold DL, Cree BAC, et al. Efficacy and Safety of Tolebrutinib Versus Teriflunomide in Relapsing Multiple Sclerosis: Results From the Phase 3 GEMINI 1 and 2 Trials. 40th Congress of the European Committee for Treatment and Research in Multiple Sclerosis; 2024; Copenhagen, Denmark.
33. Reich DS, Arnold DL, Vermersch P, et al. Safety and efficacy of tolebrutinib, an oral brain-penetrant BTK inhibitor, in relapsing multiple sclerosis: a phase 2b, randomised, double-blind, placebo-controlled trial. *The Lancet Neurology.* 2021;20(9).
34. Oh J, Reich D, Traboulsee A, et al. Safety and Clinical Efficacy Outcomes from the Long-term Extension Study of Tolebrutinib in Participants with Relapsing Multiple Sclerosis: 3-Year Results. *Mult Scler J.* 2023;29(3).
35. Oh J, Syed S, Li T, Salloum N, Turner TJ, Fox RJ. Safety and Clinical Efficacy Outcomes From the Long-term Extension Study of Tolebrutinib in Participants With Relapsing Multiple Sclerosis: 2.5-Year Results. *Neurology.* 2023;100(17).
36. Oh J, Syed S, Orogun L, Xu Z, Turner TJ, Fox RJ. Safety and clinical efficacy outcomes from the Long-term extension study of tolebrutinib in patients with relapsing multiple sclerosis: 2-year results. *Mult Scler J.* 2022;28(3).
37. Fox R, Oh J, Arnold D, et al. MRI, Efficacy, and Safety of Tolebrutinib in Patients with Highly Active Disease (HAD): 2- Year Data from the Phase 2b Long-term Safety (LTS) Study. *Neurology.* 2023;100(17).
38. Cagol A, Schaedelin S, Barakovic M, et al. Association of Brain Atrophy With Disease Progression Independent of Relapse Activity in Patients With Relapsing Multiple Sclerosis. *JAMA Neurol.* 2022;79(7):682-692.

39. Clinicaltrials.gov. Nonrelapsing Secondary Progressive Multiple Sclerosis (NRSPMS) Study of Bruton's Tyrosine Kinase (BTK) Inhibitor Tolebrutinib (SAR442168) (HERCULES). https://clinicaltrials.gov/study/NCT04411641?tab=table. Published 2025. Accessed April 14, 2025.
40. Sanofi. Media Update: Patient enrollment of phase III tolebrutinib trials paused in the U.S. https://www.sanofi.com/en/media-room/press-releases/2022/2022-06-30-05-30-00-2471767. Published 2022. Accessed.
41. Fox RJ, Bar-Or A, Traboulsee A, et al. 153. Efficacy and Safety of Tolebrutinib Versus Placebo in Non-Relapsing Secondary Progressive Multiple Sclerosis: Results From the Phase 3 HERCULES Trial. *Mult Scler Relat Disord.* 2024;92.
42. Forbes RB, Lees A, Waugh N, Swingler RJ. Population based cost utility study of interferon beta-1b in secondary progressive multiple sclerosis. *Bmj.* 1999;319(7224):1529-1533.
43. Kobelt G, Jönsson L, Henriksson F, Fredrikson S, Jönsson B. Cost-utility analysis of interferon beta-1b in secondary progressive multiple sclerosis. *Int J Technol Assess Health Care.* 2000;16(3):768-780.
44. Touchette DR, Durgin TL, Wanke LA, Goodkin DE. A cost-utility analysis of mitoxantrone hydrochloride and interferon beta-1b in the treatment of patients with secondary progressive or progressive relapsing multiple sclerosis. *Clin Ther.* 2003;25(2):611-634.
45. Mauskopf J, Fay M, Iyer R, Sarda S, Livingston T. Cost-effectiveness of delayed-release dimethyl fumarate for the treatment of relapsing forms of multiple sclerosis in the United States. *J Med Econ.* 2016;19(4):432-442.
46. Tappenden P, McCabe C, Chilcott J, et al. Cost-effectiveness of disease-modifying therapies in the management of multiple sclerosis for the Medicare population. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research.* 2009;12(5):657-665.
47. Zimmermann M, Brouwer E, Tice JA, et al. Disease-Modifying Therapies for Relapsing-Remitting and Primary Progressive Multiple Sclerosis: A Cost-Utility Analysis. *CNS Drugs.* 2018;32(12):1145-1157.
48. Scalfari A, Neuhaus A, Degenhardt A, et al. The natural history of multiple sclerosis: a geographically based study 10: relapses and long-term disability. *Brain.* 2010;133(Pt 7):1914-1929.
49. Knox KB, Saini A, Levin MC. The Dilemma of When to Stop Disease-Modifying Therapy in Multiple Sclerosis: A Narrative Review and Canadian Regional Reimbursement Policies. *Int J MS Care.* 2020;22(2):75-84.
50. Wiyani A, Badgujar L, Khurana V, Adlard N. How have Economic Evaluations in Relapsing Multiple Sclerosis Evolved Over Time? A Systematic Literature Review. *Neurol Ther.* 2021;10(2):557-583.
51. Pokorski RJ. Long-term survival experience of patients with multiple sclerosis. *J Insur Med.* 1997;29(2):101-106.
52. Institute for Clinical and Economic Review. Disease-Modifying Therapies for Relapsing-Remitting and Primary-Progressive Multiple Sclerosis: Effectiveness and Value. 2017.
53. IPD Analytics. Payer & Provider Insights. https://www.ipdanalytics.com. Published 2025. Accessed February 24.
54. Hernandez L, Guo S, Kinter E, Fay M. Cost-effectiveness analysis of peginterferon beta-1a compared with interferon beta-1a and glatiramer acetate in the treatment of relapsing-remitting multiple sclerosis in the United States. *Journal of Medical Economics.* 2016;19(7):684-695.

55. Kobelt G, Berg J, Atherly D, Hadjimichael O. Costs and quality of life in multiple sclerosis: a cross-sectional study in the United States. *Neurology.* 2006;66(11):1696-1702.
56. Wasem J, Heer Y, Karamasioti E, et al. Cost and Quality of Life of Disability Progression in Multiple Sclerosis Beyond EDSS: Impact of Cognition, Fatigue, and Limb Impairment. *Pharmacoecon Open.* 2024;8(5):665-678.
57. Kalinowski A, Cutter G, Bozinov N, et al. The timed 25-foot walk in a large cohort of multiple sclerosis patients. *Mult Scler.* 2022;28(2):289-299.
58. Acaster S, Perard R, Chauhan D, Lloyd AJ. A forgotten aspect of the NICE reference case: an observational study of the health related quality of life impact on caregivers of people with multiple sclerosis. *BMC Health Serv Res.* 2013;13:346.
59. Mott DJ, Schirrmacher H, Al-Janabi H, et al. Modelling Spillover Effects on Informal Carers: The Carer QALY Trap. *Pharmacoeconomics.* 2023;41(12):1557-1561.
60. Henry E, Al-Janabi H, Brouwer W, et al. Recommendations for Emerging Good Practice and Future Research in Relation to Family and Caregiver Health Spillovers in Health Economic Evaluations: A Report of the SHEER Task Force. *Pharmacoeconomics.* 2024;42(3):343-362.
61. Bose G, Greene N, Healy B, et al. Characteristics of Multiple Sclerosis Patients by Phenotype: A Cross-Sectional Analysis Using the CLIMB Study (P5-3.006). *Neurology.* 2023;100(17_supplement_2):0096.
62. US Census Bureau. 2017 National Population Projections Database. https://www.census.gov/data/datasets/2017/demo/popproj/2017-popproj.html. Published 2017. Accessed.
63. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology.* 1983;33(11):1444-1452.
64. Hobart J, Blight AR, Goodman A, Lynn F, Putzki N. Timed 25-foot walk: direct evidence that improving 20% or greater is clinically meaningful in MS. *Neurology.* 2013;80(16):1509-1517.
65. Ottersen T, Førde R, Kakad M, et al. A new proposal for priority setting in Norway: Open and fair. *Health Policy.* 2016;120(3):246-251.
66. van de Wetering EJ, Stolk EA, van Exel NJ, Brouwer WB. Balancing equity and efficiency in the Dutch basic benefits package using the principle of proportional shortfall. *Eur J Health Econ.* 2013;14(1):107-115.
67. Stolk EA, van Donselaar G, Brouwer WB, Busschbach JJ. Reconciliation of economic concerns and health policy: illustration of an equity adjustment procedure using proportional shortfall. *Pharmacoeconomics.* 2004;22(17):1097-1107.
68. National Institute for Health and Care Excellence: Guidelines. Multiple sclerosis in adults: management. In: *Multiple sclerosis in adults: management.* London: National Institute for Health and Care Excellence (NICE)Copyright © NICE 2022.; 2022.
69. Consortium of Multiple Sclerosis Centers. Best Practices In Multiple Sclerosis Therapies. https://mscare.sharefile.com/share/view/s36f525b3783d490fb121e4db71fd67a6. Published 2022. Accessed.
70. Montalban X, Gold R, Thompson AJ, et al. ECTRIMS/EAN guideline on the pharmacological treatment of people with multiple sclerosis. *Eur J Neurol.* 2018;25(2):215-237.
71. Cook DJ, Mulrow CD, Haynes RB. Systematic reviews: synthesis of best evidence for clinical decisions. *Ann Intern Med.* 1997;126(5):376-380.
72. Higgins J, Thomas, J, Chandler, J, Cumpston, M, Li, T, Page, MJ, Welch, VA. Cochrane Handbook for Systematic Reviews of Interventions version 6.1 (updated September 2020). https://training.cochrane.org/handbook/current. Published 2020. Accessed.
73. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ.* 2021;372:n71.

74. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ.* 2019;366:l4898.
75. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ (Clinical research ed).* 2019.
76. Langer-Gould AM, Gonzales EG, Smith JB, Li BH, Nelson LM. Racial and Ethnic Disparities in Multiple Sclerosis Prevalence. *Neurology.* 2022;98(18):e1818-e1827.
77. Ollendorf D, Pearson, SD. ICER Evidence Rating Matrix: A User's Guide. https://icer.org/evidence-rating-matrix/. Published 2020. Updated January 31, 2020. Accessed.
78. Ollendorf DA, Pearson SD. An integrated evidence rating to frame comparative effectiveness assessments for decision makers. *Medical care.* 2010;48(6 Suppl):S145-152.
79. Oh J. Paramagnetic Rim Lesions as a Prognostic and Predictive Biomarker in the Tolebrutinib Phase 3 Trials for Disability Outcomes. Americas Committee for Treatment and Research in Multiple Sclerosis Forum,; 2025; West Palm Beach.
80. Bayas A, Christ M, Faissner S, et al. Disease-modifying therapies for relapsing/active secondary progressive multiple sclerosis - a review of population-specific evidence from randomized clinical trials. *Ther Adv Neurol Disord.* 2023;16:17562864221146836.
81. Oh J, Alikhani K, Bruno T, et al. Diagnosis and management of secondary-progressive multiple sclerosis: time for change. *Neurodegener Dis Manag.* 2019;9(6):301-317.
82. Boyko A, Therapontos C, Horakova D, et al. Approaches and challenges in the diagnosis and management of secondary progressive multiple sclerosis: A Central Eastern European perspective from healthcare professionals. *Mult Scler Relat Disord.* 2021;50:102778.
83. Sanders GD, Neumann PJ, Basu A, et al. Recommendations for Conduct, Methodological Practices, and Reporting of Cost-effectiveness Analyses: Second Panel on Cost-Effectiveness in Health and Medicine. *Jama.* 2016;316(10):1093-1103.
84. Pickard AS, Law EH, Jiang R, et al. United States Valuation of EQ-5D-5L Health States Using an International Protocol. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research.* 2019;22(8):931-941.
85. Learmonth YC, Dlugonski D, Pilutti LA, Sandroff BM, Klaren R, Motl RW. Psychometric properties of the Fatigue Severity Scale and the Modified Fatigue Impact Scale. *J Neurol Sci.* 2013;331(1-2):102-107.
86. Gani R, Giovannoni G, Bates D, Kemball B, Hughes S, Kerrigan J. Cost-effectiveness analyses of natalizumab (Tysabri) compared with other disease-modifying therapies for people with highly active relapsing-remitting multiple sclerosis in the UK. *Pharmacoeconomics.* 2008;26(7):617-627.
87. Orme M, Kerrigan J, Tyas D, Russell N, Nixon R. The effect of disease, functional status, and relapses on the utility of people with multiple sclerosis in the UK. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research.* 2007;10(1):54-60.
88. Montgomery S, Woodhouse F, Vudumula U, Gudala K, Duddy M, Kroes M. Stick or twist? Cost-effectiveness of siponimod compared with continuing existing disease-modifying therapies in the treatment of active secondary progressive multiple sclerosis in the UK. *J Med Econ.* 2022;25(1):669-678.
89. Schur N, Gudala K, Vudumula U, et al. Cost Effectiveness and Budget Impact of Siponimod Compared to Interferon Beta-1a in the Treatment of Adult Patients with Secondary Progressive Multiple Sclerosis with Active Disease in Switzerland. *Pharmacoeconomics.* 2021;39(5):563-577.
90. Cortesi PA, Antonazzo IC, Gasperini C, Nica M, Ritrovato D, Mantovani LG. Cost-effectiveness and budget impact analysis of siponimod in the treatment of secondary progressive multiple sclerosis in Italy. *PLoS One.* 2022;17(3):e0264123.

91. Institute for Clinical and Economic Review. 2020-2023 Value Assessment Framework. https://icer.org/our-approach/methods-process/value-assessment-framework/. Published 2020. Accessed.
92. Pearson SD. The ICER Value Framework: Integrating Cost Effectiveness and Affordability in the Assessment of Health Care Value. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research.* 2018;21(3):258-265.

Supplemental Materials

A. Background: Supplemental Information

A1. Definitions

<u>*Disease Specific*</u>

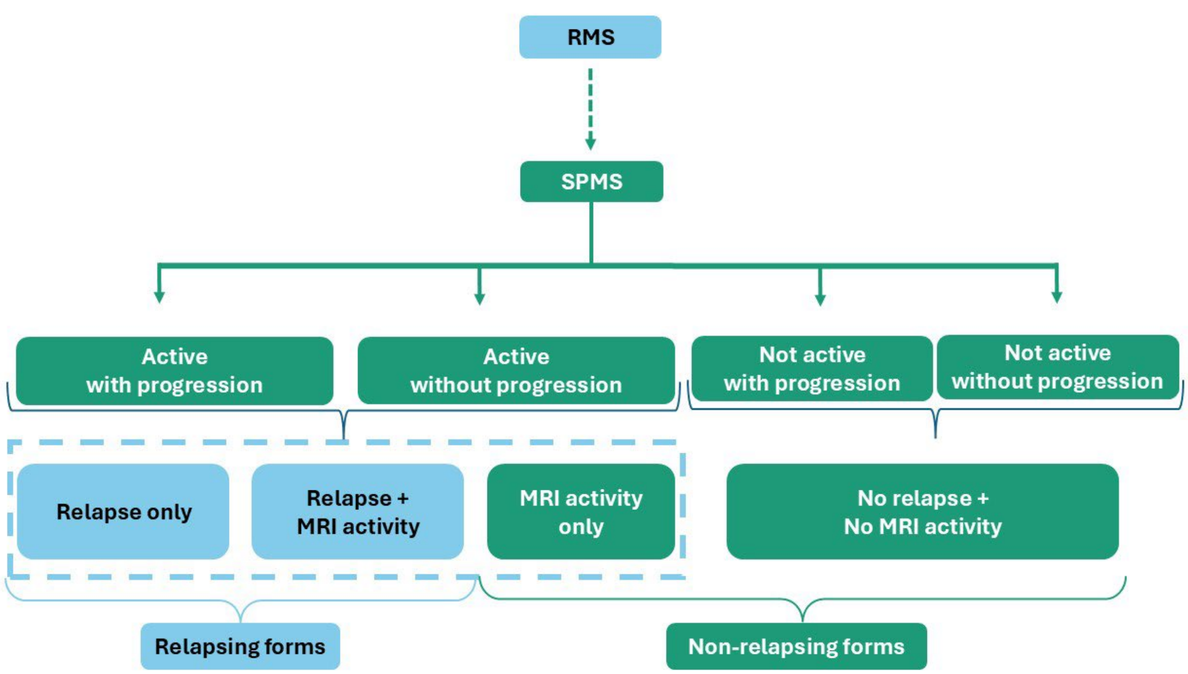
Non-relapsing Multiple Sclerosis: A period of the disease course defined by the absence of relapse signs, though progressive worsening of disability may still occur over time.[13]

Active Multiple Sclerosis: Multiple sclerosis is considered active when there is clinical evidence of relapse or inflammatory activity, such as new or enlarging lesions or gadolinium-enhancing lesions detected on MRI.[11]

Non-active Multiple Sclerosis: Non-active multiple sclerosis is defined as MS that is free of relapses, with no signs of new inflammatory activity detected on MRI.[11]

Secondary Progressive Multiple Sclerosis (SPMS): Initial relapsing remitting MS that is followed by disability progression. SPMS can occur with disease activity (relapses and/or new MRI changes) or as non-active disease, with or without progression, during the course of the disease.[11] Non-relapsing SPMS (nrSPMS) includes active SPMS with MRI activity only and non-active SPMS (Figure A1.1).

Figure A1.1 Phenotypes of SPMS



Criteria for Diagnosis

McDonald Criteria (2017 Revision): The International Panel on Diagnosis of MS reviewed the 2010 McDonald criteria and recommended revisions incorporating: 1) the presence of cerebrospinal fluid specific oligoclonal bands in patients with a typical clinically isolated syndrome and clinical or MRI demonstration of dissemination in space, to allow a diagnosis of MS and; 2) the use of symptomatic lesions to demonstrate dissemination in space or time in patients with supratentorial, infratentorial, or spinal cord syndrome and; 3) the use juxtacortical/cortical lesions to demonstrate dissemination in space.[8]

Outcomes/Measures

Expanded Disability Status Scale (EDSS): The EDSS ranges from zero to ten in increments of 0.5, where zero is a normal examination and ten is death from MS. A clinician assigns a functional score to a patient in eight neurologic systems (pyramidal, cerebellar, brainstem, sensory, bladder and bowel, vision, cerebral, other) based on a detailed neurologic examination. Functional System scores range from 0-6 with higher scores indicating greater disability.[63]

Confirmed Disability Progression (CDP): Worsening of neurologic deficits, usually defined as an increase on the EDSS scale of ≥1 point for those with a baseline EDSS ≤5.0 or of ≥0.5 points for those with a baseline EDSS ≥5.5, confirmed after a three- or six-month period.[21]

Confirmed Disability Improvement (CDI): Decreases of ≥1.0 point from baseline EDSS score confirmed over at least six months.[21]

Brain Volume Loss: Detected by MRI, brain volume loss is correlated with the extent of disability, as measured by the percentage change from month six.[21]

Timed 25 Foot Walk Test (25FWT): Measures gait velocity by calculating the average time it takes for a patient to complete two 25-foot walks, with less than five minutes between each walk. Patients are allowed to use assistive devices during the walk. A change of 20% or greater is considered clinically significant.[31,64]

Nine-hole Peg Test (9HPT): A brief, standardized, quantitative test of upper extremity function. Patients repeatedly place and then remove nine pegs into nine holes, one at a time, as quickly as possible, once with each hand. A change of more than 20% is considered clinically meaningful.[30,31]

Other Relevant Definitions

Absolute and Proportional Shortfalls: Absolute and proportional shortfalls are empirical measurements that capture different aspects of society's instincts for prioritization related to the severity or burden of an illness. The absolute shortfall is defined as the total absolute amount of future health patients with a condition are expected to lose without the treatment that is being assessed.[65] The ethical consequences of using absolute shortfall to prioritize treatments is that conditions that cause early death or that have very serious lifelong effects on quality of life receive the greatest prioritization. Thus, certain kinds of treatments, such as treatments for rapidly fatal conditions of children, or for lifelong disabling conditions, score highest on the scale of absolute shortfall. The proportional shortfall is measured by calculating the proportion of the total health units of remaining life expectancy that would be lost due to untreated illness.[66,67] The proportional shortfall reflects the ethical instinct to prioritize treatments for patients whose illness would rob them of a large percentage of their expected remaining lifetime. As with absolute shortfall, rapidly fatal conditions of childhood have high proportional shortfalls, but high numbers can also often arise from severe conditions among older adults who may have only a few years left of average life expectancy but would lose much of that to the illness without treatment. Details on how to calculate the absolute and proportional QALY and evLY shortfalls can be found in ICER's reference case. Shortfalls will be highlighted when asking the independent appraisal committees to vote on unmet need despite current treatment options as part of characterizing a treatment's benefits beyond health and special ethical priorities (Section 5).

Health Improvement Distribution Index (HIDI): The HIDI identifies a subpopulation that has a higher prevalence of the disease of interest and therefore, creates an opportunity for proportionately more health gains within the subpopulation. This opportunity may be realized by achieving equal access both within and outside the identified subpopulation to an intervention that is known to improve health. The HIDI is defined as the disease prevalence in the subpopulation divided by the disease prevalence in the overall population. For example, if a disease has a prevalence of 10% among Black Americans whereas the disease prevalence among all Americans is 4%, then the Health Improvement Distribution Index is 10%/4%=2.5. In this example, a HIDI of 2.5 means that Black Americans as a subpopulation would benefit more on a relative basis (2.5 times more) from a new effective intervention compared with the overall population. HIDIs above one suggest that more health may be gained on the relative scale in the subpopulation of interest when compared to the population as a whole. The HIDI may be helpful in characterizing a treatment's benefits beyond health and special ethical priorities (Section 5). ICER did not calculate the HIDI for this report due to sparse data on racial and ethnic differences in incidence and prevalence of SPMS.

A2. Potential Cost-Saving Measures in SPMS

ICER includes in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create headroom in health care budgets for higher-value innovative services (for more information, see https://icer.org/our-approach/methods-process/value-assessment-framework/). These services are ones that would not be directly affected by therapies for SPMS (e.g., non-DMT drug costs, physical therapy, nursing care), as these services will be captured in the economic model. Rather, we are seeking services used in the current management of SPMS beyond the potential offsets that arise from a new intervention. During stakeholder engagement and public comment periods, ICER encouraged all stakeholders to suggest services (including treatments and mechanisms of care) currently used for patients with SPMS that could be reduced, eliminated, or made more efficient. No suggestions were received.

A3. Patient Input on Clinical Trial Design

Manufacturers were asked to submit a written explanation of how they engaged patients in the design of their clinical trials, including the methods used to gather patient experience data and how they determined the outcomes that matter most to patients. ICER did not receive input on this specific inquiry.

B. Patient Community Insights: Supplemental Information

B1. Methods

Interview Methods

We interviewed eight persons living with MS and one caregiver. All participants were referred by patient advocacy groups and participated in either multi-person or individual interviews led by the ICER research team. We interviewed seven women and one man diagnosed with SPMS, with a range of disability from ambulatory to wheelchair-bound. Participants lived in various regions of the U.S. and were seeing neurologists or MS specialists. All participants with MS had experience with DMT, often with multiple DMTs. The caregiver was interviewed in conjunction with the person he was caring for.

We also interviewed seven MS experts, six neurologists, and one PhD neurology researcher. The neurologists practiced in the Midwest, East Coast, and West Coast, and included persons who practiced in academic medical centers and integrated health systems.

MS Coalition Survey Methods[5]

The survey was a cross-sectional survey administered in December 2022 and January 2023, targeting persons living with MS. Inclusion criteria included adults with a self-reported diagnosis of multiple sclerosis or clinically isolated syndrome, or caregivers answering on behalf of an adult with MS. Individuals incarcerated the time of the survey were excluded. Participants were invited to participate in the survey through e-mail and social media distribution to members of the Multiple Sclerosis Coalition.

Overall, there were 1,412 responses to the survey, with females making up 78% of respondents. The average age of respondents was 55 (range 17-89), and the population was predominantly white (87%). The majority of respondents (71.7%) had RRMS; SPMS (14.9%) and PPMS (8.9%) were the other common diagnoses, and the majority of participants had been living with MS for more than 10 years.

Survey questions asked about symptoms, treatment experience and decision-making, costs and access to care, and impact of MS on independence, emotional health, relationships, career, finances, and also future research needs.

Response data for the SPMS subgroup were provided to ICER by the MS Coalition.

C. Clinical Guidelines

In the 2023 ICER report, we summarized relevant clinical guidelines in detail. Following that report, we did not identify new guidelines and/or recommendations for the treatment of SPMS from any HTA agency or clinical society. Here, we briefly describe the recommendations related to DMTs and their use in treating patients with SPMS.

American Academy of Neurology, 2018[16]

In 2018, the American Academy of Neurology released practice guideline recommendations for DMTs to treat MS. Treatment decisions should take into account patient preferences regarding safety, administration route, lifestyle, cost, efficacy, and tolerability. For SPMS, those with relapses or active MRI-detected new lesions can benefit from DMTs. No RCTs have directly addressed when, or if, DMTs should be discontinued in people with SPMS. Clinicians should assess the risk of future relapses in individuals with SPMS by considering factors such as age, disease duration, relapse history, and MRI activity. Discontinuation of DMTs may be considered after at least two years without relapses or MRI activity, and EDSS is seven or greater.

National Institute of Health and Care Excellence, 2022[68]

In 2022, the National Institute for Health and Care Excellence issued updated guidelines on the diagnosis and treatment of MS. The guidelines emphasize the importance of comprehensive care for individuals with MS, including an annual review of their care, ongoing information and support about the disease, referrals to social services for additional care needs, discussions about childbearing plans, and advance care planning. The guidelines also cover the assessment and treatment of MS symptoms such as fatigue, mobility issues, spasticity, pain, and cognitive difficulties using both pharmacologic and non-pharmacologic approaches. Regarding DMTs, the National Institute for Health and Care Excellence recommends the use of Siponimod for SPMS.

Consortium of MS Centers, 2022[69]

In 2022, the Consortium of MS Centers released the Best Practices in MS Therapies, which outlines recommendations developed by a group of MS specialists. DMTs should be initiated following a diagnosis of clinically isolated syndrome, RRMS, or active SPMS. Switching DMTs may be warranted if there is a suboptimal response to treatment, such as significant relapses, new activity on MRI, unexpected progression of disability, or worsening neurologic findings. Additionally, patient-related factors such as adherence, lifestyle or work issues, insurance challenges, or quality of life concerns should be considered. Finally, a subgroup of patients may be able to safely stop DMTs without experiencing disease-related consequences. Overall, this guideline suggested considering all approved DMTs for the treatment of active SPMS and attempting to individualize therapy as much as possible.

European Committee of Treatment and Research in MS/European Academy of Neurology, 2018[70]

In 2018, the European Committee for Treatment and Research in MS and the European Academy of Neurology issued a joint guideline on the pharmacologic treatment of people with MS. The choice of drug depends on various factors, including patient characteristics, comorbidities, disease severity and activity, the drug's safety profile, and its accessibility. The guidelines recommend to continue DMT if a patient remains clinically stable on MRI and experiences no safety or tolerability issues. Although labeled as weak recommendations, this guideline suggested interferon beta 1a subcutaneously, interferon beta 1b, mitoxantrone, ocrelizumab, and cladribine for patients with active SPMS.

D. Comparative Clinical Effectiveness: Supplemental Information

D1. Detailed Methods

PICOTS

Population

The population of focus for the review is adults with non-relapsing secondary progressive multiple sclerosis.

The absence of clear diagnostic indicators makes it difficult to determine the point at which RRMS transitions to SPMS, as well as transition from active to non-active SPMS. Nevertheless, regulatory agencies and clinical trial eligibility criteria tend to dichotomize MS into these phenotypes. If data permits, we will examine heterogeneity of treatment effect across patient subgroups stratified by race/ethnicity, age, disease duration, disease activity (active vs. non-active), and level of disability.

Interventions

The full list of interventions is as follows:

- Tolebrutinib

Comparators

- Best supportive care, defined as pharmacological and non-pharmacological treatments to alleviate the symptoms of MS.

Outcomes

The outcomes of interest are described in the list below.

- Patient-Important Outcomes
    - Disability progression or improvement as measured by
        - Expanded Disability Status Score (EDSS)
        - Multiple Sclerosis Functional Composite (MSFC) which consists of three components: timed 25-foot walk test (T25FW), 9-hole peg test (9HPT), and paced auditory serial addition test (PASAT-3)
    - Mobility

- Health-Related Quality of Life measures (e.g., Multiple Sclerosis Impact Scale (MSIS-29)
    - Cognitive function
    - Pain
    - Fatigue
    - Bladder and bowel dysfunction
    - Depression
    - Discontinuations due to adverse events
    - Adverse events including
        - Serious adverse events
        - Liver enzyme levels
- Other Outcomes
    - MRI disease activity (e.g., new/enlarging T2 brain lesions, and brain volume)
    - Caregiver impact
        - Caregiver quality of life
        - Caregiver health
        - Caregiver productivity
    - Other adverse events

Timing

Evidence on intervention effectiveness will be derived from studies of at least 12 weeks duration.

Settings

All relevant settings will be considered, including inpatient, clinic, and outpatient settings in the United States.

Study Design

Randomized controlled trials and non-randomized controlled trials with any sample size will be included. High-quality comparative observational studies will also be included if available.

Table D1.1 PRISMA 2020 Checklist

Section and Topic	Item #	Checklist Item
TITLE		
Title	1	Identify the report as a systematic review.
ABSTRACT		
Abstract	2	See the PRISMA 2020 for Abstracts checklist.
INTRODUCTION		
Rationale	3	Describe the rationale for the review in the context of existing knowledge.
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.
METHODS		
Eligibility Criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.
Information Sources	6	Specify all databases, registers, websites, organizations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.
Search Strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.
Selection Process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.
Data Collection Process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.
Data Items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g., for all measures, time points, analyses), and if not, the methods used to decide which results to collect.
	10b	List and define all other variables for which data were sought (e.g., participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.
Study Risk of Bias Assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.
Effect Measures	12	Specify for each outcome the effect measure(s) (e.g., risk ratio, mean difference) used in the synthesis or presentation of results.

Section and Topic	Item #	Checklist Item
Synthesis Methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g., tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g., subgroup analysis, meta-regression).
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.
Reporting Bias Assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).
Certainty Assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.
RESULTS		
Study Selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.
Study Characteristics	17	Cite each included study and present its characteristics.
Risk of Bias in Studies	18	Present assessments of risk of bias for each included study.
Results of Individual Studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g., confidence/credible interval), ideally using structured tables or plots.
Results of Syntheses	20a	For each synthesis, briefly summarize the characteristics and risk of bias among contributing studies.
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g., confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.
	20c	Present results of all investigations of possible causes of heterogeneity among study results.
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.
Reporting Biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.
Certainty of Evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.

Section and Topic	Item #	Checklist Item
DISCUSSION		
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.
	23b	Discuss any limitations of the evidence included in the review.
	23c	Discuss any limitations of the review processes used.
	23d	Discuss implications of the results for practice, policy, and future research.
OTHER INFORMATION		
Registration and Protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.
	24c	Describe and explain any amendments to information provided at registration or in the protocol.
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.
Competing Interests	26	Declare any competing interests of review authors.
Availability of Data, Code, and Other Materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.

From: Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *PLoS Med.* 2021;18(3):e1003583.

Data Sources and Searches

Procedures for the systematic literature review assessing the evidence on tolebrutinib for non-relapsing secondary progressive multiple sclerosis followed established best research methods.[71,72] We reported the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[73] The PRISMA guidelines include a checklist of 27 items (see Table D1.1).

We searched MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials for relevant studies. Each search was limited to English-language studies of human subjects and excluded articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items. We included abstracts from conference proceedings identified from the systematic literature search. All search strategies were generated utilizing the Population, Intervention, Comparator, and Study Design elements described above. The proposed search strategies included a combination of indexing terms (MeSH terms in MEDLINE and EMTREE terms in EMBASE), as well as free-text terms.

To supplement the database searches, we performed manual checks of the reference lists of included trials and systematic reviews and invited key stakeholders to share references germane to the scope of this project. We also supplemented our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature when the evidence met ICER standards (for more information, see the Policy on Inclusion of Grey Literature in Evidence Reviews. Where feasible and deemed necessary, we also accepted data submitted by manufacturers "in-confidence," in accordance with ICER's published guidelines on acceptance and use of such data).

Table D1.2. Search Strategy of Medline 1996 to Present with Daily Update and Cochrane Central Register of Controlled Trials

1	exp multiple sclerosis/
2	(“multiple sclerosis” or “sclerosis, multiple” or “progressive MS” or “progressive multiple sclerosis” or “multiple sclerosis, secondary progressive” or “secondary progressive multiple sclerosis” or “non-relapsing secondary progressive multiple sclerosis” or “SPMS” or “nrSPMS” or “relapsing-remittent MS” or “relapsing remitting multiple sclerosis” or “remitting relapsing multiple sclerosis” or “acute relapsing multiple sclerosis” or “relapsing-remittent multiple sclerosis” or “relapsing-remitting MS” or “relapsing-remitting multiple sclerosis” or “remittent-relapsing MS” or “remittent-relapsing multiple sclerosis” or “remitting-relapsing MS” or “remitting-relapsing multiple sclerosis” or “RR-multiple sclerosis” or “RRMS” or "primary progressive multiple sclerosis" or "multiple sclerosis, primary progressive" or "PPMS" or "chronic progressive multiple sclerosis").ti,ab.
3	1 or 2
4	(“SAR442168” or “SAR-442168” or “SAR 442168, BTKi ('168)” or “PRN2246” or “PRN-2246” or “PRN 2246” or “BTK inhibitor ‘168” or “BTK inhibitor 168” or “Tolebrutinib” or “BTK inhibitor tolebrutinib”).ti,ab.
5	3 and 4
6	(animals not (humans and animals)).sh.
7	5 not 6
8	(addresses or autobiography or bibliography or biography or comment or congresses or consensus development conference or dictionary or directory or duplicate publication or editorial or encyclopedia or festschrift or guideline or interactive tutorial).pt
9	7 not 8
10	limit 9 to English language
11	Remove duplicates from 10

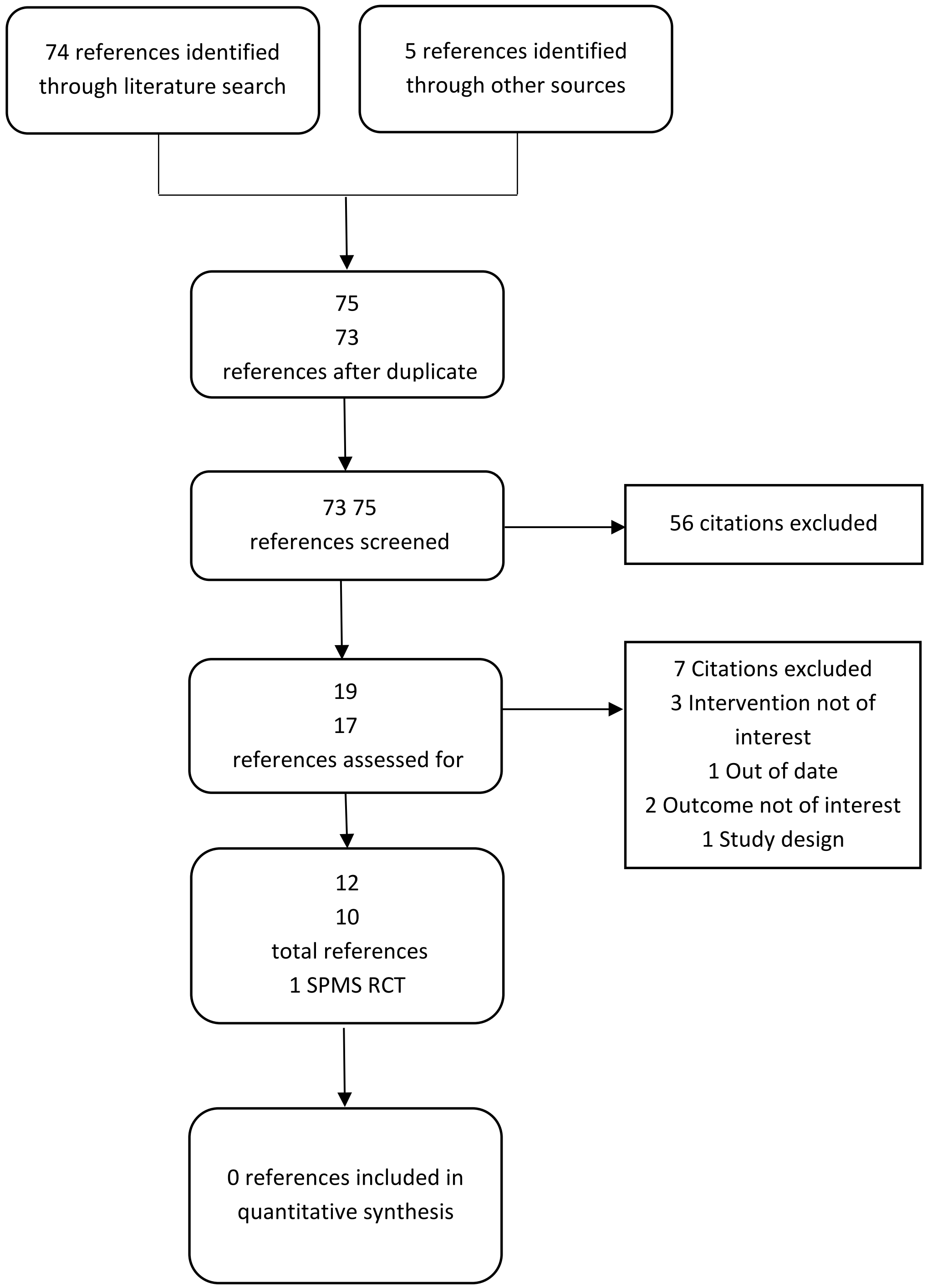
Date of search: January 6th, 2025

Table D1.3. Search Strategy of EMBASE SEARCH

1	'multiple sclerosis'/exp
2	('multiple sclerosis' or 'sclerosis, multiple' or 'progressive MS' or 'progressive multiple sclerosis' or 'multiple sclerosis, secondary progressive' or 'secondary progressive multiple sclerosis' or 'non-relapsing secondary progressive multiple sclerosis' or 'SPMS' or 'nrSPMS' or 'relapsing-remittent MS' or 'relapsing remitting multiple sclerosis' or 'remitting relapsing multiple sclerosis' or 'acute relapsing multiple sclerosis' or 'relapsing-remittent multiple sclerosis' or 'relapsing-remitting MS' or 'relapsing-remitting multiple sclerosis' or 'remittent-relapsing MS' or 'remittent-relapsing multiple sclerosis' or 'remitting-relapsing MS' or 'remitting-relapsing multiple sclerosis' or 'RR-multiple sclerosis' or 'RRMS' or 'primary progressive multiple sclerosis' or 'multiple sclerosis, primary progressive' or 'PPMS' or 'chronic progressive multiple sclerosis'):ti,ab
3	#1 or #2
4	'tolebrutinib'/exp
5	('sar 442168' or 'sar442168' or 'prn 2246' or 'prn2246' or 'tolebrutinib' or 'BTK inhibitor 168' or 'BTK inhibitor tolebrutinib'):ti,ab
6	#4 or #5
7	#3 and #6
8	('animal'/exp or 'nonhuman'/exp or 'animal experiment'/exp) not 'human'/exp
9	#7 not #8
10	#9 and [english]/lim
11	#10 and [medline]/lim
12	#10 not #11
13	#12 and ('chapter'/it or 'conference review'/it or 'editorial'/it or 'letter'/it or 'note'/it or 'short survey'/it)
14	#12 not #13

Date of search: January 6th, 2025

Figure D1.1. PRISMA Flow Chart Showing Results of Literature Search for Tolebrutinib



Study Selection

We performed screening at both the abstract and full-text level. Two investigators independently screened all titles and abstracts identified through electronic searches according to the inclusion and exclusion criteria described earlier using Nested Knowledge (Nested Knowledge, Inc, St. Paul, Minnesota); a third reviewer worked with the initial two reviewers to resolve any issues of disagreement through consensus. We did not exclude any study at abstract-level screening due to insufficient information. For example, an abstract that did not report an outcome of interest would be accepted for further review in full text. We retrieved the citations that were accepted during abstract-level screening for full text appraisal. One investigator reviewed full papers and provided justification for exclusion of each excluded study.

Data Extraction

Data were extracted into Microsoft Word and Microsoft Excel. The basic design and elements of the extraction forms followed those used for other ICER reports. Elements included a description of patient populations, sample size, duration of follow-up, funding source, study design features, interventions (agent, dosage, frequency, schedules), concomitant therapy allowed and used (agent, dosage, frequency, schedules), outcome assessments, and results. The data extraction was performed in the following steps:

1. One reviewer extracted information from the full articles, and a second reviewer validated the extracted data.
2. Extracted data were reviewed for logic, and a random proportion of data were validated by a third investigator for additional quality assurance.

Risk of Bias Assessment

We examined the risk of bias for each randomized trial in this review using criteria published in the Cochrane Risk of Bias Assessment Tool Version 2.[72,74] Risk of bias was assessed by study outcome for each of the following aspects of the trials: randomization process, deviation from the intended interventions, missing outcome data, measurement of the outcome, selection of the reported results, and overall risk of bias. Two reviewers independently assessed these domains. Any disagreements were resolved through discussion or by consulting a third reviewer. Clinical trials that did not have a corresponding peer-reviewed journal article were assessed on their publicly available sources of information, such as ClinicalTrials.gov record and statistical analysis plan.[75]

To assess the risk of bias in trials, we rated the categories as: "low risk of bias," "some concerns," or "high risk of bias." Guidance for risk of bias ratings using these criteria is presented below:

Low risk of bias*: The study is judged to be at low risk of bias for all domains for this result.*

Some concerns*: The study is judged to raise some concerns in at least one domain for this result, but not to be at high risk of bias for any domain.*

High risk of bias*: The study is judged to be at high risk of bias in at least one domain for this result or the study is judged to have some concerns for multiple domains in a way that substantially lowers confidence in the result.*

We examined the risk of bias for the outcome of 6-month confirmed disability progression. See Table D1.6.

Table D1.4. Risk of Bias Assessment for 6-month Confirmed Disability Progression[22]

Study	Randomization Process	Deviation from the Intended Interventions	Missing Outcome Data	Measurement of the Outcome	Selection of the Reported Result	Overall Risk of Bias
HERCULES	Low Risk	Low Risk	Low risk	Low Risk*	Low Risk	**Low**

* The increase in liver monitoring may have resulted in unblinding given the intensity of testing. Per the study protocol, raters were blinded to all data. However, the participants could have been unblinded and therefore there still could be some biases involved in the measurement of the outcome.

Evaluation of Clinical Trial Diversity

We evaluated the demographic diversity of clinical trials using the ICER-developed Clinical trial Diversity Rating (CDR) Tool.[28] The CDR tool was designed to evaluate the three demographic characteristics described in Table D1.5. Representation for each demographic category was evaluated by quantitatively comparing clinical trial participants with disease-specific prevalence estimates,[1,61] using the metric "Participant to Disease-prevalence Representation Ratio" (PDRR). Next, a representation score between 0 to 3 was assigned based on the PDRR estimate (See Table D1.6 for the PDRR cut points that correspond to each representation score). Finally, based on the total score of the demographic characteristics (e.g., race and ethnicity), the categories "Good," "Fair," or "Poor" are used to communicate the overall level of diversity of a clinical trial. The description of the rating categories for each demographic characteristic is provided in Table D1.7.

Table D1.5. Demographic Characteristics and Categories

Demographic Characteristics	Categories
1. Race and Ethnicity*	Racial categories: • White • Black or African American • Asian • American Indian and Alaskan Native • Native Hawaiian and Other Pacific Islanders Ethnic Category: • Hispanic or Latino
2. Sex	• Female • Male
3. Age	• Older adults (≥65 years)

*Multinational trials: For multinational clinical trials, our approach is to evaluate only the subpopulation of patients enrolled from the US on racial and ethnic diversity

Table D1.6. Representation Score

PDRR	Score
0	0
>0 and Less Than 0.5	1
0.5 to 0.8	2
≥0.8	3

PDRR: Participant to Disease-prevalence Representation Ratio

Table D1.7. Rating Categories

Demographic Characteristics	Demographic Categories	Maximum Score	Rating Categories (Total Score)
Race and Ethnicity*	Asian, Black or African American, White, and Hispanic or Latino	12	Good (11-12) Fair (7-10) Poor (≤6)
Sex	Male and Female	6	Good (6) Fair (5) Poor (≤4)
Age	Older adults (≥65 years)	3	Good (3) Fair (2) Poor (≤1)

*American Indian or Alaskan Native & Native Hawaiian or Other Pacific Islander are not factored into the overall racial and diversity rating. However, information on enrollment and PDRR estimates are reported when reliable prevalence estimates are available.

Results

Table D1.8. Diversity Ratings on Race and Ethnicity, Sex, and Age (Older Adults)

Trial	Race and Ethnicity	Sex	Age (Older Adults)
HERCULES	Fair	Good	Poor

NE: Not Estimated

Table D1.8. presents the clinical trial diversity ratings on race and ethnicity, sex, and age (older adults) for the HERCULES trial. Given that HERCULES is a multinational clinical trial and US-specific enrollment data is not publicly available, the trial was rated using the full sample. Where prevalence data for the SPMS population was not available, we supplemented estimates with prevalence data from the larger MS population.

Table D1.9. Race and Ethnicity

	White	Black/ African American	Asian	Hispanic/ Latino	Total score	Diversity Rating	AIAN	NHPI
Prevalence[1,61,76]	92.50%	3.90%	1.70%	7.00%	-	-	NR	NR
HERCULES[22]	92.93%	0.88%	4.86%	NR	-	-	NR	NR
PDRR	1.00	0.23	2.86	NC	-	-	0	0
Score	3	1	3	NC	7	Fair	NC	NC

AIAN: American Indian or Alaskan Native, NR: Not Reported, NC: Not Calculated, NE: Not Estimated, NHPI: Native Hawaiian or Pacific Islander, PDRR: Participant to Disease-prevalence Representation Ratio

Table D1.10. Sex and Age

	Sex				Age		
	Male	**Female**	**Score**	**Rating**	**Older Adults (≥65 years)**	**Score**	**Rating**
Prevalence/Incidence[1,61]	31.30%	68.70%	-	-	9.00%	-	-
HERCULES[21]	38.50%	61.50%	-	-	0%*	-	-
PDRR	1.23	0.90	-	-	0	-	-
Score	3	3	6	Good	1	1	Poor

NC: Not Calculated, PDRR: Participant to Disease-prevalence Representation Ratio
*The HERCULES trial excluded adults ≥60 years old.

Assessment of Level of Certainty in Evidence

We used the ICER Evidence Rating Matrix to evaluate the level of certainty in the available evidence of a net health benefit among each of the interventions of focus (see Appendix D).[77,78]

Assessment of Bias

As part of our quality assessment, we evaluated the evidence base for the presence of potential publication bias. Given the emerging nature of the evidence base for this newer treatment, we scanned the ClinicalTrials.gov site to identify studies completed more than two years ago. Search terms include: “Secondary Progressive Multiple Sclerosis,” “SPMS” and “tolebrutinib.” We scanned the site to identify studies which would have met our inclusion criteria and for which no findings have been published and did not find any evidence of publication bias.

Data Synthesis and Statistical Analyses

We summarized relevant data on key outcomes of the HERCULES trial narratively in the body of the review and evidence tables (see Supplement Section D3). We assessed the feasibility of quantitative synthesis but determined it was not possible due to there being a single trial and no Food and Drug Administration (FDA) approved alternative treatment options to compare against.

D2. Additional Clinical Evidence

Our main report discusses the HERCULES trial that primarily informs our review of tolebrutinib for the treatment of non-relapsing SPMS. Here, we present additional clinical benefits from the HERCULES trial and harms from four clinical trials assessing tolebrutinib in the RRMS population.

Evidence Base

GEMINI 1 and 2 were two identical, randomized 1:1, active-controlled, Phase III trials (N=1,873) comparing tolebrutinib (60 mg orally once daily) and teriflunomide (14 mg orally once daily) in adult participants aged 18-55 years old with a confirmed diagnosis of relapsing MS and an EDSS score of ≤5.5. Participants with a prior diagnosis of primary progressive MS or non-relapsing SPMS were excluded from these trials.[25,26] The median trial follow-up was 139 weeks for both trials.[24]

NCT03889639 was a randomized, placebo-controlled, dose-finding, Phase IIb trial that enrolled 130 adult participants with relapsing MS. The treatment period was 16 weeks, with an additional follow-up of 4 weeks.[27]

NCT03996291 was a long-term efficacy and safety study evaluating tolebrutinib 60 mg and only enrolled participants completing the Phase IIb trial (N=125). The trial duration was around 62 months including an eight-week post-treatment visit.[20]

These four trials assessing tolebrutinib in the RRMS population were only evaluated for harms related to tolebrutinib. Additional details about these trial designs can be found in Supplement Table D3.1.

Clinical Benefits

Here, we present additional secondary outcomes from the HERCULES trial.

Three-Month CDP

In the HERCULES trial, the primary endpoint was confirmed disease progression sustained over ≥6 months whereas this secondary endpoint was CDP sustained over ≥3 months. At 24 months of follow-up, participants receiving tolebrutinib had a 24% risk reduction in three-month CDP compared to those receiving placebo (28% versus 34%, HR 0.76; 95% CI 0.61 to 0.94).[22] Additional follow-up at 45 months suggested a greater difference in the proportions of patients achieving this outcome between the two groups (33% in the tolebrutinib arm vs. 42% in the placebo arm).[21]

Paramagnetic Rim Lesions

Paramagnetic rim lesions (PRLs), which appear as a distinct ring around lesions on MRI, are seen as a promising indicator of chronic neuroinflammation in MS and are linked with disability accumulation.[79] PRL imaging data was available for 39% of the participants from the HERCULES trial and a post hoc analysis evaluated the primary endpoint of six-month CDP across three PRL subgroups (0, 1-3, >4). Risk of 6-month CDP was reduced in participants with PRLs, with the greatest decrease in risk compared with placebo in those with the most PRLs at baseline although the risks were numerically similar across all subgroups of tolebrutinib-treated participants.[79]

Harms

The overall safety profile of tolebrutinib appears to be similar to teriflunomide in the two Phase III trials (GEMINI 1 and 2). One patient died in the tolebrutinib arm but the death was not related to the treatment. Similar to the HERCULES trial, a small proportion of participants in the tolebrutinib arm (0.5%) experienced severe liver injury, as defined by a peak ALT increase of at least 20 times the upper limit of normal, within the first three months of the trial.[32] In the Phase IIb trial, one patient had a mild ALT elevation at screening, then ALT >3 x ULN at four weeks when the placebo run-in period ended. The patient received a 60 mg dose of Tolebrutinib and ALT concentrations decreased gradually reaching the normal range at week 12.[33] Six participants (5%) had liver enzyme elevations (ALT >3 times the upper limit of normal) in the Phase II long-term safety study.[34] Except for higher frequencies in headache, alopecia, and minor bleeding events, harms from GEMINI trials were largely similar to those observed in the HERCULES trial.

D3. Evidence Tables

Table D3.1. Study Design

NCT/Trial	Study Design	Inclusion/Exclusion	Primary Endpoint
Phase III			
GEMINI 1[24,32] **NCT04410978** **+** **GEMINI 2**[24,32] **NCT04410991**	Phase III, randomized, double-blind study N=974 (GEMINI 1) N=899 (GEMINI 2) <u>Population</u> Adults aged 18-55 with relapsing forms of multiple sclerosis <u>Duration</u> 36 months <u>Arms</u> - Tolebrutinib oral 60 mg - Teriflunomide oral 14 mg	Inclusion -The participant must have been diagnosed with relapsing MS according to the 2017 revision of the McDonald diagnostic criteria -The participant has an expanded disability status scale score ≤5.5 at the first Screening Visit -The participant must have at least 1 of the following prior to screening: ≥1 documented relapse within the previous year OR ≥2 documented relapses within the previous 2 years, OR ≥1 documented Gd enhancing lesion on an MRI scan within the previous year Exclusion -The participant has been diagnosed with primary progressive multiple sclerosis according to the 2017 revision of the McDonald diagnostic criteria or with non-relapsing secondary progressive multiple sclerosis	Annualized Adjudicated Relapse Rate: number of confirmed adjudicated protocol defined relapses [up to 36 months]

NCT/Trial	Study Design	Inclusion/Exclusion	Primary Endpoint
HERCULES[21,22] **NCT04411641**	Phase III, randomized, double-blind, placebo-controlled study N=1131 <u>Population</u> Adults aged 18-60 with non-relapsing secondary progressive multiple sclerosis <u>Duration</u> 48 months <u>Arms</u> - Tolebrutinib oral 60 mg - Placebo oral	Inclusion -Diagnosis of non-relapsing secondary progressive multiple sclerosis according to the 2017 McDonald criteria -Expanded disability status scale between 3.0 to 6.5 points inclusive, at screening -The participant must have documented evidence of disability progression observed during the 12 months before screening -Absence of clinical relapses for at least 24 months Exclusion -The participant has received medications/treatments for MS within a specified time frame. -Receiving potent and moderate inducers or inhibitors of cytochrome P450 3A (CYP3A) or potent inhibitors of CYP2C8 hepatic enzymes.	Time to onset of 6-month confirmed disability progression [up to 48 months]
		Phase II	
NCT03889639[33]	Phase IIb, randomized, double-blind, placebo-controlled, crossover, dose-finding study N=130 <u>Population</u> Adults with relapsing multiple sclerosis <u>Duration</u> Treatment period of 16 weeks and a follow-up period of up to 4 weeks <u>Arms</u> - Tolebrutinib oral (5 mg, 15 mg, 30 mg, and 60 mg) - Placebo oral	Inclusion - 18 to 55 years of age - Diagnosed with relapsing multiple sclerosis according to the 2017 McDonald criteria - ≥1 relapse within the previous year, OR ≥2 relapses within the previous 2 years, OR ≥1 active Gadolinium enhancing brain lesion on an MRI scan in the past 6 months Exclusion - Diagnosed with primary progressive or non-relapsing secondary progressive multiple sclerosis according to the 2017 McDonald criteria - Expanded Disability Status Scale score >5.5 - Presence of liver injury	Number of New Gadolinium Enhancing T1-hyperintense Lesions [after 12 weeks of treatment for Tolebrutinib reporting arms and at 4 weeks for placebo]

NCT/Trial	Study Design	Inclusion/Exclusion	Primary Endpoint
NCT03996291 [20]	Long term safety and efficacy study N = 125 Population Adults with relapsing multiple sclerosis Duration Approximately 62 months including the 8 weeks post-treatment visit Arms - Tolebrutinib oral 60 mg	Inclusion - Participants must have completed treatment in the NCT03889639 study Exclusion - The participant has received a non-study MS disease modifying treatment between the last treatment in NCT03889639 and inclusion in extension study, which by judgement of the Investigator may add unjustified risk to switching back and continuing treatment with Tolebrutinib	Number of Participants with Adverse Events and Serious Adverse Events [up to 60 months]

Mg: milligram, MS: multiple sclerosis, N: number

Table D3.2. HERCULES Baseline Characteristics21,22

Arms		Tolebrutinib	Placebo
N		754	377
Age, Years ± SD		48.9 ± 8.0	48.9 ± 8.0
Female, n (%)		454 (60.2)	242 (64.2)
Race, n (%)	White	703 (93.2)	348 (92.3)
	Black	6 (0.8)	4 (1.1)
	Asian	36 (4.8)	19 (5.0)
	Other, unknown, or not reported	9 (1.2)	6 (1.6)
EDSS Score	Mean (±SD)	5.6 ± 0.9	5.6 ± 0.9
	Median (Range)	6 (4.8, 6.3)	6 (5.0, 6.3)
Time since RRMS symptom onset, mean years (±SD)		17.1 (8.3)	17.6 (8.4)
Time since diagnosis of SPMS, mean years (±SD)		7.9 (7.3)	8.4 (7.8)
Time since most recent relapse, mean years (±SD)		7.4 (5.3)	7.6 (5.5)
Number of previous disease-modifying therapies received, n (%)	0	205 (27.2)	89 (23.6)
	1	200 (26.5)	102 (27.1)
	≥2	349 (46.3)	186 (49.3)
Previous disease-modifying therapies received, n (%)	Interferons	354 (46.9)	177 (46.9)
	Glatiramer Acetate	176 (23.3)	99 (26.3)
	Fingolimod	113 (15.0)	66 (17.5)
	Dimethyl Fumarate	93 (12.3)	61 (16.2)
	Ocrelizumab	89 (11.8)	48 (12.7)
	Teriflunomide	82 (10.9)	49 (13.0)
	Natalizumab	72 (9.5)	42 (11.1)
	Rituximab	47 (6.2)	23 (6.1)
	Other	115 (15.3)	66 (17.5)
Participants with ≥1 Gd-Enhancing T1 Lesions, n (%)		93 (12.5)	49 (13.1)
Number of Gd-Enhancing T1 lesions		0.4 (2.0)	0.6 (3.5)
Number of T2 Lesions, Median (IQR)		50 (35, 73)	49 (33, 75)
T2 Lesion Volume, cm^3, Median (IQR)		15.3 (7.2, 25.8)	14.9 (7.5, 28.3)

cm: centimeter, DMT: disease-modifying therapy, EDSS: Expanded Disability Status Scale, Gd-enhancing: gadolinium-enhancing, IQR: interquartile range, N: number, RRMS: relapsing remitting multiple sclerosis, SD: standard deviation, SPMS: secondary progressive multiple sclerosis

Table D3.3. HERCULES Results[21,22]

Trial		HERCULES	
Arms		Tolebrutinib	Placebo
N		754	377
Confirmed Disability Progression Sustained for ≥6 Months*	Number of Events (%)†	171 (22.6)	116 (30.7)
	Kaplan–Meier Estimate at 24 Months, % (95% CI)	21.9 (18.8, 25.1)	30.2 (25.3, 35.1)
	HR (95% CI; p Value)	0.69 (0.55, 0.88; 0.003)	
Confirmed Disability Progression Sustained for ≥3 Months*	Number of events (%)	208 (27.6)	129 (34.2)
	Kaplan–Meier Estimate at 24 Months, % (95% CI)	26.7 (23.5, 30.2)	33.3 (28.5, 38.7)
	HR (95% CI; p Value)	0.76 (0.61, 0.94; 0.013)	
Annualized Rate of New or Enlarging Lesions on T2-Weighted MRI	Mean Estimate (95% CI)	1.84 (1.44, 2.34)	2.95 (2.24, 3.88)
	Relative Rate (95% CI; p Value)	0.62 (0.43, 0.90; 0.01)	
20% Increase in the Score on the Nine-Hole Peg Test Sustained for ≥3 Months	Number of Events (%)	143 (19.0)	74 (19.6)
	Kaplan–Meier Estimate at 24 Months, % (95% CI)	17.1 (14.5, 20.2)	16.4 (12.9, 20.8)
	HR (95% CI; p Value)	0.97 (0.74, 1.29; 0.84)	
20% Increase in the Score on the Timed 25-foot Walk Sustained for ≥3 Months	Number of Events (%)	310 (41.1)	187 (49.6)
	Kaplan–Meier Estimate at 24 Months, % (95% CI)	36.9 (33.4, 40.7)	46.9 (41.7, 52.4)
	HR (95% CI)	0.77 (0.64, 0.92)	
Confirmed Disability Improvement Sustained for 6 Months‡	Number of Events (%)	65 (8.6)	17 (4.5)
	Kaplan–Meier Estimate at 24 Months, % (95% CI)	8.3 (6.5, 10.7)	4.3 (2.6, 7.1)
	HR (95% CI)	1.88 (1.10, 3.21)	
Percentage Change in Brain Volume from Month 6 to End-of-Trial Visit	Least-Squares Mean Change (±SE)	−0.69 ± 0.03	−0.78 ± 0.05
	Least-Squares Mean Difference, Tolebrutinib vs. Placebo (95% CI)	0.08 (-0.03, 0.20)	
Relapse Rate§	Adjusted Annualized Adjudicated Rate (95% CI)	0.033 (0.024, 0.045)	0.032 (0.021, 0.049)

CI: confidence interval, HR: hazard ratio, SE: standard error, %: percent

*Confirmed disability progression was defined as an increase from baseline in the EDSS score of at least 1.0 point if the baseline score was 5.0 or less, or an increase from baseline of at least 0.5 points if the baseline score was greater than 5.0.

†The percentages were calculated on the basis of the number of events after multiple imputations.

‡Confirmed lessening of disability (disability improvement) was defined as a decrease in the EDSS score of at least 1.0 point from baseline.

§Tertiary end point.

Table D3.4. HERCULES Harms[21,22]

Arms		Tolebrutinib	Placebo
N		**752**	**375**
Any Adverse Events, n (%)		613 (81.5)	293 (78.1)
Serious Adverse Events, n (%)		113 (15.0)	39 (10.4)
Serious Infection, n (%)		39 (5.2)	13 (3.5)
Discontinued Trial, n (%)		174 (23.1)	88 (23.3)
Any AE Leading to Treatment Discontinuation, n (%)		29 (3.9)	11 (2.9)
Most Common AEs (≥5% in the Tolebrutinib Arm), n (%)	**Fall**	72 (9.6)	41 (10.9)
	Headache	54 (7.2)	27 (7.2)
	Arthralgia	49 (6.5)	19 (5.1)
	Influenza	42 (5.6)	13 (3.5)
	Hypertension	38 (5.1)	11 (2.9)

AE: adverse event, %: percent

Table D3.5. GEMINI and Phase II Harms[24,32-34,37]

Trial		GEMINI 1 & 2		NCT03889639	NCT03996291	
Arms		Tolebrutinib	Teriflunomide	Tolebrutinib 60 mg	3-Year follow up	2-Year follow up
N		933	939	32	125	125
Discontinued trial, n (%)		140 (15)	146 (15.5)	NR	22 (17.6)	NR
Any TEAE, n (%)		792 (84.9)	810 (86.3)	16 (50)	NR	111 (88.8)
Any Serious TEAE, n (%)		91 (9.8)	77 (8.2)	1 (3)	NR	7 (5.6)
Any TEAE Leading to Treatment Discontinuation, n (%)		42 (4.5)	41 (4.4)	0	NR	3 (2.4)
Death, n (%)		1 (0.1)	2 (0.2)	0	NR	0
Most common TEAEs (≥5% in the tolebrutinib arm), n (%)	Urinary Tract Infection	59 (6.3)	57 (6.1)	NR	NR	NR
	Nasopharyngitis	119 (12.8)	105 (11.2)	3 (9)	20 (16)	14 (11)
	Headache	117 (12.5)	98 (10.4)	4 (13)	17 (14)	17 (14)
	Arthralgia	NR	NR	NR	9 (7)	7 (6)
	Back Pain	58 (6.2)	55 (5.9)	0	12 (10)	NR
	COVID-19 Infection	225 (24.1)	252 (26.8)	NR	43 (34)	26 (21)
	Upper Respiratory Tract Infection	77 (8.3)	82 (8.7)	1 (3)	14 (11)	14 (11)
	Alopecia	73 (7.8)	146 (15.5)	1 (3)	NR	NR
	Viral Upper Respiratory Tract Infection	50 (5.4)	59 (6.3)	NR	9 (7)	NR
	Accidental Overdose	NR	NR	3 (9)	NR	NR
	Gastroenteritis	NR	NR	2 (6)	NR	NR
	Alanine Aminotransferase Increased	NR	NR	3 (2)	NR	NR
	Peripheral Oedema	NR	NR	2 (6)	NR	NR
	Muscle Spasticity	NR	NR	2 (6)	NR	NR
	Cystitis Bacterial	NR	NR	NR	9 (7)	9 (7)
	Pharyngitis	NR	NR	NR	8 (6)	NR
	Nausea	NR	NR	NR	7 (6)	NR
	Increased ALT Levels	NR	NR	NR	6 (5)	NR
	Pain in Extremity	NR	NR	NR	6 (5)	NR
	Pyrexia	NR	NR	NR	6 (5)	6 (5)

ALT: alanine aminotransferase, mg: milligram, N: number, NR: not reported, TEAE: treatment emergent adverse event, %: percent

Table D3.6. HERCULES and GEMINI Liver Toxicity22,24

Trial		HERCULES		GEMINI I & II	
Arms		Tolebrutinib	Placebo	Tolebrutinib	Teriflunomide
Liver Toxicity, n (%)	ALT >3×ULN	30 (4)	6 (1.6)	52 (5.6)	58 (6.3)
	ALT 3–5×ULN	15 (2)	3 (0.8)	20 (2.2)	28 (3)
	ALT 5–10×ULN	8 (1.1)	2 (0.5)	19 (2)	21 (2.3)
	ALT 10–20×ULN	3 (0.4)	1 (0.3)	8 (0.9)	8 (0.9)
	ALT >20×ULN	4 (0.5)	0	5 (0.5)	1 (0.1)
	ALT >3×ULN + Total BILI >2×ULN	3 (0.4)	0	4 (0.4)	1 (0.1)

ALT: alanine aminotransferase, BILI: bilirubin, ULN: upper limit of normal, %: percent

D4. Ongoing Studies

Table D4.1. Ongoing Studies

NCT/Trial	Study Design	Inclusion/Exclusion	Primary Endpoint
PERSEUS NCT04458051	Phase III, randomized, double-blind, placebo-controlled study N=766 <u>Population</u> Adults aged 18-55 with primary progressive multiple sclerosis <u>Duration</u> 60 months <u>Arms</u> - Tolebrutinib 60mg oral - Placebo oral	Inclusion - Diagnosis of PPMS according to the 2017 McDonald criteria -Expanded disability status scale (EDSS) score between 2.0 to 6.5 points, at screening inclusive -Positive cerebrospinal fluid oligoclonal bands and/or elevated Immunoglobulin G index either during screening or documented previous history. Exclusion -The participant has received medications/treatments for MS within a specified time frame. -Receiving potent and moderate inducers or inhibitors of cytochrome P450 3A (CYP3A) or potent inhibitors of CYP2C8 hepatic enzymes.	Time to onset of 3-month composite Confirmed Disability Progression [up to 60 months]
NCT06372145	Phase III, non-randomized, open label study N=2500 (estimated) <u>Population</u> Participants who completed the Phase IIb or one of the Phase III pivotal tolebrutinib trials <u>Duration</u> 3 years <u>Arms</u> Tolebrutinib 60mg oral	Inclusion - Participants with RMS, PPMS, or NRSPMS who completed the Phase IIb or one of the Phase III pivotal tolebrutinib trials	Number of participants with adverse events [up to 3 years]

NCT/Trial	Study Design	Inclusion/Exclusion	Primary Endpoint
NCT04742400	Phase II, non-randomized, open label study N=12 Population Adults aged 18 and older with MS who are on an anti-CD20 therapy Duration 96 weeks Arms - Tolebrutinib 60mg orally - Tolebrutinib 120mg orally	Inclusion - Diagnosed with MS according to the 2017 revision of the McDonald diagnostic criteria - No new lesion formation by comparison of baseline MRI scan with a historical MRI scan at least 6 months prior - On anti-CD20 antibody treatment for at least 6 months, with the most recent dose at most 6 months prior to enrollment Exclusion - MS relapse in the 6 months prior to dosing	Disappearance of paramagnetic rim lesions [48 weeks]

Source: www.ClinicalTrials.gov

MS: multiple sclerosis, N: number, PPMS: Primary progressive multiple sclerosis

D5. Previous Systematic Reviews and Technology Assessments

Our review found no ongoing health technology assessments or systematic literature reviews relevant to tolebrutinib and SPMS. However, the National Institute for Health Care and Excellence (NICE) is currently assessing tolebrutinib for the treatment of RMS (ID6351). Several reviews exist regarding the diagnosis and management of SPMS,[11,13,80-82] two of which are summarized below.

Ziemssen et al 2023. Secondary Progressive Multiple Sclerosis: A Review of Clinical Characteristics, Definition, Prognostic Tools, and Disease-Modifying Therapies[11]

This review provides an overview of the baseline characteristics of participants with SPMS enrolled in selected Phase III clinical trials, registries, and real-world evidence, providing detailed information about the heterogeneity of the SPMS population and uncertainties in diagnosis. For example, the review points out that SPMS patients may be underrepresented in registries and other forms of real-world evidence because of the difficulty of making the diagnosis of SPMS, including delays in diagnosis. Additionally, evidence that relies on EDSS scales may miss progression in other domains not covered by EDSS. The authors also point out that current methods of diagnosing SPMS may not diagnose SPMS early enough and suggest algorithms and digital tools for MS disease monitoring and assessment. Finally, the authors discuss treatments for SPMS, particularly highlighting the role of symptom management using both pharmacologic and nonpharmacologic approaches. This review did not discuss any specific DMTs and their role in treating SPMS.

Bayas et al 2023. Disease-modifying therapies for relapsing/active secondary progressive multiple sclerosis – a review of population-specific evidence from randomized clinical trials[80]

This review first discusses the definition of SPMS, emphasizing that relapse-associated worsening (RAW) and progression independent of relapse activity (PIRA) as drivers of progression of RMS to SPMS. The authors then summarize treatments and treatment recommendations from clinical practice guidelines for active SPMS. The summary includes descriptions of the DMTs already approved for active SPMS including describing and summarizing data from key trials. Finally, the authors highlight that evidence assessing these DMTs in the SPMS populations is limited and FDA approvals are mostly based on the assumption that reduction in relapse seen in patients with RRMS could be extrapolated to the SPMS population as well.

E. Long-Term Cost Effectiveness: Supplemental Information

E1. Detailed Methods

Table E1.1. Impact Inventory

Sector	Type of Impact (Add additional domains, as relevant)	Included in This Analysis from […] Perspective?		Notes on Sources (if quantified), Likely Magnitude & Impact (if not)
		Health Care Sector	Societal	
Formal Health Care Sector				
Health Outcomes	Longevity effects	X	X	
	Health-related quality of life effects	X	X	
	Adverse events	X	X	
Medical Costs	Paid by third-party payers	X	X	
	Paid by patients out-of-pocket	☐	☐	
	Future related medical costs	X	X	
	Future unrelated medical costs	X	X	
Informal Health Care Sector				
Health-Related Costs	Patient time costs	NA	☐	
	Unpaid caregiver-time costs	NA	☐	
	Transportation costs	NA	☐	
Non-Health Care Sector				
Productivity	Labor market earnings lost	NA	X	
	Cost of unpaid lost productivity due to illness	NA	X	
	Cost of uncompensated household production	NA	☐	
Consumption	Future consumption unrelated to health	NA	☐	
Social Services	Cost of social services as part of intervention	NA	☐	
Legal/Criminal Justice	Number of crimes related to intervention	NA	☐	
	Cost of crimes related to intervention	NA	☐	
Education	Impact of intervention on educational achievement of population	NA	☐	
Housing	Cost of home improvements, remediation	NA	☐	
Environment	Production of toxic waste pollution by intervention	NA	☐	
Other	Other impacts (if relevant)	NA	☐	

NA: not applicable

Note that caregiver health-related quality of life effects were included in the societal perspective analysis.

Adapted from Sanders et al[83]

Description of evLY Calculations

The equal value life year (evLY) considers any extension of life at the same "weight" no matter what treatment is being evaluated or what population is being modeled. Below are the stepwise calculations used to calculate the evLY.

1. First, we attribute a utility of 0.851, the age- and sex-adjusted utility of the general population in the US that are considered healthy.[84]
2. We calculate the evLY for each model cycle.
3. Within a model cycle, if using the intervention results in additional life years versus the primary comparator, we multiply the general population utility of 0.851 with the additional life years gained (ΔLY gained) within the cycle.
4. The life years shared between the intervention and the comparator use the conventional utility estimate for those life years within the cycle.
5. The total evLY for a cycle is calculated by summing steps 3 and 4.
6. The evLY for the comparator arm is equivalent to the QALY for each model cycle.
7. The total evLYs are then calculated as the sum of evLYs across all model cycles over the time horizon.

Finally, the evLYs gained is the incremental difference in evLYs between the intervention and the comparator arm.

Target Population

The target population consists of adults ages 18 years and older in the United States with the non-relapsing form of SPMS. Table E1.2 presents the baseline population characteristics**.**

Table E1.2. Base-Case Model Cohort Characteristics

Characteristic	Tolebrutinib (N=754)	Placebo (N=377)	Source/Notes
Mean Age (SD)	48.9 (8.0)	48.9 (8.0)	Data by group: ECTRIMS[41]
Female, %	454 (60.2)	242 (64.2)	
Mean EDSS (SD)	5.49 (0.99)	5.59 (0.94)	
Median EDSS (IQR)	6.0 (4.8-6.3)	6.0 (5.0-6.3)	

EDSS: Expanded Disability Status Scale, IQR: Interquartile Range, SD: Standard Deviation

Treatment Strategies

The list of interventions was determined based on input from patient organizations, clinicians, manufacturers, and payers on which treatments to include.

- The intervention of interest for this review is tolebrutinib (Sanofi).
- The comparator for this intervention is the best supportive care, which is defined as pharmacological and non-pharmacological treatments to alleviate the symptoms of SPMS.

E2. Model Inputs and Assumptions

Please find the key assumptions described in the main report (Table 4.1). See below for additional details not provided in the main report on inputs and assumptions.

The model schematic can be found in Figure 4.1. The model grouped EDSS scores into whole-unit increments, with patients transitioning between states annually over a lifetime horizon. Over time, a patient's EDSS score either increased (reflecting progression) or remained stable, but it did not decrease (reflecting improvement). Patients could experience progression, MS-related death, or all-cause death, and those who discontinued treatment followed best supportive care transitions reflecting the natural history of the disease. Patients were assumed to continue with tolebrutinib for a lifetime. Scenario analyses examined various stopping rules such as reaching non-ambulatory status (i.e., EDSS score ≥7).

Each EDSS health state was associated with health-related quality of life, mortality risk, and related and unrelated health care costs. Total drug costs for each therapy included acquisition, administration, and monitoring expenses. Additional costs were assigned to each health state, covering inpatient and outpatient care, diagnostic tests, non-disease-modifying therapy (non-DMT) prescriptions, and supportive resources (such as wheelchairs and mobility services). Costs related to adverse events were not included because of a lack of evidence from the HERCULES trial. A societal perspective that considers indirect costs and caregiver burden was included in scenario analyses.

Model Inputs

Clinical Inputs

Clinical inputs were derived using both the natural history of SPMS and treatment effects from the phase III trials for tolebrutinib. Key clinical inputs include disease progression, adverse events, discontinuation, and mortality. Treatment effectiveness, as measured by disease progression, was defined using the tolebrutinib arm hazard ratio for disability progression to higher EDSS states, while the comparator arm will follow the natural history of disease progression (Table E2.2). Data permitting, in a scenario analysis, we plan to model disability improvement (Table E2.3). We requested post-trial EDSS state distributions from the manufacturer to incorporate this improvement into the modeling analysis.

Table E2.2. Disability Progression

	Proportion of Patients Achieving 6-Month Disability Progression at 45 Months	Hazard Ratio for 6-Month Disability Progression (CI)	Primary Source
Tolebrutinib	26.9%	0.69 (0.55 to 0.88)	ECTRIMS 2024[41]
Placebo	37.2%	NA	

CI: Confidence Interval, NA: Not Available

Table E2.3 Disability Improvement

	Proportion of Patients Achieving 6-Month Disability Improvement at 45 Months	Primary Source
Tolebrutinib	10%	ECTRIMS 2024[41]
Placebo	5%	

Transition Probabilities

Transition probabilities between EDSS states for patients with SPMS in the absence of treatment are provided in Table E2.4.

Table E2.4. Natural History Annual Transition Probabilities for SPMS

EDSS at Cycle Start	EDSS at Cycle End								
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
1	0.769	0.154	0.077	0	0	0	0	0	0
2	0	0.636	0.271	0.062	0.023	0.008	0	0	0
3	0	0	0.629	0.253	0.077	0.033	0.003	0.005	0
4	0	0	0	0.486	0.35	0.139	0.007	0.018	0
5	0	0	0	0	0.633	0.317	0.022	0.026	0.002
6	0	0	0	0	0	0.763	0.19	0.045	0.002
7	0	0	0	0	0	0	0.805	0.189	0.006
8	0	0	0	0	0	0	0	0.926	0.074
9	0	0	0	0	0	0	0	0	1

EDSS: Expanded Disability Status Scale

Caregiver Disutility

The impact of SPMS on caregivers is a key consideration in treatment evaluations aimed at reducing disability and was analyzed separately in the modified societal perspective scenario. Caregiver disutility has been previously modeled, with Acaster et al. (2013) providing estimates based on Patient Determined Disease Steps (PDDS), which can be mapped to EDSS states.[58] We used the regression equation EDSS score=2.9 + 0.63 (PDDS score) published by Learmonth et al. (2013) to create a crosswalk from PDDS states to EDSS states.[85] See the 'Crosswalked disutility' column in Table E2.5.

Table E2.5 Crosswalk Between PDDS and EDSS

PDDS	EDSS
0	3
1	3.5
2	4
3	5
4	5.5
5	6
6	6.5
7	7.5
8	8

PDDS: Patient Determined Disease Steps, EDSS: Expanded Disability Status Scale

Applying the crosswalk and averaging the scores for whole-unit EDSS states, we estimated the caregiver disutilities by EDSS states (Table E2.6). Notably, Acaster et al. (2013) found that caregiver disutility decreases at more advanced stages of MS (EDSS ≥7). In contrast, a study by Gani et al. (2008),[86] recently referenced in a NICE technology appraisal submission, used a proxy approach to estimate MS caregiver disutility based on Alzheimer's disease and the proportion of time spent providing care. Unlike Acaster et al. (2013), Gani et al. (2008) estimated substantially higher caregiver disutilities in more progressed states, based on the assumption that caregiving demands increase with disease progression. These conflicting approaches highlight ongoing controversy in how caregiver disutilities are incorporated into MS models.

To address these discrepancies, we conducted a scenario analysis that assigned a uniform disutility value for EDSS ≥4 while assuming no caregiver disutility for lower EDSS states. This estimate was the average of EDSS disutility scores above EDSS state 4 (0.103).

Table E2.6 Estimated Caregiver Disutilities

EDSS	Crosswalked Disutility
0	0.000
1	0.000
2	0.000
3	0.002
4	0.045
5	0.094
6	0.167
7	0.066
8	0.095
9	0.095

EDSS: Expanded Disability Status Scale

Economic Inputs

All costs used in the model were updated to 2024 US dollars.

Administration and Monitoring Costs

In addition to the annual cost of tolebrutinib, we will also include drug monitoring costs which are detailed in Table E2.7. The monitoring costs were based on the HERCULES trial protocol, which specifies that MRI scans are conducted every six months for the first two years, followed by annual scans thereafter. Additionally, follow-up visits and liver function tests are scheduled every three months throughout the monitoring period.

Table E2.7. Drug Monitoring Unit Costs

Category	Unit Cost	Source
MRI (CPT 70543)	$473	Physician Schedule Fee, 2024[19]
Provider Visit (CPT 99215)	$175	
Liver Function Test (HCPCS 80076)	$62	

CPT: Current Procedural Terminology, MRI: Magnetic Resonance Imaging

Productivity Costs

In the modified societal perspective analysis, the model assigned indirect costs based on EDSS state inclusive of productivity losses, changes in labor employment participation, and informal care. Table E2.7 reports annual indirect costs that were modeled for each EDSS state.

Table E2.8 Annual Indirect Costs by EDSS

EDSS Level	Cost	Source
2	$17,075	ICER's 2023 Review inflated to 2024 dollars using US BLS[19]
3	$20,695	
4	$24,315	
5	$27,935	
6	$31,555	
7	$35,175	
8	$38,795	
9	$42,416	

EDSS: Expanded Disability Status Scale

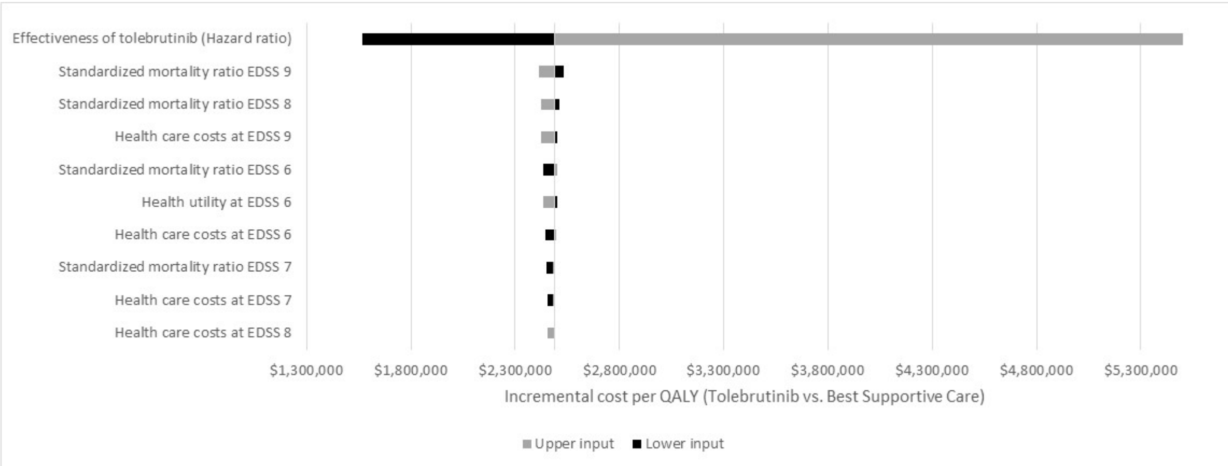
E3. Results

Base case results are described in the main report.

E4. Sensitivity Analyses

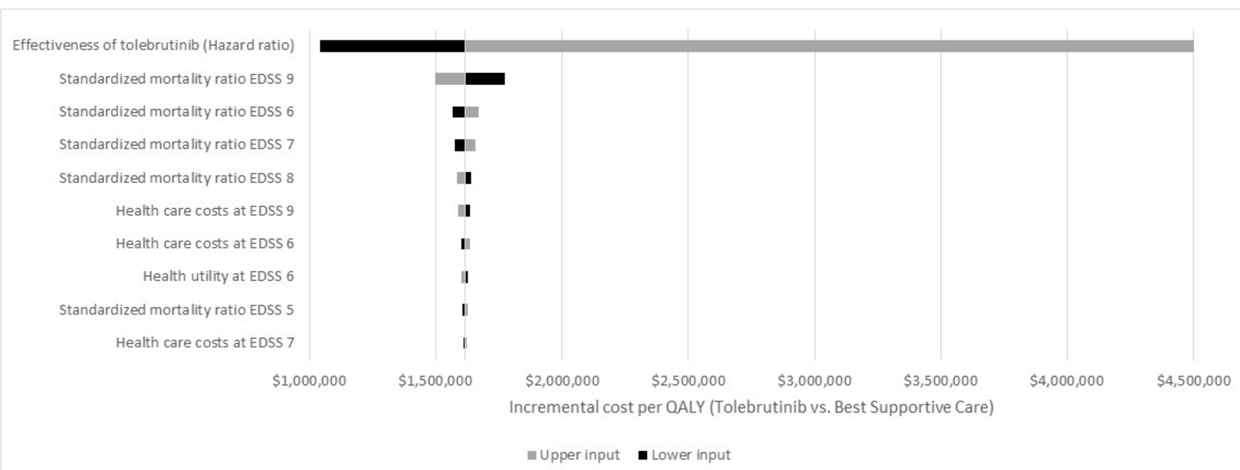
To demonstrate the effects of uncertainty on both costs and health outcomes, we varied input parameters using available measures of parameter uncertainty (i.e., standard errors) or reasonable ranges to evaluate changes in cost per QALY and cost per evLY.

Figure E4.1. Tornado Diagram for Incremental Cost per QALY (Tolebrutinib vs. Best Supportive Care)*



QALY: quality-adjusted life years; EDSS: expanded disability status scale
*Based on placeholder price

Figure E4.2. Tornado Diagram for Incremental Cost per evLY (Tolebrutinib vs. Best Supportive Care)*



evLY: equal value of life year; EDSS: expanded disability status scale
*Based on placeholder price

Table E4.1. Tornado Diagram Inputs and Results for Tolebrutinib versus Best Supportive Care (Incremental Cost per QALY)

	Lower Incremental CE Ratio*	Upper Incremental CE Ratio*	Lower Input†	Upper Input†
Effectiveness of Tolebrutinib (Hazard Ratio)	$1,569,024	$7,035,434	0.55	0.88
Standardized Mortality Ratio EDSS 9	$2,534,255	$2,411,621	5.25	7.77
Standardized Mortality Ratio EDSS 8	$2,510,652	$2,422,359	3.62	5.36
Health Care Costs at EDSS 9	$2,500,569	$2,426,000	$26,846	$72,626
Standardized Mortality Ratio EDSS 6	$2,434,528	$2,504,115	1.85	2.74
Health Utility at EDSS 6	$2,499,540	$2,436,753	0.40	0.42
Health Care Costs at EDSS 6	$2,445,236	$2,496,555	$19,096	$51,660
Standardized Mortality Ratio EDSS 7	$2,452,779	$2,481,360	2.52	3.74
Health Care Costs at EDSS 7	$2,457,167	$2,481,341	$21,679	$58,648
Health Care Costs at EDSS 8	$2,478,350	$2,454,331	$24,262	$65,636

CE: cost-effectiveness

*Based on a placeholder price

†Note lower input may reflect either upper or lower ICER value depending on the direction that the input has on the ICER output.

Table E4.2. Tornado Diagram Inputs and Results for Tolebrutinib versus Best Supportive Care (Incremental Cost per evLY)

	Lower Incremental CE Ratio*	Upper Incremental CE Ratio*	Lower Input†	Upper Input†
Effectiveness of Tolebrutinib (Hazard Ratio)	$1,043,503	$4,536,937	0.55	0.88
Standardized Mortality Ratio EDSS 9	$1,772,995	$1,499,447	5.25	7.77
Standardized Mortality Ratio EDSS 6	$1,566,159	$1,672,357	1.85	2.74
Standardized Mortality Ratio EDSS 7	$1,576,312	$1,655,588	2.52	3.74
Standardized Mortality Ratio EDSS 8	$1,640,080	$1,582,901	3.62	5.36
Health Care Costs at EDSS 9	$1,637,192	$1,588,370	$26,846	$72,626
Health Care Costs at EDSS 6	$1,600,964	$1,634,564	$19,096	$51,660
Health Utility at EDSS 6	$1,628,653	$1,602,979	0.40	0.42
Standardized Mortality Ratio EDSS 5	$1,603,980	$1,628,724	1.50	2.22
Health Care Costs at EDSS 7	$1,608,776	$1,624,603	$21,679	$58,648

CE: cost-effectiveness

*Based on a placeholder price

†Note lower input may reflect either upper or lower ICER value depending on the direction that the input has on the ICER output.

Table E4.3. Results of Probabilistic Sensitivity Analysis for Tolebrutinib versus Best Supportive Care

	Tolebrutinib Mean	Best Supportive Care Mean	Incremental
Costs	$2,200,000*	$654,000	$1,500,000*
QALYs	4.29	3.66	0.63
evLYs	4.62	3.66	0.97
Incremental CE Ratio	$2,500,000 per QALY; $1,600,000 per evLY		

CE: cost-effectiveness, evLYs: equal-value life year, QALY: quality-adjusted life year

*Based on a placeholder price for tolebrutinib

E5. Scenario Analyses

The main results of the scenario analyses are described in Table 4.7 in the main report. Table E5.1 demonstrates the different societal perspective results using alternative approaches to capturing caregiver disutility and an alternative source for health state utility inputs. We used the following approaches:

- Caregiver Disutility Approach 1: Sum patient QALYs with caregiver QALYs where caregiver QALYs rely on the average US population quality of life and survival minus the disutility associated with carer impacts in each cycle by EDSS (Patient utility in each cycle + (caregiver utility in each cycle-caregiver disutility) weighted by proportion in each EDSS state each cycle).[60] This is known as the additive QALY approach where 1 caregiver and 1 patient create a total family QALY estimate.

- Caregiver Disutility Approach 2: A constant disutility input value equal to the average of carer disutility values over EDSS state 4 (0.103).

- Alternative Utility Approach: In this scenario, we updated the base-case utility values to estimates from a United Kingdom population with utilities that decline to negative values in states 8 and 9 (health utility on average was 0.491 but varied from 0.70 in EDSS 2 to -0.195 in EDSS 9).[87]

Table E5.1 Additional Scenario Analysis Results Using Alternative Approaches to Caregiver Disutility for the Modified Societal Perspective and Alternative Health State Utility Values for the Base Case

Treatment	Base-Case Results*	Caregiver Disutility Approach 1*	Caregiver Disutility Approach 2*	Alternative Utility Approach*
Tolebrutinib	$2,500,000 per QALY and $1,600,000 per evLY	$1,600,000 per QALY and $1,100,000 per evLY†	$2,500,000 per QALY and $1,600,000 per evLY	$1,800,000 per QALY and $1,200,000 per evLY

*Placeholder price

†The incremental cost per QALY for the Caregiver Disutility Approach 1 should be interpreted as the QALY gains experienced by the family unit. The QALY gains experienced by the family unit include the patient and caregiver QALY gains for tolebrutinib compared to best supportive care. The following inputs were used to calculate the Incremental CE ratio comparing Tolebrutinib vs. BSC: Incremental patient discounted lifetime QALYs (from base-case): 4.30 – 3.66 = 0.63; Incremental caregiver discounted lifetime QALYs (caregiver utility – caregiver disutility): 10.43 – 10.08 – 0.35; Incremental discounted lifetime family QALYs (i.e., sum of patient and caregiver QALYs) = 14.72-13.73 =0.99; Incremental societal perspective costs: $2.7 million – $1.1 million = $1.6 million. The same approach was used to calculate the incremental cost-effectiveness ratio with evLYs used in the denominator.

E6. Model Validation

We used several approaches to validate model findings. First, we had two different model experts review the model structure, assumptions, and inputs. Second, we performed internal model validation by varying inputs to identify any errors or illogical results. Third, we replicated a previous SPMS ICER review (2019) and identified model inputs that can be consistently compared (e.g., life years gained and years able to walk without a wheelchair in best supportive care arm) and results were within a relative 10% of findings between both models. Finally, as part of ICER's efforts in acknowledging modeling transparency, we offered to share the model with the manufacturer for external validation.

Prior Economic Models

Our current model builds upon previous cost-effectiveness analyses conducted by ICER, specifically the 2019 review on SPMS and the SPMS model arm of the 2023 review focusing on RRMS.[19] While the 2019 model included both the overall SPMS population and a subpopulation with active SPMS, and the 2023 model primarily targeted RRMS but accounted for the transition to SPMS, our model specifically focuses on non-relapsing SPMS.

Structurally, all models used a Markov framework with EDSS scores but differed slightly in implementation. The 2019 and 2023 models initiated the SPMS phase at EDSS 1, whereas our model starts at EDSS 2, aligning with the HERCULES trial inclusion criteria (EDSS ≥3.0 to ≤6.5). Like the previous models, we utilized the London, Ontario MS dataset to estimate natural history transition probabilities for best supportive care and applied a hazard ratio to reflect treatment effects.

Regarding treatment discontinuation, the 2019 model assumed siponimod discontinuation at EDSS 7, while the 2023 model allowed patients to remain on treatment for their lifetime. Our model assumes treatment continues until death but includes scenario analyses for discontinuation at EDSS 7 or 8. Mortality assumptions were consistent across models, using data from Pokorski (1997) for EDSS-specific mortality ratios.[51]

For health state utilities, we followed the approach from the 2023 model, which differs from the 2019 model by depicting a more gradual decline in utility from EDSS 0-7 instead of a sharp drop after EDSS 7. To estimate utilities for EDSS 8 and 9, we adopted the 2023 ICER methodology, which accounted for sample size limitations. In terms of caregiver disutility, while the 2019 model used inputs from Acaster (2013) and the 2023 model excluded this aspect, we applied Acaster (2013) as well but introduced a crosswalk from the Patient Determined Disease Step (PDDS) to EDSS via a regression equation, resulting in slight variations.[58]

Concerning annual non-drug MS-related health care costs, our model—like the 2019 model—relies on Kobelt (2006) but incorporates a more updated extrapolation from Hernandez, estimating costs at \$1,115 × EDSS + \$4,593 (R^2=0.995).[54,55]

Cost-effectiveness analyses specifically focusing on non-relapsing SPMS are limited, making it challenging to directly compare the findings of this report with those from other studies. The ICER report in 2019 reviewed SPMS-specific models evaluating disease-modifying therapies used for SPMS patients. Accordingly, we briefly describe a few relevant models published afterward, which we identified through our literature search.

Montgomery et al. (2022) employed a cohort Markov model with a lifetime horizon to assess the cost-effectiveness of siponimod compared to continued disease-modifying therapies (DMTs) for active SPMS patients in the UK[88]. This study incorporated data from the EXPAND clinical trial and other published literature to calculate incremental cost-effectiveness ratios (ICERs). Schur et al. (2021) conducted a cost-effectiveness and budget impact analysis using a Markov model with a lifetime horizon to compare siponimod to interferon beta-1a for active SPMS in Switzerland[89]. Their analysis integrated clinical data from the EXPAND and Nordic SPMS trials, estimating costs over the first three years. Cortesi et al. (2022) performed a cost-effectiveness and budget impact analysis of siponimod versus interferon beta-1b for SPMS patients in Italy, utilizing a Markov model with a lifetime horizon and estimating the financial impact over three years based on clinical and cost data from the literature.[90]

The methods used by Montgomery et al., Schur et al., and Cortesi et al. are aligned with our model as they all apply Markov models, utilize EDSS-based health states, and have a one-year cycle length. These studies rely on confirmed disability progression as a trial outcome. However, they differ in terms of patient population, as they focus on active SPMS and siponimod, while our model targets non-relapsing SPMS and evaluates Tolebrutinib against best supportive care. Additionally, the published costs and resource use data are country-specific (UK, Switzerland, and Italy) and therefore not comparable with our US-focused study.

F. Potential Budget Impact: Supplemental Information

Methods

We used results from the same model employed for the cost-effectiveness analyses to estimate total potential budget impact. Potential budget impact was defined as the total differential cost of using the new therapy rather than relevant existing therapy for the treated population, calculated as differential health care costs (including drug costs) minus any offsets in these costs from averted health care events. All costs were undiscounted and estimated over one- and five-year time horizons.

The potential budget impact analysis included the candidate populations eligible for treatment: adults with non-relapsing SPMS. To estimate the size of the potential candidate populations for treatment, we used inputs for the average US adult population projected over the next 5 years (269,395,454), the prevalence of MS in the US (0.32%)[1], and the percentage of patients with non-relapsing SPMS (20.5%)[61]. Applying these sources results in estimates of 177,994 eligible patients in the US. For the purposes of this analysis, we assumed that 20% of these patients would initiate treatment in each of the five years, or 35,599 patients per year.

ICER's methods for estimating potential budget impact are described in detail elsewhere and have recently been updated.[91,92] The intent of our revised approach to budgetary impact is to document the percentage of patients that could be treated at selected prices without crossing a budget impact threshold that is aligned with overall growth in the US economy.

Once estimates of budget impact are calculated, we compare our estimates to an updated budget impact threshold that represents a potential trigger for policy mechanisms to improve affordability, such as changes to pricing, payment, or patient eligibility. As described in ICER's methods presentation (Value Assessment Framework), this threshold is based on an underlying assumption that health care costs should not grow much faster than growth in the overall national economy. From this foundational assumption, our potential budget impact threshold is derived using an estimate of growth in US gross domestic product (GDP) +1%, the average number of new drug approvals by the FDA over the most recent two-year period, and the contribution of spending on retail and facility-based drugs to total health care spending.

For 2024-2025, therefore, the five-year annualized potential budget impact threshold that should trigger policy actions to manage access and affordability is calculated to total approximately $880 million per year for new drugs.