REPORT AT A GLANCE: SECONDARY PROGRESSIVE MULTIPLE SCLEROSIS

KEY FINDINGS

Intervention	Comparators	Evidence Rating	US Price	Health-Benefit Price Benchmark
tolebrutinib (Sanofi)	Best supportive care, defined as: • Pharmacological and non-pharmacological treatments to alleviate the symptoms of MS	"P/I" promising but inconclusive	Not yet approved	$3,250 to $5,900 per year

"There is a large unmet need for effective treatments in non-relapsing SPMS, particularly with the non-active type. Clinical trial evidence suggests that tolebrutinib slows disease progression in patients with non-relapsing SPMS; however, there are still uncertainties about the balance of its overall efficacy and adverse events, as reflected in the voting results of the independent appraisal committee at ICER's public meeting. Longer-term data will help define the overall net health benefit of tolebrutinib."

– ICER's Senior Vice President of Research, Foluso Agboola, MBBS, MPH

THEMES AND RECOMMENDATIONS

- Trial inclusion criteria are a reasonable starting point for developing coverage policies for tolebrutinib to identify patients with SPMS. Payers should engage clinical experts and patient representatives in considering how to address coverage requests for which there is limited or no evidence at the current time.
- Manufacturers have a responsibility to release clinical trial data in a timely manner such that all relevant data is available to payers, clinicians, and patients prior to the time of FDA approval to facilitate timely coverage and treatment decisions.
- Clinical specialty societies should endeavor to facilitate the education of general neurologists about SPMS diagnosis and treatment, including education to help make more prompt diagnoses of SPMS, standard of care treatment for SPMS, and the efficacy and safety of new therapies such as tolebrutinib.

Clinical Analyses

KEY CLINICAL BENEFITS STUDIED IN CLINICAL TRIALS

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.Symptoms of MS, including weakness, fatigue, vision changes, memory and concentration problems, and pain, can cause physical, emotional, and cognitive impairment. MS is a costly disease, with an estimated annual economic burden in the US over $85 billion.

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 magnetic resonance imaging (MRI) changes) or non-active disease, with or without progression of disability. Active SPMS with MRI activity only (no clinical relapses and no MRI activity) 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. 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.

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. Inclusion criteria also included 12 months of documented disease progression. The participants, who had a mean age of 49 years, were predominantly 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 (22.6% versus 30.7%, 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 outcomes were mixed; while the tolebrutinib group had fewer new or enlarging lesions on T2-weighted MRI, the change in 9-hole peg test (9HPT) did not show a statistically significant difference (HR 0.97, 95% CI 0.74 to 1.29). As such, other secondary hierarchical outcomes including timed 25 foot walk test, disability improvement, and brain volume were not evalutated futher.

Clinical Analyses

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 four 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, there was not a consistent effect of tolebrutinib demonstrated among secondary outcomes. Additionally, there is a small but non-trivial risk of severe liver toxicity; though this risk may be mitigated by intensive 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)**.

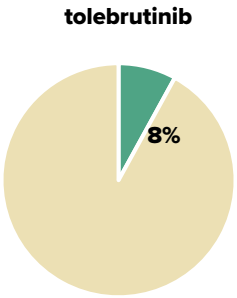
Economic Analyses

LONG-TERM COST EFFECTIVENESS

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 $3.4 million per QALY gained, $2.9 million per evLY gained, $7 million per life year gained, and $1.5 million per year without a wheelchair. The cost-effectiveness findings are primarily driven by the placeholder acquisition costs for tolebrutinib. We estimate that tolebrutinib would meet commonly cited cost-effectiveness thresholds at an annual price of $3,250 to $5,900. If we make the optimistic assumption that use of tolebrutinib universally leads to confirmed disability improvement, the incremental cost-effectiveness ratios would still be higher than the common cost-effectiveness thresholds at an annual placeholder price of $115,000 per year, although the cost-effectiveness results will improve and the health benefit price benchmark range would increase under that assumption. In summary, treatment with tolebrutinib may slow disability progression of SPMS compared with placebo, though its use may be limited by the risk of liver toxicity. If approved, the actual cost-effectiveness of tolebrutinib will depend on its price.

POTENTIAL BUDGET IMPACT

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.



Percent of eligible patients with secondary progressive multiple sclerosis that could be treated in a given year before crossing the ICER potential budget impact threshold

Public Meeting Deliberations

VOTING RESULTS

ICER's Virtual Public Meeting: Voting Results on Clinical Effectiveness and Contextual Considerations

ICER assessed, and the independent appraisal committee voted on the evidence for the net health benefit of tolebrutinib in adults with non-relapsing secondary progressive multiple sclerosis.

- A majority of the panelists (12-1) found that current evidence is **not adequate** to demonstrate a net health benefit of tolebrutinib when compared to best supportive care (defined as pharmacological and non-pharmacological treatments to alleviate the symptoms of multiple sclerosis).

Panel members also weighed potential benefits and disadvantages beyond the direct health effects and weighed special ethical priorities. Voting highlighted the following as particularly important for payers and other policymakers to note:

- There is substantial unmet need despite currently available treatments.
- Multiple sclerosis is of substantial relevance for people from a racial/ethnic group that has not been equitably served by the healthcare system.

ICER's Virtual Public Meeting: Voting Results on Long-Term Value for Money

Tolebrutinib has not yet been approved by the FDA, and the manufacturer has not announced a US price if approved.

Consistent with ICER's process, because there is no firm estimate yet of a potential launch price for the treatment, the panel did not take a vote on the treatment's long-term value for money.

ICER has calculated a health-benefit price benchmark (HBPB) to be between $3,250 and $5,900 per year.

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.