Tolebrutinib for Secondary Progressive Multiple Sclerosis

Revised Background and Scope

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Background

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system affecting almost three-quarters of a million people in the United States.[1] It causes damage to the myelin sheath (i.e., a protective covering that surrounds nerve fibers) and eventually degenerates axons (i.e., long threadlike part of a nerve cell), causing symptoms such as weakness, fatigue, vision changes, pain, and eventually leading to physical and cognitive impairments.[2] 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 also appear to develop MS earlier in life.[1,3] 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 McDonald Criteria.[5] Relapsing-remitting MS (RRMS) is the most common form of MS at disease-onset, affecting 85% of patients and is marked by periods of symptom flares (relapses) followed by recovery.[2] People with RRMS are classified as having active or non-active disease, depending on clinical and MRI activity,[6] and there may also be worsening of disability in this phase, both associated with relapses (known as relapse-associated worsening [RAW]) and independent of relapses (known as progression independent of relapse activity [PIRA]).[7-9] If left untreated, a majority of patients eventually transition to a non-relapsing form of MS, called secondary progressive MS (SPMS). SPMS is marked by progressive worsening of disability over time, independent of relapses, with a median time to transition of 32.4 years from disease onset.[10] Risk factors associated with progression include older age at MS onset, male sex, multifocal disease onset, and higher baseline Expanded Disability Status Scale (EDSS) score.[11] SPMS is a retrospective diagnosis; there are no imaging findings or biomarkers that demarcate the transition between RRMS and SPMS in real-time.[10] 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; there are no imaging findings or biomarkers that demarcate the transition between RRMS and SPMS in real-time. 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.[12] Furthermore, persons 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.[10]

Treatment for MS requires a comprehensive approach focusing on preventing relapses, delaying progression and worsening of disability, symptom control, psychological support, rehabilitation, and lifestyle interventions. There are a variety of disease-modifying treatments (DMTs) including monoclonal antibodies, interferons, fumarates, and S1P receptor modulators approved to treat MS, primarily the relapsing forms of the disease. In particular, monoclonal antibodies show efficacy in preventing relapse and slowing down disease progression, but also carry an increased risk of infections. There are no current treatments approved for non-active SPMS. Bruton's Tyrosine Kinase Inhibitors (BTKIs) are being investigated as potential treatments for both relapsing and non-relapsing forms of progressive 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 to treat both relapsing forms of MS and non-relapsing SPMS. The manufacturer is expected to submit the new drug application (NDA) for tolebrutinib for MS in the second half of 2024.

Stakeholder Input

This scoping document was developed with input from diverse stakeholders, including patients and their families, clinicians, researchers, and the manufacturer of tolebrutinib. This document incorporates feedback gathered during preliminary calls with stakeholders, open input submissions from the public, and information from prior ICER reviews focused on MS.[13] 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 persons living with MS is to maintain independence and the ability to perform normal activities, early diagnosis and comprehensive treatment are critical, and DMTs are central to treatment. However, although DMTs can be very effective at preventing relapses, some symptoms may not be adequately treated by existing DMTs. For example, pain, fatigue, numbness, urinary incontinence, and cognitive difficulties may persist despite treatment and continue to have a large impact on daily functioning, even outside of relapses. Persons living with MS may also have a substantial medication burden outside of DMTs to treat symptoms such as

bladder dysfunction and spasticity. Furthermore, at later stages of the disease and at older ages, particularly after the loss of ambulation, there is fear that treatment may not be as aggressive and that newer treatments may not even be offered to patients. Finally, there is often a delay in diagnosing SPMS, as both persons with MS may be reluctant to report progression, and clinicians may be reluctant to establish an earlier diagnosis of SPMS because of the lack of effective treatment options.

As persons living with MS have progression of disability, living independently becomes more difficult. For example, due to balance issues, persons living with MS often need walking aids. However, they may need multiple aids depending on the situation (e.g., walker for flat surfaces and cane for stairs, multiple walkers if the house has more than one level, scooter), and thus the logistics of maintaining mobility can become very complex. Travel can also be difficult due to mobility limitations and requires extensive planning. Working can also become very difficult due to symptoms of MS, and many persons with MS eventually leave the workforce prematurely.

The caregiving burden for people with MS is high, with almost half of people receiving informal care from family and friends for at least 30 hours per week.[14] Persons living with MS described how caregivers need to "do the job of two people", picking up tasks that the person with MS is unable to accomplish. If persons living with MS are unable to drive, this adds additional burden to caregivers, requiring caregivers to take time off work to drive to appointments, etc. Since MS is a lifelong disease, it also affects children, with children often shouldering the burden of worrying about a sick parent.

Clinical experts stated that treatment of SPMS was an area of great unmet need and that new clinical trials and treatments may push clinicians to make an earlier diagnosis of SPMS. Additionally, a new oral medication that is highly effective such as a BTKI may improve access, as other highly effective DMTs are intravenous infusions or injections, though side effects such as liver toxicity may dampen enthusiasm to use BTKIs. Finally, given the heterogeneity of MS and the difficulty identifying when the transition to SPMS takes place, clinical experts were interested in potential biomarkers that would give better insight into disease phenotypes.

Report Aim

This project will evaluate the health and economic outcomes of tolebrutinib for non-relapsing SPMS. The ICER value framework includes both quantitative and qualitative comparisons across treatments to ensure that the full range of benefits and harms – including those not typically captured in the clinical evidence, such as innovation, public health effects, reduction in disparities, and unmet medical needs – are considered in the judgments about the clinical and economic value of the interventions.

Scope of Clinical Evidence Review

The proposed scope for this assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence will be abstracted from randomized controlled trials as well as high-quality systematic reviews; high-quality comparative cohort studies will be considered, particularly for long-term outcomes and uncommon adverse events. Our evidence review will include input from patients and patient advocacy organizations, data from regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see ICER's grey literature policy).

All relevant evidence will be synthesized qualitatively or quantitatively. Wherever possible, we will seek out head-to-head studies of the interventions and comparators of interest. Data permitting, we will also consider the combined use of direct and indirect evidence in network meta-analyses of selected outcomes. Full details regarding the literature search, screening strategy, data extraction, and evidence synthesis will be provided after the revised scope in a research protocol published on the Open Science Framework website (https://osf.io/7awvd/).

Populations

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

As described above, 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 and harms 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.

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 would not have been considered as part of the evidence on comparative clinical effectiveness. These general elements (i.e., not specific to a given disease) are listed in the table below.

Table 1.1. Benefits Beyond Health and Special Ethical Priorities

Benefits Beyond Health and Special Ethical Priorities*
There is substantial unmet need despite currently available treatments.
This condition is of substantial relevance for people from a racial/ethnic group that have not been equitably served by the healthcare system.
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.
The treatment offers a substantial opportunity to improve access to effective treatment by means of its mechanism of action or method of delivery.

*Benefits beyond health and special ethical priorities shape to some extent how the value of any effective treatments for a particular condition will be judged and are meant to reflect the broader effects of a specific treatment on patients, caregivers, and society. For additional information, please see the ICER Value Assessment Framework.

ICER encourages stakeholders to provide input on these elements in their public comment submissions.

Scope of Comparative Value Analyses

A detailed economic model analysis plan with proposed methodology, model structure, model parameters, model inputs, and model assumptions will be published on February 24, 2025. This scoping document provides early thoughts about the overall model structure.

As a complement to the evidence review, we will develop an economic model to assess the lifetime cost-effectiveness of tolebrutinib compared to best supportive care (i.e., any pharmacological and non-pharmacological treatments to alleviate the symptoms of MS but not a DMT). The model structure will be based in part on a literature review of prior published models of SPMS, including models developed for prior ICER reviews related to MS.[13] Analyses will be conducted from the health care system perspective and the modified societal perspective. The base case analysis will take a health care system perspective (i.e., focus on direct medical care costs only). Societal impacts (e.g., patient and caregiver productivity) and other indirect costs will be considered in a separate modified societal perspective analysis. This analysis will be considered as a co-base case when (a) direct data on indirect costs are available, (b) the societal costs of care are large relative to direct health care costs, and (c) the impact of treatment on these costs is substantial. This will most often

occur in cases where the incremental cost-effectiveness ratio changes by greater than 20%, greater than $200,000 per QALY, and/or when the result crosses the threshold of $100,000-$150,000 per QALY gained. If direct data are lacking on patient and/or caregiver productivity, we will implement a method to capture the potential impacts of tolebrutinib on productivity (patient and caregiver) as well as certain other impacts (e.g., patient time in treatment).

The target population will consist of adults ages 18 years and older in the US with non-relapsing forms of SPMS. The model will consist of health states defined by EDSS scores and death. A cohort of patients will transition between states during predetermined cycles of one year over a lifetime time horizon, modeling patients from treatment initiation until death. In addition, cost-effectiveness will be estimated for shorter time horizons (e.g., five years).

Key model inputs will include clinical probabilities, quality of life values, and health care costs. Probabilities, costs, and other inputs will differ to reflect varying effectiveness between interventions. Treatment effectiveness, measured as delay in disability progression will be estimated using phase III clinical trial data.

Health outcomes and costs will be dependent on time spent in each health state (defined by EDSS category), clinical events, adverse events (AEs), and direct medical costs. The health outcome of each intervention will be evaluated in terms of years able to walk without a wheelchair (EDSS <7), life-years gained, quality-adjusted life years (QALYs) gained, and equal value of life years gained (evLYG). Quality of life weights will be applied to each health state, including quality of life decrements for serious adverse events. The model will include direct medical costs, including but not limited to costs related to drug administration, drug monitoring, condition-related care, and serious adverse events. In addition, patient and caregiver productivity changes and other indirect costs will be included in a separate analysis, as available data allow. Relevant pairwise comparisons will be made between treatments, and results will be expressed in terms of the marginal cost per QALY gained, cost per evLYG, cost per life-year gained, and cost per additional year able to walk without a wheelchair (EDSS <7).

In separate analyses, we will explore the potential health care system budgetary impact of tolebrutinib over a five-year time horizon, utilizing published or otherwise publicly-available information on the potential population eligible for treatment and results from the economic model for treatment costs and cost offsets. This budgetary impact analysis will indicate the relation between treatment prices and level of use for a given potential budget impact and will allow assessment of any need for managing the cost of such interventions. More information on ICER's methods for estimating potential budget impact can be found here.

Identification of Low-Value Services

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 additional resources in health care budgets for higher-value innovative services (for more information, see ICER's Value Assessment Framework). These services are ones that would not be directly affected by treatments for SPMS (e.g., cost of nursing care or physical therapy), 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. ICER encourages all stakeholders to suggest services (including treatments and mechanisms of care) that could be reduced, eliminated, or made more efficient.

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