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Institute for Clinical and Economic Review
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Re: Draft Scoping Document for ICER Review: Tolebrutinib for Secondary Progressive Multiple Sclerosis

On behalf of the Multiple Sclerosis Coalition (MSC or the Coalition), a 501 (c) 3 network of nine independent MS organizations, thank you for the opportunity to comment on ICER's Draft Scoping Document for *Tolebrutinib for Secondary Progressive Multiple Sclerosis.*

Multiple sclerosis (MS) is a chronic immune-mediated disease of the central nervous system (CNS) characterized by neuroinflammation, demyelination, and neurodegeneration. It affects nearly 1 million people in the US and can cause significant disability. MS disease onset usually occurs between ages 20 and 40 years. Women are disproportionately affected, with a prevalence rate nearly three times higher than that of men. The estimated prevalence of MS in Black people and white people are similar[1], while the most substantial burden of MS is borne by individuals in non-White and Hispanic racial and ethnic groups.[2] The estimated total economic burden of MS in the US is $85.4 billion per year[3].

Stakeholder Input

Input from Stakeholders

The Coalition strongly recommends that ICER prioritizes the lived experience of people with MS in gathering stakeholder input. It will be important to hear from the diverse experience of life with MS, including input from a variety of people as well as caregivers across different race/ethnic backgrounds, socioeconomic status, geography, level of disability and more. Further, as this review focuses on those with secondary progressive MS, we encourage ICER to seek input from clinical experts in the progressive MS space. While this review focuses on tolebrutinib, experts who have been involved in clinical trials for other BTKI molecules will be able to provide valuable input.

Comments on Descriptions of MS in Scope

ICER's scope and review should strive to incorporate the latest scientific discussions in MS. As an example, the current scope makes no reference to the concepts of "progression independent of relapse" or PIRA. People with MS accumulate disability through relapse-associated worsening (RAW) or PIRA. PIRA is present even in the early stages of relapsing MS and often goes undetected. PIRA has been shown to be associated with unfavorable mid- and long-term outcomes, possibly suggesting that it is underpinned by neurodegenerative processes.[4] It is likely that PIRA is the driver of overall progression and disability in MS. The current scope attributes persistence of difficult symptoms like pain, fatigue, urinary incontinence and cognitive difficulties to symptoms not being adequately treated by DMTs, when the worsening of these symptoms may be due to PIRA, with underlying progression occurring even when DMTs effectively manage relapses and relapse-associated worsening.

It is unclear what is meant by "there is fear that treatment may not be as aggressive" when referencing treatment at later stages of the disease. Please clarify whether this is related to age, ongoing inflammation or another perception.

The delay in diagnosing SPMS happens for a variety of reasons including the lack of effective treatment options, as mentioned by ICER. Delays may also occur due to fears of payors limiting access to DMTs. Finally, an SPMS diagnosis tends to be retrospective, looking back at relapses, disease progression, clinical observations, patient reported outcomes and quality of life issues.[5]

The scoping document references "other highly effective DMTs are intravenous infusions". Kesimpta and Ocrevus Zunovo are also highly effective DMTs that are both administered as injections, at home and in office respectively.

Report Aim and Populations

Medications to limit or stop disease progression are an unmet need and people with progressive forms of MS often feel left behind with the advances of DMTs for relapsing forms of MS. While some current DMTs have had an impact on progression, as noted above, research has indicated that PIRA in particular could be addressed by this new mechanism of action.

While we acknowledge the clinical trial population is non-relapsing SPMS, we encourage ICER to be future focused in its review and report. It is anticipated that the MS clinical course descriptors will be revised within the next 12-24 months to more accurately reflect the biological mechanisms of disease. Connecting the biological disease to the clinical presentation could better support more personalized approaches to treatment[6] [7] and ensure treatment of the underlying biology. ICER should be cautious that this review doesn't impede the advancement of precision medicine in MS treatment.

Outcomes

We appreciate ICER providing a comprehensive list of outcomes in the scoping document. MS is a heterogenous disease that affects people in many different ways. A picture of progressive disease often evokes someone using a mobility device. In reality, progressive disease affects so much more of an individual and their day-to-day life. For example, cognition and fatigue, not physical disability, are the two most cited reasons for people with MS prematurely leaving the workforce. Additional patient-important outcomes include bladder and bowel dysfunction, which may not be discussed as often as other outcomes but greatly affect independence, quality of life and community engagement.

We applaud the inclusion of caregiver impact as outcomes. As people with MS move into progressive phases of the disease, the burden and impact on a care partner often increases.

Adverse events, including liver enzyme levels should be viewed alongside risk benefit tolerance and any planned REMS or remediation that might accompany an FDA approval.

Scope of Comparative Value Analyses

As previously noted, the effects of progressive MS extend far beyond physical disability. We encourage ICER to be thoughtful and transparent in the inclusion of these additional aspects of disability in the economic model.

Composite measures, including the timed 25 foot walk and nine hole peg test, as well as measures of cognitive function like the SDMT should be used to help understand MS disability progression and accumulation. Cognitive functioning is linked to employment outcomes in MS, with lower executive functioning and more physical disability being moderately predictive of a deterioration in employment status[8]. The EDSS alone does not sufficiently capture MS progression or disability. Common criticisms of the EDSS include heavy reliance on the ability to walk and poor assessment of upper limb function and cognitive function[9]. We strongly recommend that ICER incorporate all relevant outcome measures in the clinical trial data in the economic model.

Finally, we encourage that the collection of lived experiences, particularly those with progressive forms of MS, be equally considered within the value analyses.

Thank you for the opportunity to comment. The Coalition looks forward to continued engagement with ICER throughout the review process. If you have any questions, please contact Bari Talente, at bari.talente@nmss.org or 202-408-9485.

Respectfully Submitted on Behalf of the Nine Member Organizations of the MS Coalition
Kathy Costello, President

Accelerated Cure Project
Can Do MS
Consortium of MS Centers
International Organization of MS Nurses
MS Views and News
Multiple Sclerosis Association of America
Multiple Sclerosis Foundation
National MS Society
United Spinal

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I'm hoping this format is acceptable as a public comment for inclusion as ICER reviews treatment options for Secondary Progressive Multiple Sclerosis.

I was diagnosed with Multiple Sclerosis (MS) at age 22, over 34years ago. I became disabled in August 2012 from a severe exacerbation, forcing me to leave my Director of Quality job as a RN. I was put on Medicare. I have been receiving disability via SSI and a LTD policy I had paid for.

Upon the time I was put out of work, BCBS denied me IVIG, even on appeal. I have no idea of knowing if this promising treatment may have returned me to the workforce. I was then approved to be on Tysabri IV which put me at risk for PML, so I decided not to be on IV steroids for relapses. I had relapses more frequently than prior, every six months, on Tysabri, the then latest and greatest. My relapses last four month without steroids so, in the two years I was on this I was sick 16 out of 24 months. I took myself off this treatment, against medical advice.

I was then doiing dietary changes, LDN, and estrogen topically as discussed with a pharmacist. I went 19 moths with no relapse.

Ocrevus was finally FDA approved and I wanted to try it with profile that attacked B cells. I was on that for 2 years with relapses every 9 months with the risk of PML again, so refused IV steroids.i was sick 12 mos the two years on Ocrevus. Again,I went off it against medical advice.

since then I have done much research and have been diagnosed with progression to Secondary Progressive MS in 2000. Areas of extensive research considered have been infectious MS (?lyme) and various stem cell treatments.

Timeline: Diagnosed RRMS 1990. Every two yr relapses, started Avonex 1997. Started having annual relapses. Big relapse 2012 and out of work. Tysabri 2014-2016 with relapses every 6 months. No traditional meds 2016-2017 went 19 mos with no relapse, meds out of pocket. 7/2017- 4/2019 Ocrevus with relapses every 9 mos. 2019- current seeing integrative doc and doing non traditional treatments, mostly out of pocket. Relapses approx every18 mos.

Seeing NIH since 2020 for a longitudal study with T7 MRIs, showing grey matter lesions where prior T3 MRIs before study had not shown progression.