Siponimod for the Treatment of Secondary Progressive Multiple Sclerosis: Effectiveness and Value

Draft Background and Scope
October 31, 2018

Background

Multiple sclerosis (MS) is a chronic, immune-mediated inflammatory, neurodegenerative, and demyelinating disease of the central nervous system (CNS).[1] Approximately 400,000 Americans have MS, although emerging evidence estimates the prevalence to be much higher.[2,3] MS disproportionately affects women and is typically diagnosed between the ages of 25 to 45.[4] The onset of symptoms often coincides with an individual's most productive years at home, work, and in their community. Indirect costs from lost productivity, coupled with the direct medical costs associated with MS management, have been estimated to total $24.2 billion per year in the United States.[5] As price increases for MS disease-modifying therapies (DMTs) outpace prescription drug inflation, cost estimates are expected to rise.[5,6]

MS is grouped into relapsing and progressive phenotypes.[7] Relapsing-remitting MS (RRMS) is a relapsing phenotype that presents initially for 85% to 90% of MS patients. It is characterized by "relapses" during which neurologic symptoms appear and then partially or completely resolve. RRMS is classified as "active" (versus "not active") in the presence of clinical relapse or inflammatory activity on magnetic resonance imaging (MRI). There is no progression of disease disability during remission; if full recovery does not occur after a relapse, patients experience a step-wise accumulation of disability.

Progressive MS comprises primary progressive MS (PPMS) and secondary progressive MS (SPMS).[7] Progressive disease is further described as "active" or "not active" (as per the criteria mentioned above for RRMS), and "with progression" or "without progression", determined by worsening of disability. The clinical course in PPMS and SPMS is gradual progressive neurologic disability, despite fewer relapses and less inflammatory activity when compared to RRMS. Studies conducted prior to the advent of MS DMTs showed that most patients with RRMS transitioned to SPMS within 25 years.[8,9] However, the extent to which DMTs affect the transition time to SPMS remains uncertain.

Distinguishing between relapsing and progressive phenotypes can be challenging.[7] There is no biomarker differentiating the entities and the transition from relapsing to progressive phenotypes is only evident retrospectively. Further, clinicians are sometimes hesitant to label a patient as "progressive" given that doing so may eliminate insurance coverage for certain medications.[10]

These factors complicate both MS disease phenotype classification and diagnosis and muddle reporting of the epidemiology of progressive MS.

The therapeutic goal in MS is to decrease disease activity and progression to disability. The Food and Drug Administration (FDA) has approved more than 10 disease-modifying therapies (DMTs) which modulate immune response for relapsing MS. There are few FDA-approved therapies for progressive MS. Ocrelizumab is approved for PPMS and mitoxantrone is approved for SPMS, although use of the latter has been limited because of its adverse effect profile. In the absence of approved or efficacious treatments for progressive MS, many medications are used "off-label" particularly in patients with active, progressive disease.

On October 8, 2018, the Food and Drug Administration (FDA) announced that it granted Priority Review Designation to siponimod (Novartis) for use in SPMS, with plans to issue a decision in March 2019. Siponimod is a selective sphingosine-1-phosphate (S1P) receptor modulator that is known to cross the blood-brain barrier. Given the lack of highly effective therapies for SPMS, the clinical and cost effectiveness of siponimod compared to other DMTs and supportive care is of interest to various stakeholder groups.

Stakeholder Input

This draft scoping document was developed with input from diverse stakeholders, including patients, clinicians, researchers, and manufacturers of the agents of focus in this review. This document incorporates feedback gathered during preliminary calls with stakeholders and open input submissions from the public.

All stakeholders identified the challenges of making the diagnosis of progressive MS, as discussed in "Background", and the lack of effective treatment directed towards disease progression when it occurs independent of inflammatory activity.

There was consensus that multiple therapies are used in patients with progressive MS, and that treatment reflected shared-decision making rather than standardized protocols. Notably, therapies studied for use in PPMS are often tried in SPMS, reflecting the perception that progressive MS phenotypes may share a common pathophysiology. Patient groups noted that those affected with progressive MS may become disabled and sometimes home-bound or reside in nursing homes. As disability worsens, patients' engagement with healthcare services, educational resources, and advocacy efforts may diminish. Caregiver and patient burden are particularly heavy in this population and there is often a decrease in or loss of the ability to work for both.

A final scoping document will be posted following a three-week public comment period. 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.

Report Aim

This project will evaluate the health and economic outcomes of siponimod for 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

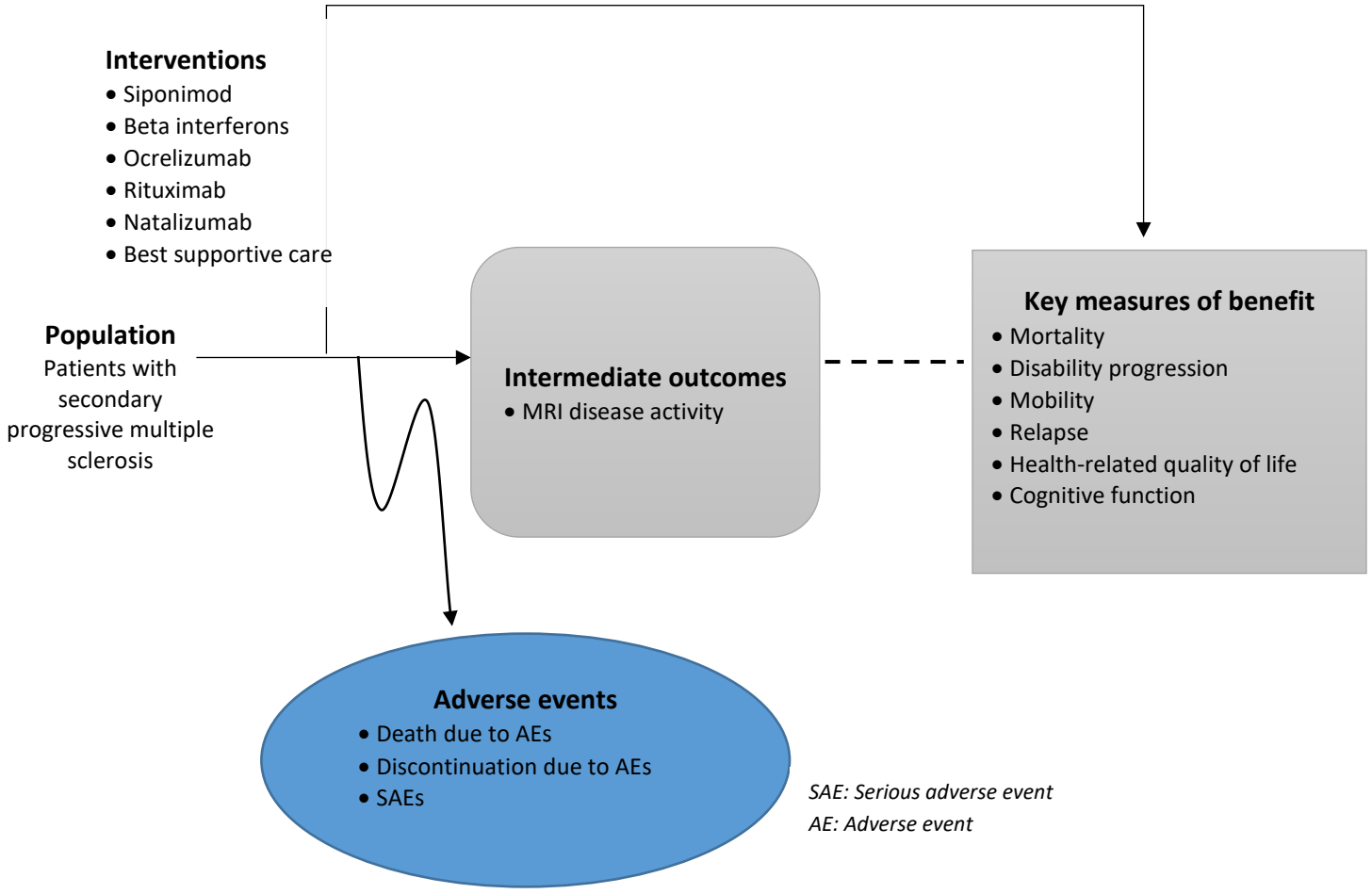
The proposed scope for this assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence will be abstracted from randomized controlled trials as well as high-quality systematic reviews; high-quality comparative 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 https://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/).

All relevant evidence will be synthesized qualitatively. Wherever possible, we will seek out head-to-head studies of the interventions and comparators of interest. Data permitting, we will also consider 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 finalized scope in a research protocol published on the Open Science Framework website (https://osf.io/7awvd/).

Analytic Framework

The general analytic framework for assessment of siponimod for secondary progressive multiple sclerosis is depicted in Figure 1.

Figure 1. Analytic Framework: Siponimod for Secondary Progressive Multiple Sclerosis



The diagram begins with the population of interest on the left. Actions, such as treatment, are depicted with solid arrows which link the population to outcomes. For example, a treatment may be associated with specific health outcomes. Outcomes are listed in the shaded boxes; those within the rounded boxes are intermediate outcomes (e.g., MRI disease activity), and those within the squared-off boxes are key measures of benefit (e.g., disability progression). The key measures of benefit are linked to intermediate outcomes via a dashed line, as the relationship between these two types of outcomes may not always be validated. Curved arrows lead to the adverse events of treatment which are listed within the blue ellipse.[11]

Populations

The population of focus for this review is adults ages 18 years and over with 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. Nevertheless, regulatory agencies and

clinical trial eligibility criteria tend to dichotomize MS into relapsing and progressive phenotypes. If data permit, we will examine heterogeneity of treatment effect across patient subgroups stratified by age, disease duration, disease activity, relapse history, and level of disability.

Interventions

The intervention of interest for this review is the selective sphingosine 1-phosphate (S1P) receptor modulator siponimod (Novartis).

Comparators

Comparators of interest were determined with input from patient organizations, clinicians, and manufacturers. The comparators of focus for this review represent medications that have shown some efficacy in progressive MS and are most used in practice, irrespective of whether they have FDA indications for SPMS.

- Beta interferons (interferon β-1a and interferon β-1b)
- Ocrelizumab
- Rituximab
- Natalizumab
- Best supportive care

Although mitoxantrone is FDA-approved for SPMS, several stakeholders advised us that this treatment is not commonly used due to toxicity concerns. As such, it will not be included in our review.

Outcomes

The outcomes of interest are described in Table 1 below.

Table 1. Outcomes and Harms

Outcomes	Harms
Mortality	Adverse events associated with death
Disability progression	Serious adverse events
Mobility	Adverse events leading to discontinuation
MRI disease activity	Cardiac toxicity
Relapse	Infections, including progressive multifocal leukoencephalopathy
Health-related quality of life and the symptoms that affect quality of life (e.g. fatigue)	Other adverse events related to S1P- receptor modulators
Cognitive function	
Healthcare utilization	
Productivity	
Caregiver burden	

Timing

Evidence on intervention effectiveness and harms will be derived from studies of at least three months duration.

Settings

All relevant settings will be considered, including inpatient, clinic, and outpatient settings.

Potential Other Benefits and Contextual Considerations

Our reviews seek to provide information on potential other benefits 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 elements are listed in the table below.

Table 2. Potential Other Benefits and Contextual Considerations

Potential Other Benefits
This intervention offers reduced complexity that will significantly improve patient outcomes.
This intervention will reduce important health disparities across racial, ethnic, gender, socio-economic, or regional categories.
This intervention will significantly reduce caregiver or broader family burden.
This intervention offers a novel mechanism of action or approach that will allow successful treatment of many patients for whom other available treatments have failed.
This intervention will have a significant impact on improving return to work and/or overall productivity.
Other important benefits or disadvantages that should have an important role in judgments of the value of this intervention.
Potential Other Contextual Considerations
This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.
This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.
This intervention is the first to offer any improvement for patients with this condition.
Compared to "the comparator," there is significant uncertainty about the long-term risk of serious side effects of this intervention.
Compared to "the comparator," there is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.
There are additional contextual considerations that should have an important role in judgments of the value of this intervention.

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

Scope of Comparative Value Analyses

As a complement to the evidence review, we will develop a simulation model to assess the lifetime cost-effectiveness of the treatment of interest, Siponimod, relative to relevant comparator treatments. The model structure will be based in part on a literature review of prior published models of progressive multiple sclerosis including the model developed by the University of Washington for the previous ICER review of RRMS and PPMS.[12-14] The base case analysis will take a health-system perspective (i.e., focus on direct medical care costs only). Data permitting, productivity losses will be considered in a separate analysis. The target population will consist of patients newly diagnosed with SPMS. The model will likely consist of health states based on EDSS levels and an absorbing death state. A cohort of patients will transition between states during predetermined yearly cycles over a lifetime time horizon, modeling patients from treatment initiation until death. In addition, cost-effectiveness may be estimated for shorter time horizons (e.g., five years) if deemed relevant.

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. Should data permit, findings from a network meta-analysis may be used to estimate treatment effectiveness.

Health outcomes and costs will be dependent on time spent in each health state, clinical events, adverse events (AEs), and direct medical costs. The health outcome of each intervention will be evaluated in terms of total life-years and quality-adjusted life years (QALYs) gained. 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, long-term care, and serious adverse events. In addition, productivity losses will be included in a separate analysis if 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 and cost per life-year gained. Subgroup analyses will be conducted if adequate data are available.

In separate analyses, we will explore the potential health system budgetary impact of treatment over a five-year time horizon, utilizing published or otherwise publicly-available information on the potential population eligible for treatment and results from the simulation 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 at: http://icer-review.org/wp-content/uploads/2018/05/ICER-value-framework-v1-21-18.pdf.

Identification of Low-Value Services

As described in its Final Value Assessment Framework for 2017-2019, ICER will now include 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 https://icer-review.org/material/final-vaf-2017-2019/). These services are ones that would not be directly affected by siponimod (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 secondary progressive multiple sclerosis 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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