Oral and Monoclonal Antibody Treatments for Relapsing Forms of Multiple Sclerosis: Effectiveness and Value

Draft Evidence Report

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The funding for this report comes from government grants and non-profit foundations, with the largest single funder being the Arnold Ventures. No funding for this work comes from health insurers, pharmacy benefit managers, or life science companies. ICER receives approximately 24% 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 Genentech, Novartis, and 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/.

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In the development of this Report, ICER's researchers consulted with several clinical experts, patients, manufacturers, and other stakeholders. The following experts provided input that helped guide the ICER team as we shaped our scope and Report. It is possible that expert reviewers may not have had the opportunity to review all portions of this draft Report. None of these individuals is responsible for the final contents of this report, nor should it be assumed that they support any part of it. The Report should be viewed as attributable solely to the ICER team and its affiliated researchers.

For a complete list of stakeholders from whom we requested input, please visit: https://icer.org/wp-content/uploads/2022/04/ICER_MS_Stakeholder-List_042122.pdf.

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Supplemental Materials

List of Acronyms and Abbreviations Used in this Report

CDP	Confirmed disability progression
CI	Confidence interval
DMT	Disease-modifying therapy
EDSS	Expanded Disability Status Scale
EQ-5D	EuroQol Five Dimensions Questionnaire
evLY	Equal-value life year
FDA	Food and Drug Administration
HR	Hazard ratio
ICER	Institute for Clinical and Economic Review
IV	Intravenous
MS	Multiple sclerosis
MRI	Magnetic resonance imaging
MSFC	Multiple Sclerosis Functional Composite
NMA	Network meta-analysis
NR	Not reported
PDUFA	Prescription Drug User Fee Act
PICOTS	Population, Intervention, Comparator, Outcomes, Timing, Setting
PPMS	Primary-progressive multiple sclerosis
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QALY	Quality-adjusted life year
RCT	Randomized controlled trial
RRMS	Relapsing-remitting multiple sclerosis
RR	Rate ratio or risk ratio
SPMS	Secondary-progressive multiple sclerosis
US	United States

Executive Summary

Multiple sclerosis (MS) is a chronic autoimmune disorder of the central nervous system affecting almost one million Americans, with women affected almost three times more than men. It is characterized by an inflammatory cascade of demyelination and axonal loss, which results in neurologic damage and causes symptoms such as weakness, fatigue, vision changes, pain, and balance problems. The median time for the need of a walking aid is approximately 20 years in untreated people with MS.[1] Since symptoms of MS most commonly appear in the third decade of life and treatment may last for decades, MS has a high economic burden, estimated in 2019 to be $85 billion, which is accounted for by $63.3 billion in direct medical costs and $22.1 billion in indirect and nonmedical costs.[2] Access and cost of medication were mentioned as barriers to treatment by people with MS.

Treatment of MS is focused on preventing relapses, disease progression, worsening of disability, and management of symptoms affecting daily life. Patients, clinicians, and patient groups identified prevention or slowing of disability as the most important outcome. Disease modifying therapies (DMTs) have become standard of care for patients with relapsing-remitting MS (RRMS), which accounts for 85% of cases, and treatment is generally long term if not lifelong. Several classes of oral medications have been developed, including sphingosine 1-phosphate (S1P) receptor modulators (fingolimod [Gilenya®], ozanimod [Zeposia®], siponimod [Mayzent®], ponesimod [Ponvory®]), fumarates (dimethyl fumarate [Tecfidera®], monomethyl fumarate [Bafiertam®], diroximel fumarate [Vumerity®]), and teriflunomide [Aubagio®], all of which modulate the immune system in various ways. Monoclonal antibodies (ocrelizumab [Ocrevus®], ofatumumab [Kesimpta®], rituximab [Rituxan®], natalizumab [Tysabri®]) reduce inflammation and prevent the formation of central nervous system lesions. Ublituximab is a new monoclonal antibody currently under review at the United States (US) Food and Drug Administration (FDA).

Due to significant disease heterogeneity, current clinical practice guidelines recommend considering the risks and benefits of each treatment strategy on a patient-by-patient basis.[3] As a result, the choice of initial therapy varies, with some clinicians and people with MS opting to begin treatment with a lower efficacy DMT and escalating as needed; other clinicians and people with MS opt to begin treatment with more aggressive therapy such as monoclonal antibodies.[4]

We conducted a review of the clinical effectiveness of oral and monoclonal antibody treatments that are considered first-line DMTs for the treatment of relapsing forms of MS. Because there were very few head-to-head trials between our treatments of interest, we conducted indirect comparisons via a network meta-analysis (NMA). We focused on ublituximab as a key intervention because of its status as the newest DMT awaiting a regulatory decision by the FDA.

We found that all DMTs decreased the annualized relapse rate (ARR) compared with placebo. Ublituximab showed comparable reduction in ARR versus other monoclonal antibodies and a relatively greater reduction compared with oral DMTs. For the outcome of confirmed disability progression (CDP), there was more uncertainty in the results. Changes to CDP at six months were not statistically different for ublituximab compared with other monoclonal antibodies. However, overall, the monoclonal antibodies had numerically greater effects on CDP than oral DMTs. We had direct head-to-head randomized controlled trial (RCT) evidence for ublituximab compared with teriflunomide, which demonstrated a significant reduction in ARR and magnetic resonance imaging (MRI) lesions in the ublituximab group compared with teriflunomide.

Limitations to our conclusions about the efficacy of first-line oral and monoclonal antibody DMTs in treating MS include changing diagnostic criteria for MS over time such that trial populations may not be entirely comparable and uncertainty in the data for CDP outcome that limits how informative this outcome is in distinguishing between DMTs, despite its importance to patients. Finally, the data on ublituximab is limited to short-term follow-up from clinical trials; given that MS treatment is expected to span decades, long-term data on the efficacy and safety are needed to fully compare with older DMTs.

Based on the results of the NMA and accounting for the limitations in the evidence base, we assessed the clinical effectiveness of ublituximab compared with other monoclonal antibodies and oral DMTs for first-line treatment of relapsing forms of MS, and no DMT, as represented by the placebo arm of clinical trials. We found insufficient evidence to differentiate the net health benefit of ublituximab compared with other monoclonal antibodies. Compared with oral DMTs, we had moderate certainty that ublituximab is comparable or better in terms of reductions in ARR and CDP. For teriflunomide, based on head-to-head trial data, we had high certainty that ublituximab has a small net health benefit over teriflunomide. We did not have sufficient evidence to rate ublituximab versus siponimod due to differences in trial populations. Finally, ublituximab showed superior net health benefit compared with no DMT.

Table ES1. Evidence Ratings

Treatment	Comparator	Evidence Rating
Adults with RRMS		
Ublituximab	Natalizumab	I: Insufficient
	Ofatumumab	I: Insufficient
	Ocrelizumab	I: Insufficient
	Rituximab	I: Insufficient
	Fumarate class (dimethyl, diroximel, monomethyl)	C++: Comparable or better
	Fingolimod	C++: Comparable or better
	Ozanimod	C++: Comparable or better
	Ponesimod	C++: Comparable or better
	Siponimod	I: Insufficient
	Teriflunomide	B: Incremental
	Placebo/no DMT	A: Superior

DMT: disease-modifying therapy, RRMS: relapsing-remitting multiple sclerosis

To estimate the cost effectiveness of each monoclonal antibody treatment with sufficient comparative clinical effectiveness evidence, we used a decision analytic model with model inputs that included relative treatment effectiveness from our NMA and other sources. The primary cost-effectiveness analyses compared each monoclonal antibody to the market-leading oral treatment and generically available dimethyl fumarate. Table ES2 presents the incremental cost-effectiveness ratios over a lifetime time horizon from the health system perspective. All treatments had base-case results greater than $150,000 per quality-adjusted life year (QALY) gained and equal-value life year (evLY) gained. Cost effectiveness was driven by each treatments' effect on Expanded Disability Status Scale (EDSS) progression and annualized DMT net price differences between the monoclonal antibodies and generic dimethyl fumarate. Limitations of the EDSS as well as the aforementioned recommendations related to the NMA should be considered when interpreting the cost-effectiveness estimates.

Table ES2. Incremental Cost-Effectiveness Ratios for the Base Case versus Dimethyl Fumarate

Treatment	Cost per Additional Year without Ambulatory Restrictions*	Cost per Additional Year without a Wheelchair†	Cost per QALY Gained	Cost per Life Year Gained	Cost per evLY Gained
Ublituximab‡	$400,000	$446,000	$608,000	$1,600,000	$543,000
Natalizumab	$528,000	$612,000	$820,000	$2,100,000	$742,000
Ofatumumab	$539,000	$599,000	$815,000	$2,100,000	$727,000
Ocrelizumab	$201,000	$240,000	$315,000	$829,000	$288,000

EDSS: Expanded Disability Status Scale, evLY: equal-value life year, QALY: quality-adjusted life year

*As measured by time in EDSS health states less than 5.

†As measured by time in EDSS health states less than 7.

‡Assuming a placeholder price for ublituximab equivalent to the net price of ocrelizumab.

In summary, we found that oral and monoclonal antibody DMTs used for first-line treatment for relapsing forms of MS were effective in reducing relapses; we are less certain about the impact of these DMTs on confirmed disability progression. We found insufficient evidence to assess whether there were clinically meaningful differences in efficacy or safety for ublituximab compared with other monoclonal antibodies. Ublituximab appeared to be more effective for reducing relapses and possibly slowing disability progression compared with oral therapies and no DMT. At its placeholder price, ublituximab did not meet typical thresholds for cost effectiveness when compared to the market-leading oral, in large part due to differences in net price. These findings should be interpreted in the context of the aforementioned data-related uncertainties and limitations.

1. Background

Multiple sclerosis (MS) is a chronic, autoimmune disorder of the central nervous system characterized by an inflammatory cascade of demyelination and axonal loss, which results in neurologic damage. The exact cause of MS is unknown, but genetic, environmental, and lifestyle factors may contribute to the development of the disease, and recent evidence suggests a link with Epstein-Barr virus infection.[5,6] MS affects more than 900,000 people in the United States (US).[7] Women are affected almost three times more than men, and there are racial/ethnic differences in MS prevalence.[8] In the US, African Americans are at higher risk of both developing MS and having poorer outcomes compared with Whites Americans.[8,9] The total annual economic burden of MS in the US is estimated to be $85 billion, with direct medical costs accounting for more than $63 billion.[2]

Symptoms of MS most commonly appear in the third decade of life, with symptoms correlating to areas of demyelination in the central nervous system. For example, demyelination of the optic nerve results in vision changes and eye pain (optic neuritis) and lesions in the spinal cord can lead to weakness, impaired sensation, and ataxia (partial myelitis).[5] Fatigue, pain, spasticity in muscles, balance problems, bowel and bladder dysfunction, insomnia, depression, and impaired memory and concentration are also possible symptoms.[10] Diagnosis of MS is based on the 2017 Revised McDonald Criteria, which involves a combination of clinical findings, imaging, and laboratory data, and requires the demonstration of MS disease characteristics in space (i.e., presence of lesions in distinct locations in the central nervous system) and time (development of new lesions over time).[11]

Relapsing forms of MS are the most common form of MS and include relapsing-remitting MS (RRMS), a subgroup secondary-progressive MS (SPMS), smaller subgroup of primary-progressive MS (PPMS) and, by older diagnostic criteria, clinically isolated syndrome. Within relapsing forms of MS, RRMS—characterized by periodic relapses with complete or near recovery—is most common, affecting 85% of people. Disability accumulates over time with the median time for the need of a walking aid being approximately 20 years in untreated people with MS.[1] Black Americans with MS may have poorer disease outcomes, possibly due to both differences in disease characteristics and disparities in access to treatment.[12,13] Additionally, approximately 20% of people with RRMS may develop progressive neurological decline and transition to SPMS around 15 to 20 years after diagnosis.[14] Life expectancy in people with MS is approximately seven years shorter than average, with people with RRMS living longer than those with other forms of MS.[15]

Treatment of MS is focused on preventing relapses, disease progression, and worsening of disability. Comprehensive treatment of MS includes both supportive treatment, including symptom control, psychological support, management of comorbidities, lifestyle interventions, and rehabilitation, and disease-modifying therapies (DMTs) that reduce neuroinflammation. Diagnosis and management of comorbidities such as depression is particularly important, as comorbidities can impact disease outcomes.[16] Additionally, medications to manage symptoms such as bladder dysfunction, pain, and spasticity are often required in addition to DMTs to improve quality of life.

DMTs have become the standard of care for patients with MS. There are multiple classes of DMTs with a variety of delivery mechanisms, efficacy, and risk of adverse events. The earliest DMTs approved for the treatment of MS were injectable immunomodulating medications such as interferons and glatiramer acetate (Copaxone®). Subsequently, several classes of oral medications have been developed, including sphingosine 1-phosphate (S1P) receptor modulators (fingolimod [Gilenya®], ozanimod [Zeposia®], siponimod [Mayzent®], ponesimod [Ponvory®]), fumarates (dimethyl fumarate [Tecfidera®], monomethyl fumarate [Bafiertam®], diroximel fumarate [Vumerity®]), and teriflunomide [Aubagio®], all of which also modulate the immune system in various ways. The newest class of DMTs are intravenous or subcutaneous monoclonal antibodies. Monoclonal antibodies reduce inflammation and prevent the formation of central nervous system lesions, either by targeting the CD20 receptor on lymphocytes (ocrelizumab [Ocrevus®], ofatumumab [Kesimpta®], rituximab [Rituxan®]) or binding to $\alpha_4\beta_1$-integrin (natalizumab [Tysabri®]). Use of other oral and monoclonal antibodies such as cladribine (Mavenclad®) and alemtuzumab (Lemtrada®) is limited due to potential serious side effects and thus these are considered second-line therapies.

Choice of initial therapy varies, with some clinicians and people with MS opting to begin treatment with medications that have lower efficacy and escalating as needed; other clinicians and people with MS opt to start treatment with more aggressive therapies such as monoclonal antibodies, which are more effective at suppressing disease activity but may carry a higher risk of serious adverse events.[4] Treatment is generally lifelong, though the discontinuation of DMTs has been proposed in older, stable people with MS with non-active disease and low risk of progression,[17] and the safety of such strategies is the subject of ongoing clinical trials (e.g., DISCOMS [NCT03073603], DOT-MS [NCT04260711], STOP-I-SEP [NCT03653273]).

In addition to DMTs already approved by the Food and Drug Administration (FDA), there are additional agents in development, including Bruton's tyrosine kinase inhibitors. Furthermore, for some people, hematopoietic stem cell transplantation has shown promise as a treatment for MS, though the ideal treatment population and optimal timing for hematopoietic stem cell transplantation have not yet been established.[18]

In this class review of DMTs for MS, we will evaluate the clinical and cost effectiveness of oral medications and monoclonal antibodies that are considered first-line options for treatment of MS (Table 1.1). While injectable medications are still commonly used in practice, they were a focus of the 2017 ICER Report for MS therapies and because no new evidence for their effectiveness has emerged, we will not re-review those therapies. Additionally, we will frame most comparative clinical effectiveness questions on ublituximab versus alternatives. Ublituximab (TG Therapeutics) is a new, intravenously administered anti-CD20 monoclonal antibody, which is currently undergoing

FDA review, with an expected Prescription Drug User Fee Act (PDUFA) date of December 28, 2022. The cost-effectiveness analyses will focus on comparisons of the monoclonal antibodies, including ublituximab, to the market-leading oral, generically available dimethyl fumarate.

Table 1.1. Interventions of Interest

Intervention Brand Name (Generic Name)	Mechanism of Action	Delivery Route	Prescribing Information (Maintenance Dose*)
Monoclonal Antibodies			
Tysabri® (Natalizumab)	$\alpha_4\beta_1$-integrin antagonist	IV	300 mg every 4 or 6 weeks
Kesimpta® (Ofatumumab)	Anti-CD20	Subcutaneous	20 mg once monthly
Ocrevus® (Ocrelizumab)	Anti-CD20	IV	600 mg every 6 months
Rituxan® (Rituximab)	Anti-CD20	IV	500 mg every 6 months
Ublituximab	Anti-CD20	IV	450 mg every 6 months
Oral Therapies			
Tecfidera® (Dimethyl Fumarate)	Anti-oxidative	Oral	240 mg twice daily
Vumerity® (Diroximel Fumarate)	Anti-oxidative	Oral	462 mg twice daily
Bafiertam® (Monomethyl Fumarate)	Anti-oxidative	Oral	190 mg twice daily
Gilenya® (Fingolimod)	S1P receptor modulator	Oral	0.5 mg once daily
Zeposia® (Ozanimod)	S1P receptor modulator	Oral	0.92 mg once daily
Ponvory® (Ponesimod)	S1P receptor modulator	Oral	20 mg once daily
Mayzent® (Siponimod)	S1P receptor modulator	Oral	2 mg once daily
Aubagio® (Teriflunomide)	Dihydro-orotate dehydrogenase inhibitor	Oral	7 mg or 14 mg daily

IV: intravenous, mg: milligram, S1P: sphingosine-1-phosphate

*Dose listed is the maintenance dose. Some treatments require induction doses.

2. Patient and Caregiver Perspectives

To gain insight into living with MS, we interviewed eight patients from a variety of ages, backgrounds, and disease stages, as well as patient advocates. We also discussed treatment of people with MS with four neurologists with expertise in treating MS, one payer, and six manufacturers. The following section represents a summary of our discussions.

Because the onset of MS is early in life, the disease has impact not only on the physical and emotional health of people with MS, but can also affect family planning, work and educational productivity, and social and leisure activities. One person described living with MS as a “ball and chain,” due to managing the daily symptoms that may or may not be apparent to others and also because of the need to work to maintain health insurance and have a budget for high treatment and medical costs. Although ambulation is an important marker of disability, other symptoms such as pain, fatigue, numbness, urinary incontinence, and cognitive difficulties have a large effect on daily functioning. Furthermore, these symptoms are present even when people with MS are not having a relapse and without new lesions appearing on magnetic resonance imaging (MRI). Therefore, even when their disease is deemed “stable” by those criteria, their daily life is still greatly affected. Thus, people with MS would like to see greater use of new imaging technologies and assessments that may be more sensitive to changes in the central nervous system associated with symptoms outside of relapses.

The primary goal for people with MS is to remain independent, maintaining the ability to continue working and performing normal activities. Thus, early diagnosis and comprehensive treatment are critical to minimizing the impact of MS on a person’s life. Disease-modifying therapies are central to treatment. Because there are a variety of DMTs available with differing efficacy, tolerability, mode of delivery, and cost, shared decision-making is an important part of choosing the appropriate DMT for each patient. For example, some DMTs are delivered by daily injection, and for patients on those medications for many years, “needle fatigue” (running out of suitable places to inject medication) can cause patients to skip doses or stop medication, which may lead to relapse. For people with MS of childbearing age, the impact of therapy on family planning is also an important consideration. Other factors associated with treatment—e.g., site of treatment, time needed off work and travel distance for infusions, response to COVID-19 vaccines—were also mentioned as important considerations in the decision-making process. Insurance coverage may also influence choice of DMT, as people with MS described that the burden of prior authorization and step therapy may delay or restrict access to effective treatments. It is important to note that DMTs do not necessarily have an impact on all patient-important outcomes (e.g., a DMT might have an impact on relapses but not necessarily on bladder dysfunction) and thus additional treatments besides DMTs may be necessary for comprehensive symptom control. Finally, at later stages of the disease, particularly after people with MS lose the ability to ambulate, there is fear that treatment and care may not be as aggressive due to the focus on prevention of mobility loss. "I'm afraid of being forgotten. I'm still here, I still want to be relevant," was how one person with MS who uses a wheelchair described the fear.

The economic burden of MS is enormous, with a total estimated annual burden of $85.4 billion dollars in the US, including direct medical costs and nonmedical costs.[2] Direct medical costs are estimated to be around $63 billion, with medication (primarily DMTs) accounting for two-thirds of the cost. We heard from people with MS that paying for medication can be very challenging. For example, Medicare patients are not eligible for manufacturer coupon programs, and thus have few ways of reducing their financial burden. For the commercially insured, out-of-pocket costs may be counterintuitively *higher* for generic orals if they are included within a specialty tier with high co-insurance or co-pays and no manufacturer coupon assistance. Furthermore, those who are uninsured or underinsured may face a choice between paying for medication or for other basic necessities. Indirect costs of MS are estimated to be more than $20 billion, and include losses due to leaving the workforce prematurely, absenteeism, presenteeism, and lost social productivity.[2] Costs were higher for people with MS younger than 65 years old compared with those over 65. MS can also have an impact on caregivers, particularly with progression of patient disability, and caregivers can experience high levels of distress and decreased quality of life.[19]

Clinical experts agreed that the main goal of treatment for MS is to prevent or delay progression of disability and noted that the choice of starting with a moderate or high efficacy DMT is dependent on patient characteristics as well as patient and clinician preferences. Clinical trials such as TREAT-MS (NCT03500328) and DELIVER-MS (NCT03535298) are currently in progress to ascertain the best treatment strategies for MS. Additionally, clinical experts mentioned that there is both under- and over-treatment of the disease. For example, some patients would benefit from treatment with more aggressive therapies (i.e., under treatment); on other hand, older patients with non-MS-related life-limiting conditions may continue to be treated despite not having active disease (i.e., over treatment). Furthermore, clinicians advised that the Expanded Disability Status Scale (EDSS), the current standard for measuring disability in clinical trials, may not be optimal for measuring all aspects of disability and quality of life for people with MS, particularly related to cognitive function. Finally, patient groups identified that there is substantial practice variation in treatment of MS, particularly based on whether the treating physician is a MS specialist or general neurologist.

Manufacturers noted some challenges in interpreting clinical trials, including the changing criteria for diagnosis and the shifting standard of care over time as well as the difficulty in identifying people who have transitioned from RRMS to SPMS. Additionally, manufacturers discussed the limitations of trial outcomes such as the EDSS in characterizing the impact of treatments for MS. Finally, manufacturers cautioned against the inclusion of DMTs that do not have an FDA-approved indication for MS, as evidence of efficacy for such agents in the treatment of MS may be limited.

3. Comparative Clinical Effectiveness

3.1. Methods Overview

Procedures for the systematic literature review are described in Supplement D1. A research protocol is published on Open Science Framework and is registered with PROSPERO (CRD42022339608).

Scope of Review

We reviewed the clinical effectiveness of 13 DMTs for the treatment of relapsing forms of MS. We evaluated the comparative clinical effectiveness of the latest entrant to the market, ublituximab, against an oral agent, teriflunomide 14 mg, for which there exists two head-to-head trials, and against members of the monoclonal antibody class (natalizumab, ocrelizumab, ofatumumab, and rituximab) and other oral therapies considered to be first-line treatment (fumarates, fingolimod, siponimod, ozanimod, and ponesimod) through indirect comparisons. Additional within-group and between-group comparisons of clinical effectiveness were made among the monoclonal antibody and oral DMT classes through indirect comparisons.

We sought evidence on patient-important outcomes, including relapse, disease progression, and safety. The clinical effectiveness of the DMTs in this review was assessed across several subgroups of interest, such as race/ethnicity, age, and treatment naiveté. The full scope of this review is detailed in Supplement D1.

Evidence Base

In 2019, a statement by the FDA clarified that relapsing forms of MS include clinically isolated syndrome, RRMS, and active SPMS (see Supplement A1 for expanded definitions).[20,21] The evidence base for this review consists largely of trials in RRMS, which is the most common phenotype of the disease. A qualitative review of the clinical evidence in the SPMS population is outlined below in the Subgroup Analyses and Heterogeneity section.

Clinical Outcomes

Frequency of relapse and disability progression are commonly used endpoints in MS clinical trials. Relapses are typically reported as a mean annualized relapse rate (ARR), the average number of relapses in a treatment group within one year. Time to confirmed disability progression (CDP) is measured as a sustained increase on a patient's EDSS over three-month (CDP-3) and six-month intervals (CDP-6). Some variation in the definition of disability progression exists across trials in our evidence base and is outlined in Supplement A1.

In the 2017 ICER Report, we reported the challenges of comparing DMTs on MRI, quality of life, and other patient-centered outcomes due to incomplete reporting, differing intervals of follow-up, and the evolution of diagnostic tools across more than 30 years of MS trials. In this review, we have found a similar paucity of comparable high-quality data that precluded us from performing network meta-analyses (NMA) on outcomes beyond relapses and disability progression.

Direct Evidence: Ublituximab versus Teriflunomide

Our search identified two identical randomized controlled trials (RCTs), ULTIMATE I and II, that provide direct evidence on the efficacy, safety, and tolerability of ublituximab versus teriflunomide 14 mg. In ULTIMATE I and II, patients were randomized to ublituximab plus oral placebo or oral teriflunomide plus intravenous placebo for a median follow-up of 95 weeks. The primary study outcome was ARR. There were several secondary and tertiary outcomes related to the measurement of disability progression in the trials: CDP-3, CDP-6, confirmed disability improvement at three and six months (CDI-3 and CDI-6), change in the Multiple Sclerosis Functional Composite score (MSFC), and percent of patients with no evidence of disease activity. Full definitions on these outcomes can be found in Supplement A1. MRI outcomes (gadolinium enhancing lesions per T1-weighted MRI, new or enlarging hyperintense lesions per T2-weighted MRI, and change in brain volume) were explored as secondary endpoints. Serious adverse events, discontinuation due to adverse events, and commonly reported adverse events were explored to assess the safety profile of ublituximab.

Indirect Evidence: Ublituximab versus Other DMTs and Placebo

Direct evidence of the comparative efficacy of ublituximab versus other DMTs in our review was unavailable. As such, we conducted three NMAs for an indirect comparison of ublituximab versus other DMTs and placebo on the outcomes of mean ARR and time to CDP-3 and CDP-6.

There were 23 RCTs that met our inclusion criteria for the NMAs, and they were allocated as follows: ARR (20 RCTs and 40 study arms), CDP-3 (18 RCTs and 32 study arms), and CDP-6 (18 RCTs and 32 study arms). The study design and baseline characteristics of the included RCTs across the networks are detailed below in Table 3.1, with additional study design and baseline characteristics presented in Supplement Tables D8-9.

We made several decisions regarding the design of the NMAs. All trials in the network met our inclusion criteria of a minimum of one year follow up (range: 48 to 108 weeks). We accounted for variation in follow-up using person-years (ARR) and hazard ratios (HRs) (time to CDP) in our NMA inputs. Several DMTs in our NMAs had efficacy data for multiple doses; we selected study arms that best corresponded to each drug's approved FDA label. Teriflunomide has two approved doses, 7 mg and 14 mg; we selected the 14 mg dose as the more efficacious of the two using previous NMA results. Rituximab trials did not report HRs (and associated 95% confidence intervals [CIs]) needed for the CDP-3 and CDP-6 NMAs and thus were excluded from those two networks. Diroximel fumarate and monomethyl fumarate are active metabolites of dimethyl fumarate. Both agents were approved for treatment of relapsing forms of MS based on evidence of bioequivalence to dimethyl fumarate and thus they are not included in the NMAs due to assumed efficacy equivalence.

An additional two trials, PRISMS (interferon beta-1a vs. placebo) and BRAVO (using the interferon beta-1a vs. placebo arm), were included in the CDP-3 and CDP-6 NMAs as linkages to connect ocrelizumab and ozanimod to the network.[22,23] One more trial, EVIDENCE (interferon beta-1a 44 mcg vs. 30 mcg), was included into the CDP networks as a sensitivity analysis.[24] Baseline characteristics of these trials were deemed to be comparable to the rest of the trials in the network (see Supplement Table D9). Additional details on the methodological design, inputs, and outputs of our NMAs can be found in Supplement D2.

Indirect Evidence: Monoclonal Antibodies versus Oral Therapies

Using results from the three NMAs, we sought to identify the most efficacious agents within the monoclonal antibody and oral DMT classes as well as evidence of any comparative efficacy of the monoclonal antibody class over oral DMTs.

Table 3.1. Overview of Oral and Monoclonal Antibody Treatments for Relapsing Forms of MS

Trial	Arm	Arm Size	Trial Duration, Weeks	Age, Mean (SD)	Female, %	White, %	RRMS, %	Baseline EDSS Score, Mean (SD)	Relapses in Previous 12 Months, Mean (SD)	No Prior DMT Use, %
Monoclonal Antibodies										
AFFIRM	Natalizumab	627	104	35.6 (8.5)	61.5	96.2	100	2.3 (1.2)	1.53 (0.9)	NR
	Placebo	315		36.7 (7.8)	62.5	94.0	100	2.3 (1.2)	1.5 (0.8)	NR
OPERA I	Ocrelizumab	410	96	37.1 (9.3)	65.9	NR	NR	2.9 (1.2)	1.31 (0.7)	73.8
	IFN β-1a SC 44 µg	411		36.9 (9.3)	66.2	NR	NR	2.8 (1.3)	1.33 (0.6)	71.4
OPERA II	Ocrelizumab	417	96	37.2 (9.1)	65.0	NR	NR	2.8 (1.3)	1.32 (0.7)	72.9
	IFN β-1a SC 44 µg	418		37.4 (9.0)	67.0	NR	NR	2.8 (1.4)	1.34 (0.7)	75.3
ASCLEPIOS I	Ofatumumab	465	120	38.9 (8.8)	68.4	NR	92.4	2.97 (1.4)	1.2 (0.6)	41.1
	Teriflunomide 14 mg	462		37.8 (9.0)	68.6	NR	93.9	2.94 (1.4)	1.3 (0.7)	39.4
ASCLEPIOS II	Ofatumumab	481	120	38.0 (9.3)	66.3	NR	94	2.9 (1.34)	1.3 (0.7)	40.5
	Teriflunomide 14 mg	474		38.2 (9.5)	67.3	NR	94.9	2.9 (1.37)	1.3 (0.7)	38.2
HERMES	Rituximab	69	48	39.6 (8.7)	75.4	NR	100	2.5 (0-5)*	1 (0-4)*	63.8
	Placebo	35		41.5 (8.5)	82.9	NR	100	2.5 (0-5)*	1 (0-5)*	60.0
RIFUND-MS	Rituximab	98	104	33.5 (7.7)	68.0	NR	98	1.6 (1.2)	NR	98.0
	Dimethyl fumarate	99		33.4 (7.7)	65.0	NR	97	1.7 (1.0)	NR	95.0
ULTIMATE I	Ublituximab	271	96	36.2 (8.2)	61.3	97.4	97.4	2.96 (1.2)	1.3 (0.7)	59.8
	Teriflunomide 14 mg	274		37.0 (9.6)	65.3	97.1	98.5	2.9 (1.2)	1.4 (0.7)	59.1
ULTIMATE II	Ublituximab	272	96	34.5 (8.8)	65.4	98.9	98.5	2.8 (1.3)	1.3 (0.7)	50.7
	Teriflunomide 14 mg	272		36.2 (9.0)	64.7	98.5	98.2	2.96 (1.2)	1.2 (0.7)	57.0
Oral Therapies										
CONFIRM	Dimethyl fumarate BID	359	96	37.8 (9.4)	68.2	84.7	100	2.6 (1.2)	1.3 (0.6)	71.9
	Placebo	363		36.9 (9.2)	69.1	84.0	100	2.6 (1.2)	1.4 (0.8)	69.4
DEFINE	Dimethyl fumarate BID	410	104	38.1 (9.1)	72.2	78.3	100	2.4 (1.3)	1.3 (0.7)	60.5
	Placebo	408		38.5 (9.1)	75.0	77.9	100	2.5 (1.2)	1.3 (0.7)	57.8
FREEDOMS I	Fingolimod 0.5 mg	425	104	36.6 (8.8)	69.6	NR	100	2.1 (1.1)	1.5 (0.8)	57.4
	Placebo	418		37.2 (8.6)	71.3	NR	100	2.2 (1.2)	1.4 (0.7)	59.6
FREEDOMS II	Fingolimod 0.5 mg	358	104	40.6 (8.4)	76.8	NR	100	2.4 (1.3)	1.4 (0.9)	26.3
	Placebo	355		40.1 (8.4)	81.1	NR	100	2.4 (1.3)	1.5 (0.9)	27.0
TRANSFORMS	Fingolimod 0.5 mg	431	52	36.7 (8.8)	65.4	93.7	100	2.2 (1.3)	1.5 (1.2)	44.8
	IFN β-1a IM 30 µg	435		36.0 (8.3)	67.8	93.8	100	2.2 (1.2)	1.5 (0.8)	43.7

Trial	Arm	Arm Size	Trial Duration, Weeks	Age, Mean (SD)	Female, %	White, %	RRMS, %	Baseline EDSS Score, Mean (SD)	Relapses in Previous 12 Months, Mean (SD)	No Prior DMT Use, %
RADIANCE	IFN β-1a IM 30 µg	441	104	35.1 (9.1)	68.9	98.0	98	2.5 (1.2)	1.3 (0.6)	71.4
	Ozanimod 1 mg	433		36.0 (8.9)	67.2	98.8	98.2	2.6 (1.2)	1.3 (0.6)	71.6
SUNBEAM	IFN β-1a IM 30 µg	448	52	35.9 (9.1)	67.0	99.8	98.4	2.6 (1.1)	1.3 (0.6)	66.3
	Ozanimod 1 mg	447		34.8 (9.2)	63.3	99.8	98.0	2.6 (1.2)	1.3 (0.6)	71.4
OPTIMUM	Ponesimod 20 mg	567	108	36.7 (8.7)	64.0	97.2	97.4	2.6 (1.2)	1.2 (0.6)	62.4
	Teriflunomide 14 mg	566		36.8 (8.7)	65.7	97.7	97.5	2.6 (1.2)	1.3 (0.7)	62.7
TOWER	Placebo	389	~84†	38.1 (9.1)	70.2	81.7	97.4	2.7 (1.4)	1.4 (0.8)	65.3
	Teriflunomide 14 mg	372		38.2 (9.4)	69.4	84.1	98.4	2.7 (1.4)	1.4 (0.7)	66.1
TEMSO	Placebo	363	108	38.4 (9.0)	75.8	98.1	90.6	2.7 (1.3)	1.4 (0.7)	75.2
	Teriflunomide 14 mg	359		37.8 (8.2)	71.0	96.7	92.8	2.7 (1.2)	1.3 (0.7)	71.6
TENERE	IFN β-1a SC 44 µg	104	48	37.0 (10.6)	68.3	100	100	2.0 (1.2)	1.2 (1.0)	76.0
	Teriflunomide 14 mg	111		36.8 (10.3)	70.3	100	97.3	2.3 (1.4)	1.4 (0.8)	88.3

BID: two times daily, DMT: disease-modifying therapy, EDSS: expanded disability status scale, IFN β-1a: interferon beta-1a, mg: milligram, NR: not reported, RRMS: relapse-remitting multiple sclerosis, SC: subcutaneous, SD: standard deviation, µg: microgram

*Median (range).

†The TOWER trial ended 48 weeks after the last patient was randomized. Patients had a variable duration of treatment (range: 48 to 173 weeks); median treatment duration was ~84 weeks.

3.2. Results

Clinical Benefits

Direct Evidence: Ublituximab versus Teriflunomide

In the ULTIMATE I trial, patients receiving ublituximab had an ARR of 0.08 (95% CI: 0.04, 0.14) compared to 0.19 (95% CI: 0.12, 0.28) in the teriflunomide arm (rate ratio: 0.41; 95% CI: 0.27, 0.62; p<0.001).[25] Similar results were reported in the ULTIMATE II trial with an ARR of 0.09 (95% CI: 0.05, 0.17) in patients receiving ublituximab compared to 0.18 (95% CI: 0.11, 0.29) in patients receiving teriflunomide (rate ratio: 0.51; 95% CI: 0.33, 0.78; p=0.002).[25]

CDP at three months for both trials was numerically slightly greater in patients receiving teriflunomide (5.9%) compared to ublituximab (5.2%) (HR: 0.84; 95% CI: 0.5, 1.41; p=0.51). Similar results were seen at six months with 4.8% of patients receiving teriflunomide and 3.3% of patients receiving ublituximab with CDP (HR: 0.66; 95% CI: 0.36, 1.21). Additionally, in an exploratory endpoint, nearly double the patients in the ublituximab arm compared to the teriflunomide arm reported a confirmed lessening of disability (or disease improvement) at both month three (12.0% vs. 6.0%; HR: 2.16; 95% CI: 1.41, 3.31) and month six (9.6% vs. 5.1%; HR: 2.03; 95% CI: 1.27, 3.25). No evidence of disease activity from weeks 24 to 96 was reported more in the ublituximab arms of both the ULTIMATE I (44.6% vs. 15.0%) and ULTIMATE II trials (43.0% vs. 11.4%). None of the results for disease progression, disease improvement, and no evidence of disease activity was statistically significant but all trended towards greater benefit with ublituximab.

There was statistically significant improvement in the MSFC in patients receiving ublituximab versus teriflunomide from baseline to week 96 in ULTIMATE I (ublituximab mean change: 0.47; teriflunomide mean change: 0.27; p=0.04) and in ULTIMATE II (ublituximab mean change: 0.52; teriflunomide mean change: 0.28; p=0.01).[25,26]

The mean number of gadolinium-enhancing lesions per T1-weighted MRI was significantly lower in patients receiving ublituximab compared to teriflunomide in both the ULTIMATE I (rate ratio: 0.03; 95% CI: 0.02, 0.06, p<0.001) and ULTIMATE II trials (rate ratio: 0.04; 95% CI: 0.02, 0.06; p<0.001). Similar results were observed for the mean number of new or enlarging hyperintense lesions per T2-weighted MRI with significantly lower lesions in patients receiving ublituximab. The difference in percent change in brain volume was not significantly different between treatment groups.

Figure 3.1. Base-Case Forest Plot for DMTs versus Placebo for ARR

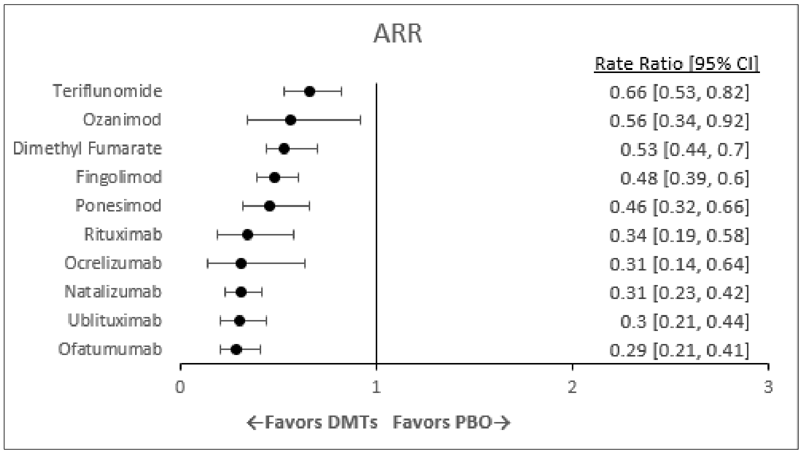


Figure 3.2. Base-Case Forest Plot for DMTs versus Placebo for Time to CDP-3

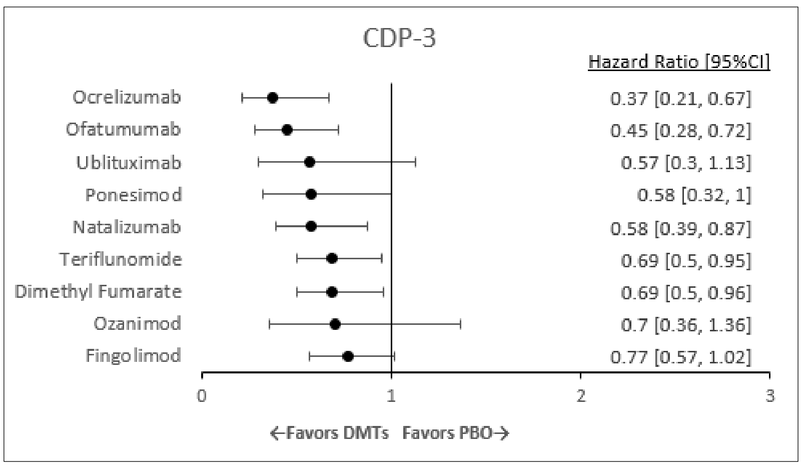
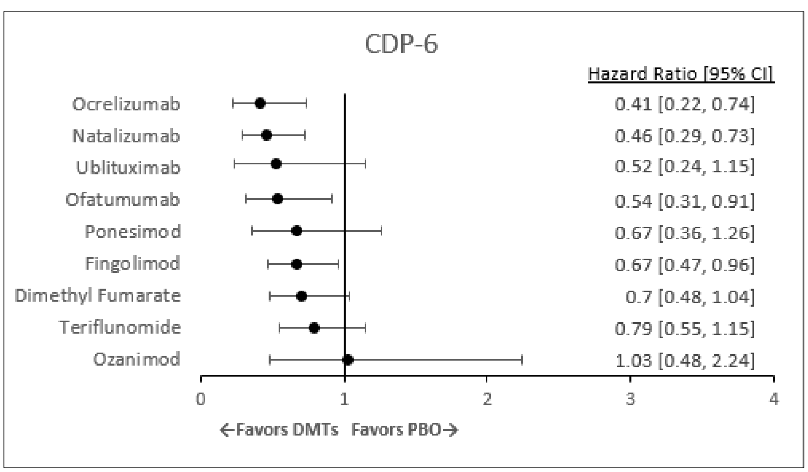


Figure 3.3. Base-Case Forest Plot for DMTs versus Placebo for Time to CDP-6



Indirect Evidence: Monoclonal Antibodies and Oral Therapies versus Placebo

Figures 3.1-3.3 provide point estimates of the relative effect of all DMTs versus placebo on the NMA outcomes of ARR and time to CDP-3 and CDP-6. A random-effects model was used for the ARR and CDP networks; results from a fixed-effects model (CDP-3 and 6) and sensitivity analyses (CDP-6) are presented in Supplement Figures D8 and D9. A comparison of this review's NMA outcomes against previously published NMAs is provided in Supplement D5.

Relapse Rate

All five agents within the monoclonal antibody class (ofatumumab, ublituximab, natalizumab, ocrelizumab, and rituximab) had a similar magnitude of benefit versus placebo, with an estimated reduction in ARR by 70%. In the 2017 MS Report, the point estimate for rituximab versus placebo was not in line with the rest of the monoclonal antibody class (RR: 0.51; 95% CI: 0.27, 0.93). In the present review, the addition of the RIFUND-MS trial to the evidence base provided greater certainty of rituximab's benefit on ARR (RR: 0.34; 95% CI: 0.19, 0.58). There was greater variation in ARR reduction among the oral DMTs, but on average, these DMTs reduced ARR by around 50%. Ponesimod, the newest S1P receptor modulator, was numerically the most efficacious oral therapy in the ARR network (RR: 0.46) and teriflunomide 14 mg the least (RR: 0.66). Overall, all 10 DMTs in the ARR NMA were superior to placebo. Results from this NMA provide evidence of high efficacy among monoclonal antibody DMTs and intermediate efficacy among oral DMTs on relapse reduction.

Disability Progression (Time to CDP-3 and CDP-6)

Ocrelizumab, ofatumumab, and natalizumab were all superior to placebo on time to CDP-3 and CDP-6. Ocrelizumab had the highest magnitude of benefit for time to CDP-3 (HR: 0.37; 95% CI: 0.21, 0.67) and CDP-6 (HR: 0.41; 95% CI: 0.22, 0.74). Ublituximab was the least efficacious agent in the monoclonal antibody class; it did not produce a significant difference versus placebo in either time to CDP-3 (HR: 0.57; 95% CI: 0.0.3, 1.13) or CDP-6 (HR: 0.52; 95% CI: 0.24, 1.15). Rituximab was not included in the CDP-3 and CDP-6 NMAs due to lack of high-quality evidence for these outcomes.

Among the oral DMTs, only dimethyl fumarate (HR: 0.69; 95% CI: 0.5, 0.96) and teriflunomide 14 mg (HR: 0.69; 95% CI: 0.5, 0.95) were statistically superior to placebo on time to CDP-3. Ponesimod had the most numerically favorable HR, but it was not statistically significant. In the time to CDP-6 network, fingolimod was the most efficacious oral DMT with the only significant difference versus placebo (HR: 0.67; 95% CI: 0.47, 0.96). There was a high level of uncertainty in ozanimod's efficacy on both CDP outcomes; while ozanimod appeared to be no different than placebo for time to CDP-3 and had a numerically inferior point estimate to placebo on time to CDP-6, the credible intervals of the point estimates for both analyses were wide. Results from the fixed-effects model and sensitivity analyses were consistent with the base-case results (See Supplement Figures D8 and D9).

Overall, the monoclonal antibody class had a greater magnitude of benefit versus placebo than oral DMTs versus placebo on the risk of time to CDP-3 and CDP-6.

Figure 3.4. Base-Case Forest Plot for Ublituximab versus Other DMTs for ARR

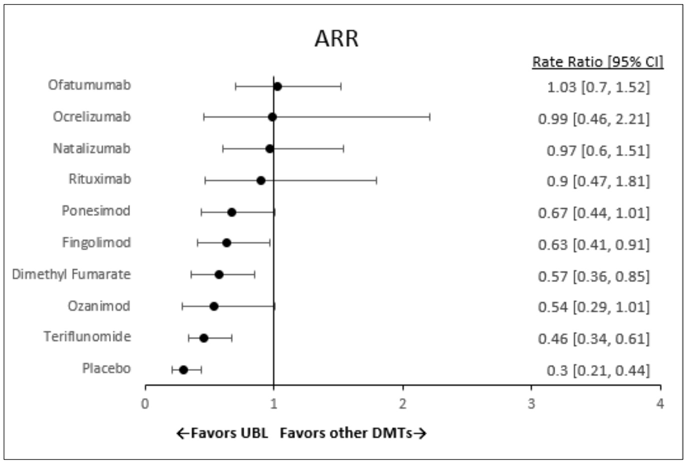


Figure 3.5. Base-Case Forest Plot for Ublituximab versus Other DMTs for CDP-3

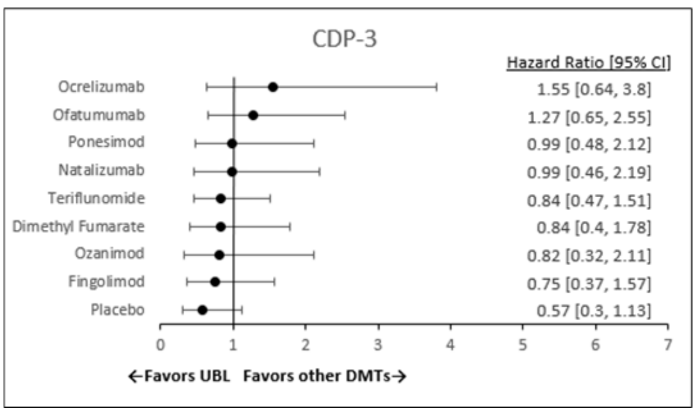
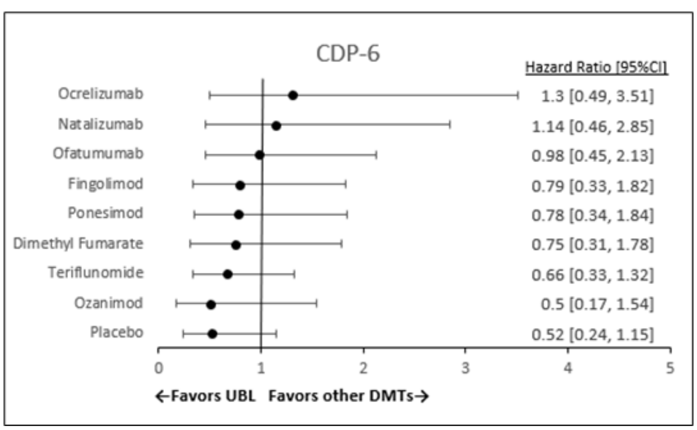


Figure 3.6. Base-Case Forest Plot for Ublituximab versus Other DMTs for CDP-6



Indirect Evidence: Ublituximab versus Other DMTs

Figures 3.4-3.6 provide point estimates of the relative effects of ublituximab compared with other DMTs on the three NMA outcomes of ARR, CDP-3, and CDP-6. A random-effects model was used for the ARR and CDP networks. League tables of NMA results are presented in Supplement D Figures D5-D7.

Relapse Rate

Ublituximab reduced ARR by a similar magnitude compared to other monoclonal antibodies. There were no statistically significant differences observed between the comparison of ublituximab and any of the other monoclonal antibodies on ARR. Compared with the oral medications, ublituximab was superior in reducing ARR, although the difference in ARR reduction with ponesimod and ozanimod was not statistically significant.

Disability Progression (Time to CDP-3 and CDP-6)

The comparison of ublituximab versus all other DMTs showed no statistically significant difference in the time to CDP-3 and CDP-6. The credible intervals for each point estimate were wide and are reflective of the uncertainty measuring disability progression across a duration of three or six months in a typical two-year MS trial. The time to CDP-6 network was particularly underpowered; many trials in the NMA were not powered to detect a significant difference on this endpoint. Results from the fixed-effects model and sensitivity analyses were consistent with the base-case results (see Supplement Figures D8 and D9).

Harms

Table 3.2 provides a summary of the potential harms associated with monoclonal antibody and oral DMTs. The rate of serious adverse events and discontinuation due to adverse events was derived from each DMT's pivotal trial(s) that had follow-up of at least two years duration to account for the natural accumulation of adverse events over time as well the infrequent dosing of some DMTs (e.g., infusions of rituximab/ocrelizumab every six months). The safety and tolerability of each DMT were evaluated in a qualitative manner and, apart from the ULTIMATE I and II direct evidence data, no direct comparisons across DMTs were made. Previous NMAs on the outcomes of serious adverse events and discontinuation due to adverse events demonstrated very few statistically significant differences among pairwise comparisons.[27-29]

Adverse events that occurred in more than 10% of patients in the DMT arm with higher frequency versus the comparator arm are outlined in Supplement Table D10.

Harms of Ublituximab versus Teriflunomide

Among the pooled safety population of ULTIMATE I and II, serious adverse events were reported in 10.8% of the patients treated with ublituximab and 7.3% of those treated with teriflunomide. There were three deaths in the ublituximab group, one of which was deemed a possible outcome of treatment-related pneumonia. A greater proportion of patients discontinued treatment due to adverse events in the ublituximab group (4.2%) versus teriflunomide (0.7%). There was a notable difference in the occurrence of discontinuation due to adverse events in the ublituximab arms of ULTIMATE I and II, 6.6% and 1.8% respectively. An explanation of this treatment discontinuation discrepancy was not provided.

Harms of Monoclonal Antibody DMTs

Ublituximab and other agents in the monoclonal antibody class carry increased risk of serious infections due their B-cell depletion mechanism of action. These infections often involve the respiratory and urinary tract. Infusion and injection-related reactions were also common among this DMT class.

Natalizumab and rituximab both carry black box warnings for the risk of progressive multifocal leukoencephalopathy (PML). PML is an opportunistic infection of the brain that is caused by the John Cunningham virus (JCV) and has the potential to cause severe disability or death. Cases of PML are rare and are associated with three risk factors: prior use of immunosuppressants, more than 24 months of natalizumab exposure, and presence of anti-JCV antibodies.[30] PML has been most frequently reported in natalizumab treatment, but rare cases have been reported with the use of rituximab, fingolimod, dimethyl fumarate, and ocrelizumab.[31,32] The risk of developing PML can be mitigated by testing for JCV in patients on higher-risk drugs; there is also evidence that extending dosing of natalizumab from every four weeks to every six weeks may lower the risk of developing PML.[33]

Discontinuation of natalizumab is associated with increased risk of rebound relapse rates.[34] This is of particular concern in the management of patients at risk for discontinuous treatment due to, for example, pregnancy, lack of access to regular care, financial, and/or insurance issues. Limited observational data on the use of monoclonal antibody DMTs (natalizumab, ofatumumab, ocrelizumab) prior to conception or during pregnancy suggests no increased risk of adverse outcomes.[35-38]

Harms of Oral DMTs

Among the oral fumarate class, the occurrence of flushing and gastrointestinal adverse events in the first month of treatment can lead to treatment discontinuation. Diroximel fumarate has a distinct chemical structure that was hypothesized to produce less irritation in the gastrointestinal tract, leading to fewer rates of gastrointestinal-related adverse effects and treatment discontinuations. Results from EVOLVE-MS-2, a five-week head-to-head trial in RRMS patients, confirmed the improved gastrointestinal tolerability profile of diroximel fumarate over dimethyl fumarate.[39]

Concerns of symptomatic bradycardia and atrioventricular conduction upon treatment initiation of fingolimod have led to requirements of first dose monitoring of the drug. First dose observations are not required in subsequent S1P receptor modulators, siponimod and ozanimod, due to their up-titration dosing strategies that have demonstrated an improved cardiac safety profile.[40,41]

There are additional concerns associated with fingolimod. There were two fatal cases of varicella-zoster virus infection reported in the fingolimod 1.25 mg arm (non-indicated dosage) of the 12-month TRANSFORMS trial.[42] Patients are recommended to be assessed for immunity to herpetic infection prior to undergoing fingolimod therapy.[43] Additionally, rebound relapses have been reported with the discontinuation of fingolimod, with patients who are of younger age and with higher disease activity appearing to be at higher risk.[44] Evidence from animal studies has shown potential teratogenic risk associated with fingolimod and teriflunomide; both agents are contraindicated in MS patients planning to conceive.[38]

Table 3.2. Harms of DMTs

Intervention	Black Box Warning	Serious Adverse Events	Serious AEs at Two Years	Discontinuation due to AEs at Two Years
Monoclonal Antibodies				
Ublituximab	N/A (FDA approval pending)	Neoplasm, infection	**ULTIMATE I & II** Ublituximab: 10.8% Teriflunomide: 7.3%	**ULTIMATE I & II** Ublituximab: 4.2% Teriflunomide: 0.7%
Natalizumab	PML	Cholelithiasis, hypersensitivity, infections (urinary tract), need for rehabilitation	**AFFIRM** Natalizumab: 19% Placebo: 24%	**AFFIRM** Natalizumab: 6% Placebo: 4%
Ocrelizumab	N/A	Neoplasm, infection, or infestation	**OPERA I** Ocrelizumab : 6.9% Interferon β-1a 44: 8.7%	**OPERA I & II** Ocrelizumab: 3.5% Interferon β-1a 44: 6.2%
Ofatumumab	N/A	Infection, injection-related reaction, neoplasm	**ASCELPIOS I & II** Ofatumumab: 9.1% Teriflunomide: 7.9%	**ASCELPIOS I & II** Ofatumumab: 5.7% Teriflunomide: 5.24%
Rituximab	Fatal infusion-related reactions, severe mucocutaneous reactions, hepatitis B virus reactivation, and PML*	Bleeding ulcer, bronchiectasis, infection, neutropenia, sinus tachycardia	**RIFUND-MS** Rituximab: 8.2% DMF: 5.2%	**RIFUND-MS** Rituximab: 3.1% DMF: 0%
Oral Therapies				
Dimethyl Fumarate	N/A	Abdominal pain, back pain, gastroenteritis, infection, pneumonia	**CONFIRM & DEFINE** DMF: 17.6% Placebo: 21.4%	**CONFIRM & DEFINE** DMF: 14.2% Placebo: 12.1%
Fingolimod	N/A	Atrioventricular block, bradycardia, chest pain, back pain, macular edema, neoplasm, urinary tract infection, herpetic infection‡	**FREEDOMS I & II** Fingolimod: 12.3% Placebo: 13.1%	**FREEDOMS I & II** Fingolimod: 12.5% Placebo: 8.9%
Ozanimod	N/A	Influenza, neoplasms, insomnia	**RADIANCE** Ozanimod 1 mg: 6.5% Interferon β-1a 30: 6.4%	**RADIANCE** Ozanimod 1 mg: 3% Interferon β-1a 30: 4.1%
Ponesimod	N/A	Hepatobiliary disorder or liver enzyme abnormality, Infections and infestations, nervous system, and gastrointestinal disorders	**OPTIMUM** Ponesimod: 8.7% TER: 8.1%	**OPTIMUM** Ponesimod: 8.7% TER: 6.0%
Siponimod	N/A	Alanine aminotransferase and aspartate aminotransferase increase, basal cell carcinoma, urinary tract infection	**EXPAND** Siponimod: 18% Placebo: 15%	**EXPAND** Siponimod: 4% Placebo: 3%
Teriflunomide	Hepatotoxicity and embryofetal toxicity†	Infection	**TEMSO** TER 14 mg: 15.9% Placebo: 12.8%	**TEMSO** TER 14 mg: 10.9% Placebo: 8.1%

AE: adverse event, DMF: dimethyl fumarate, mg: milligram, N/A: not applicable, PML: progressive multifocal leukoencephalopathy, TER: teriflunomide

*Black box warnings derived from FDA label. Rituximab is not currently approved for MS. †Black box warnings based on indirect evidence of animal data and leflunomide. ‡Two fatal cases of infection in the one-year TRANSFORMS trial.

Subgroup Analyses and Heterogeneity

The findings of the subgroup analyses are outlined in Supplement D6. We sought evidence on the clinical efficacy and safety of DMTs in our review across several patient subgroups of interest: race/ethnicity, age, and treatment-naïve status. We provide an additional overview of the evidence available for the SPMS population. No comparisons of efficacy across DMTs in any specific subgroup can be made due to the small sample sizes of subgroups, differing cutoff criteria for age and treatment-naïve classes, and post-hoc nature of these analyses.

Heterogeneity

The baseline characteristics of 20 RCTs that were included in our NMAs are outlined in Table 3.1.

Heterogeneity was observed across trial arms for the proportion of patients with history of previous DMT use (range: 26.3% to 98%), the baseline mean age (range: 33.4 to 41.5), mean EDSS score (range: 1.6 to 2.97), sex (percentage of female participants range: 61.3 to 81.1%), and race (percentage of White participants range: 77.9 to 100%). The mean number of relapses in the past year (range: 1 to 1.53) was comparable across most NMA trial arms. Trial participants in the RIFUND-MS (rituximab vs. dimethyl fumarate) study had a considerably lower baseline mean EDSS score and were largely treatment naïve (96%). The RIFUND-MS trial did not contribute evidence to the CDP-3 or CDP-6 NMAs.

People with RRMS made up the bulk of the trial population (range of 90.6% to 100% across arms). ASCEND (natalizumab) and EXPAND (siponimod) were excluded from our networks due to their exclusive recruitment of patients with SPMS.

Uncertainty and Controversies

The number of agents and the evidence base for DMTs has expanded in recent years, giving clinicians and patients more choices but also presenting challenges in terms of choosing a first-line therapy. Treatment targets for MS are still evolving, with new classes of agents such as Bruton's tyrosine kinase inhibitors in development, and recent evidence suggesting that Epstein-Barr virus may play an important role in triggering MS. Additionally, there remain questions about treatment sequence, particularly whether patients should be initially treated with higher efficacy but higher risk therapies or moderate efficacy but lower risk therapies. In this review, we evaluated the comparative effectiveness of oral and monoclonal antibodies for the first-line treatment of relapsing forms of MS. We note several limitations that reduce our certainty about the comparative benefits of DMTs.

First, the clinical diagnostic criteria for MS have evolved over the years, with addition of MRI findings on top of clinical findings in later iterations of the McDonald criteria.[51] Therefore, there may be variation in the patient population between older and newer studies. For example, patients classified with clinically isolated syndrome in earlier trials may now be classified as RRMS based on MRI lesions. Also, patients with more severe disease are now less likely to be enrolled in placebo-controlled trials due to the proven efficacy of DMTs and thus the trial populations for newer agents may be skewed towards patients with less severe disease. These issues lessen our confidence in comparisons including older trials. Additionally, trials contained very few patients who had a diagnosis of clinically isolated syndrome or SPMS, and thus we are unable to judge the clinical effectiveness of most DMTs in those populations.

In terms of clinical trial outcomes, we heard from clinicians, patients, and patient groups that preventing disability is a more important outcome than decreasing relapses. However, the most robust evidence from RCTs is for the ARR; there is more uncertainty about the impact of DMTs—particularly oral DMTs—on disability progression, as highlighted by the wider 95% credible intervals for the CDP-3 and CDP-6 outcomes that in some cases encompass no benefit when compared to placebo. This may be due to the use of EDSS as the main metric for disability, which is driven by FDA guidance for MS clinical trials. EDSS relies heavily on clinical judgment, which may increase measurement error. Additionally, trials measure disability that lasts for 12-24 weeks; however, that may capture disability that is occurring during relapses rather than accumulated disability over years, as is more typical of the MS course. While there is longer term data on some DMTs, those data rely on open-label extensions and observational data, which are subject to greater bias. Finally, EDSS is centered around the ability to ambulate, and thus other debilitating symptoms such as cognitive dysfunction may not be adequately captured. More recent trials have included other measure of disability, such as the MSFC, but these are inconsistently measured across trials and currently cannot be used for comparison. Finally, some trials have begun to measure CDI, allowing that some DMTs may actually reverse disability, but improvement is not currently measured in all trials and this outcome may be considered exploratory, making comparisons difficult.

Clinical practice guidelines emphasize shared decision-making when choosing DMTs, because of the number of choices with differing efficacy and tolerability, and an outstanding question of the best first-line therapy. However, to have effective shared decision-making conversations, physicians and patients need information about the relative similarities and differences between the agents. There is a lack of head-to-head trials between DMTs, particularly among monoclonal antibodies and across the classes of oral drugs, which makes it difficult to provide information to inform choice of first-line DMT. Thus, we relied on indirect comparisons through the NMA to compare the efficacy of DMTs. While we attempted to include trials that were as comparable as possible, the assumptions that are necessary to conduct the NMA introduce additional uncertainty. We did find that at least for the ARR outcome, the monoclonal antibodies have reductions of similar magnitude and are numerically larger than all the oral drugs. There is much more uncertainty in the CDP outcome due to several factors, including the relatively short duration of trials, trials being underpowered for this outcome, and limitations in the measurement of EDSS, and thus differentiation between agents for this outcome is much more difficult. We also await data from ongoing RCTs to assess whether first-line treatment with high efficacy therapy is necessary for all patients or a select subset.

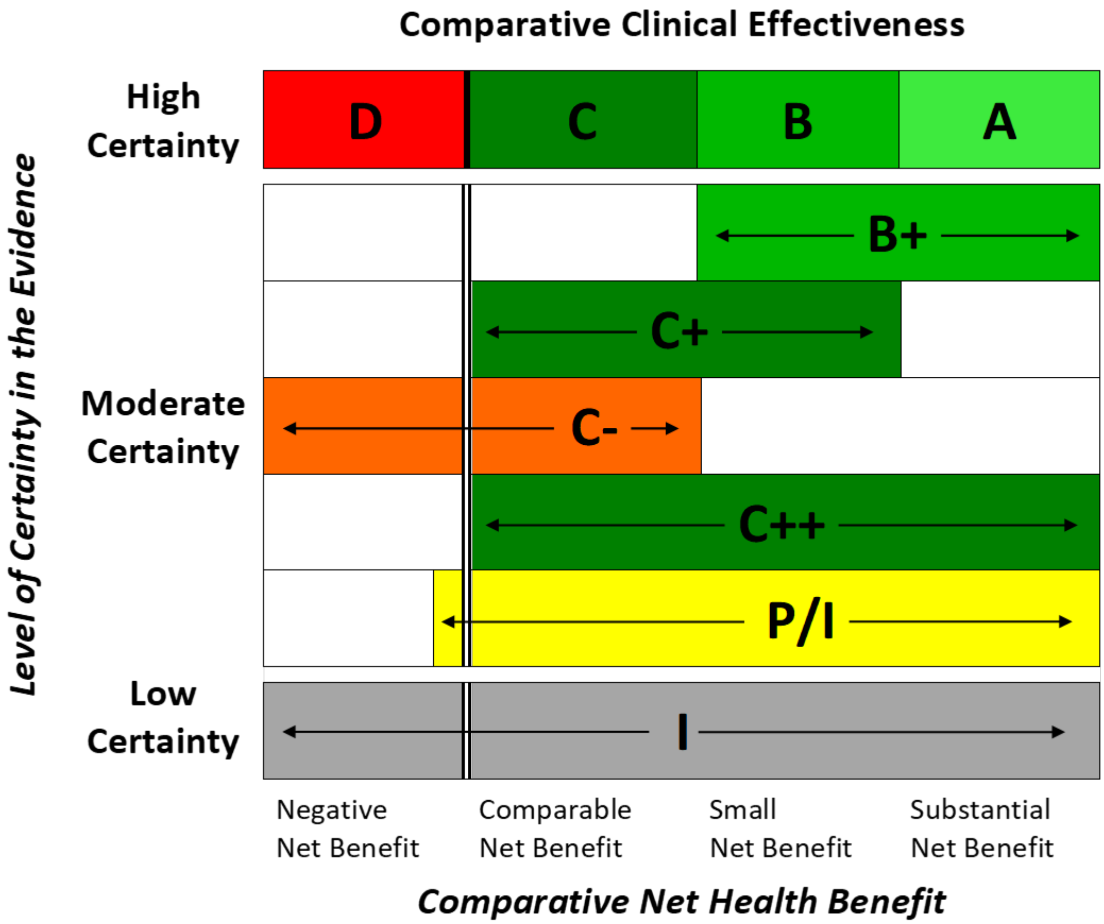
Although rituximab does not have a labeled indication for MS in the US, we found it difficult to differentiate rituximab from other monoclonal antibodies. In the RIFUND-MS Phase III trial, rituximab appears to be similarly effective to other monoclonal antibodies in reducing relapse rates. Similar to other DMTs, the effect of rituximab on CDP is less certain, though a recent meta-analysis of RCT and observational data supports the efficacy of rituximab on reducing CDP. There is wider use of rituximab for MS treatment outside of the US due to its similar mechanism of action to other monoclonal antibodies, RCT and real-world efficacy and safety data, and lower price, particularly now that biosimilars are available. These factors should be taken into consideration by clinicians, patients, and health plans when deciding whether to use rituximab for first-line treatment of MS.

Finally, the lack of head-to-head trials limits our ability to assess the comparative efficacy of ublituximab compared with other DMTs. Data from the NMA show that ublituximab may be similar to other monoclonal antibodies and likely better than oral drug classes in terms of reduction in ARR, but there is more uncertainty about the effect of ublituximab on the CDP outcomes, particularly compared with other monoclonal antibodies. Additionally, data for adverse events and serious adverse events for ublituximab are limited to the clinical trial, and long-term effects of ublituximab have yet to be determined. Thus, we await real-world post-approval data to determine if there are any rare or long-term adverse events that were not apparent during the clinical trials.

3.3. Summary and Comment

An explanation of the ICER Evidence Rating Matrix (Figure 3.7) is provided here.

Figure 3.7. 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*

There is now a variety of DMTs to treat relapsing forms of MS. In this review of the evidence base for the use of oral and monoclonal antibodies to treat relapsing forms of MS, we found varying degrees of efficacy amongst the agents as well as varying safety concerns. We are focused on assessing the efficacy of ublituximab in RRMS compared with other DMTs and no DMT in this review, because ublituximab is the newest agent pending FDA approval and RRMS is the predominant population in clinical trials. Our evidence ratings thus compare ublituximab to other DMTs and no DMT, as estimated by the placebo arms of the RCTs included in the NMA.

For **ublituximab compared with natalizumab, ofatumumab, ocrelizumab**, **and rituximab**, our NMA demonstrates that for ARR, ublituximab appears comparable. However, there is more uncertainty in the CDP outcome, with greater variability across drugs, although differences were not statistically significant. Additionally, rituximab was not included in the CDP NMA due to data limitations. Short-term safety signals appear similar across the drugs, barring a black box warning of an elevated risk of PML with natalizumab, but there is not long-term safety data for ublituximab yet. Thus, we judge that the evidence is insufficient to determine the comparative clinical effectiveness of ublituximab compared with other monoclonal antibodies (I).

For **ublituximab compared with the fumarate class (dimethyl fumarate**, **monomethyl fumarate, diroximel fumarate), fingolimod, ozanimod and ponesimod,** the NMA demonstrates a greater reduction in ARR with ublituximab. While CDP data were not statistically significant, CDP trended toward benefit for ublituximab. There are no concerning safety signals yet with ublituximab, and every six-month dosing may improve adherence over a drug that must be taken daily. We have moderate certainty that ublituximab represents a comparable, small, or substantial net benefit compared with these oral medications, with high certainty of at least a comparable benefit (C++).

For **ublituximab compared with siponimod**, we did not have sufficient evidence to make a comparative judgement since the stated population in the siponimod RCT was SPMS and there were few reported SPMS patients in the ULTIMATE trials. Thus, we have insufficient evidence to judge this comparison (I).

For **ublituximab compared with teriflunomide**, we have direct evidence from the ULTIMATE trials. In this RCT, ublituximab showed a substantial reduction in ARR and fewer brain lesions compared with teriflunomide. The difference in CDP was not statistically significant; however, it trended in favor of ublituximab. There were slightly more adverse events in the ublituximab group but no additional concerning safety signals. Thus, we have high certainty that ublituximab confers at least a small net health benefit when compared with teriflunomide (B).

For **ublituximab compared with no DMT**, we estimated the effect of no DMT with the placebo arm in the NMA. Ublituximab produced statistically significant improvements in ARR and CDP compared with no DMT. Given the progressive nature of MS and the high likelihood of disability with no DMT treatment, even with the risk of adverse events with active treatment, we judge that there is high certainty of a substantial net health benefit of ublituximab compared with no DMT (A).

Table 3.3. Evidence Ratings

Treatment	Comparator	Evidence Rating
Adults with RRMS		
Ublituximab	Natalizumab	I: Insufficient
	Ofatumumab	I: Insufficient
	Ocrelizumab	I: Insufficient
	Rituximab	I: Insufficient
	Fumarate class (dimethyl, diroximel, monomethyl)	C++: Comparable or better
	Fingolimod	C++: Comparable or better
	Ozanimod	C++: Comparable or better
	Ponesimod	C++: Comparable or better
	Siponimod	I: Insufficient
	Teriflunomide	B: Incremental
	Placebo/no DMT	A: Superior

DMT: disease-modifying therapy, RRMS: relapsing-remitting multiple sclerosis

4. Long-Term Cost Effectiveness

4.1. Methods Overview

The primary aim of this analysis was to estimate the cost effectiveness of ublituximab, natalizumab, ofatumumab, and ocrelizumab. These therapies are monoclonal antibody treatments used in patients with RRMS. An emphasis is on ublituximab, which is currently undergoing FDA review. The other monoclonal antibodies were also considered as interventions within the cost-effectiveness analysis to provide supporting context in addition to the comparative clinical assessment for these treatments. Although included in the comparative clinical assessment, rituximab was not modeled as an intervention in the cost-effectiveness analysis due to insufficient evidence on disease progression at this time. Treatment initiation of each modeled intervention was compared to treatment initiation with dimethyl fumarate. Dimethyl fumarate was selected as the comparator following numerous conversations with stakeholders suggesting it is a market leader, effective, and currently the lowest cost oral DMT. Oral therapies for relapsing forms of MS were not evaluated as interventions within the cost-effectiveness analysis. The base-case analysis took a health care sector perspective (i.e., focused on direct medical care costs only). Productivity changes and other indirect costs and effects were considered in a scenario analysis using a modified societal perspective.

We developed a *de novo* Markov model for this evaluation, informed by key clinical trials and prior relevant economic models, including models developed for prior ICER reviews related to MS.[52-57] The model was developed in Microsoft Excel and consisted of health states defined by the EDSS, a commonly used scale to describe MS disease progression. The model consisted of 20 health states, including EDSS 0-9 during RRMS, EDSS 1-9 during SPMS, and death. A relapse could occur in any of the alive health states and was modeled as an event within a health state rather than as a separate health state. Patients remained in the model until they died due to all-cause or disease-specific mortality. Patients transitioned between the health states during cycles of one year and over a lifetime time horizon. All future costs and outcomes were discounted at 3% per year. Further information on the model structure can be found in Supplement Section E.

The target population consisted of adults ages 18 years and older in the US with relapsing forms of MS. The baseline demographics and initial distribution of patients among the health states was aggregated from the pivotal evidence sources. The baseline population inputs can be found in Supplement E.

Model outcomes included total life years gained, quality-adjusted life years (QALYs) gained, equal-value life years (evLYs) gained, and total costs for each intervention. We also evaluated the years without ambulatory restrictions (defined as an EDSS score less than 5) and the years without a wheelchair (defined as an EDSS score less than 7).

4.2. Key Model Assumptions and Inputs

The model was informed by several key assumptions described in Table 4.1. Additional assumptions are detailed in the Supplement.

Table 4.1. Key Model Assumptions

Assumption	Rationale
Trial-reported discontinuation was annualized and applied over the first two years after initiating treatment. Discontinuation after two years was assumed to be related to serious adverse events only and did not vary by treatment.	We had trial evidence that approximated a two-year duration, so we annualized the trial data and applied that evidence over two years. Literature and clinical expert opinion suggested that discontinuation decreases over time,[58] and thus after two years on treatment, the only discontinuation that was modeled was assumed to be related to serious adverse events. Discontinuation was widely varied in sensitivity analyses to account for the uncertainty and variability in real-world discontinuation.
If a patient discontinued the initial therapy (either intervention or comparator), they transitioned to a subsequent treatment with cost and effectiveness similar to that of the market leading monoclonal antibody. A patient did not discontinue this subsequent treatment until death.	Utilization data and clinical opinion suggested that most RRMS and SPMS patients initiate subsequent treatment upon discontinuation. The specific subsequent treatment will vary in the real world; however, our objective is not to recommend treatment sequences or evaluate the cost-effectiveness of a specific treatment sequence. To achieve the objective of our analysis of estimating the cost effectiveness of a specific intervention, we held this subsequent treatment fixed to emphasize the potential differences in the initial treatment. Our approach standardized the treatment switch across the modeled arms (both the intervention and the comparator) and ensured the cost and effectiveness of the subsequent treatment did not drive the results. The subsequent treatment characteristics were varied in scenario analyses.
Separate from the modeled discontinuation, the cohort remained on treatment over the lifetime time horizon.	There is no clinical consensus as to when treatment should stop, but we heard from clinical experts that they would be unlikely to remove a patient from treatment if the patient was tolerating it. We conducted a scenario analysis where treatment stopped when a patient reached an EDSS of 7 or higher.
The modeled cohort continued treatment after transitioning to SPMS.	Clinical opinion supported the continued use of treatment even after transitioning to SPMS.

EDSS: Expanded Disability Status Scale, RRMS: relapsing-remitting multiple sclerosis, SPMS: secondary-progressive multiple sclerosis

Table 4.2 reports the key model inputs for each of the modeled interventions, with an exhaustive list and description of all model inputs and their respective source available in Section E of the Supplement.

Table 4.2. Key Model Inputs

Parameter	Ublituximab	Natalizumab	Ofatumumab	Ocrelizumab	Dimethyl Fumarate
HR for Six-Month Disease Progression*	0.53	0.46	0.54	0.41	0.70
Rate Ratio for Annualized Relapse Rate*	0.30	0.31	0.29	0.30	0.53
Annual Probability of Serious Adverse Events	2.2%	1.4%	1.6%	0.7%	1.2%
Annual Discontinuation, First 2 Years on Treatment	3.9%	2.5%	4.9%	4.7%	8.8%
Annual Acquisition Cost, Year 1†	$55,081‡	$100,902	$87,730	$55,081	$2,762
Annual Acquisition Cost, Years 2+†	$55,081‡	$100,902	$71,281	$55,081	$2,739

HR: hazard ratio

*Applied to annual probabilities/rates in the absence of treatment with a DMT.

†Not inclusive of any mark-up, administration cost, or monitoring cost.

‡Assuming a placeholder price for ublituximab equivalent to the net price of ocrelizumab.

4.3. Results

Base-Case Results

The lifetime discounted costs from the health care system perspective and the lifetime discounted years without ambulatory restrictions, years without a wheelchair, QALYs, life years, and evLYs are detailed in Table 4.3. Each monoclonal antibody treatment resulted in additional costs as compared to dimethyl fumarate, but also resulted in additional time without ambulatory restrictions or a wheelchair, QALYs, life years, and evLYs. We note that with an annual acquisition cost less than $3,000, dimethyl fumarate treatment costs total $421,000 due to treatment discontinuation that assumed a subsequent DMT with an annual cost equivalent to the market-leading monoclonal antibody (i.e. annual treatment cost of $55,081).

Table 4.3. Base-Case Model Outcomes Over a Lifetime Time Horizon

Treatment	Treatment Cost	Total Cost	Years Without Ambulatory Restrictions*	Years Without a Wheelchair†	QALYs	Life Years	evLYs
Ublituximab‡	$1,193,000	$1,914,000	14.58	18.02	13.40	21.36	13.56
Natalizumab	$1,982,000	$2,755,000	15.69	18.91	14.09	21.62	14.30
Ofatumumab	$1,466,000	$2,131,000	14.47	17.93	13.33	21.33	13.48
Ocrelizumab	$1,220,000	$1,912,000	16.55	19.56	14.62	21.82	14.86
Dimethyl Fumarate	$421,000	$1,112,000	12.58	16.22	12.08	20.86	12.08

EDSS: Expanded Disability Status Scale, evLY: equal-value life year, QALY: quality-adjusted life year

*As measured by time in EDSS health states less than 5.

†As measured by time in EDSS health states less than 7.

‡Assuming a placeholder price for ublituximab equivalent to the net price of ocrelizumab.

Table 4.4 presents the incremental cost-effectiveness ratios from the base-case analysis, which includes estimates for the incremental cost per additional year without ambulatory restrictions, incremental cost per additional year without a wheelchair, incremental cost per QALY gained, incremental cost per life year gained, and incremental cost per evLY gained.

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

Treatment	Cost per Additional Year without Ambulatory Restrictions*	Cost per Additional Year without a Wheelchair†	Cost per QALY Gained	Cost per Life Year Gained	Cost per evLY Gained
Ublituximab‡	\$400,000	\$446,000	\$608,000	\$1,600,000	\$543,000
Natalizumab	\$528,000	\$612,000	\$820,000	\$2,100,000	\$742,000
Ofatumumab	\$539,000	\$599,000	\$815,000	\$2,100,000	\$727,000
Ocrelizumab	\$201,000	\$240,000	\$315,000	\$829,000	\$288,000

EDSS: Expanded Disability Status Scale, evLY: equal-value life year, QALY: quality-adjusted life year

*As measured by time in EDSS health states less than 5.

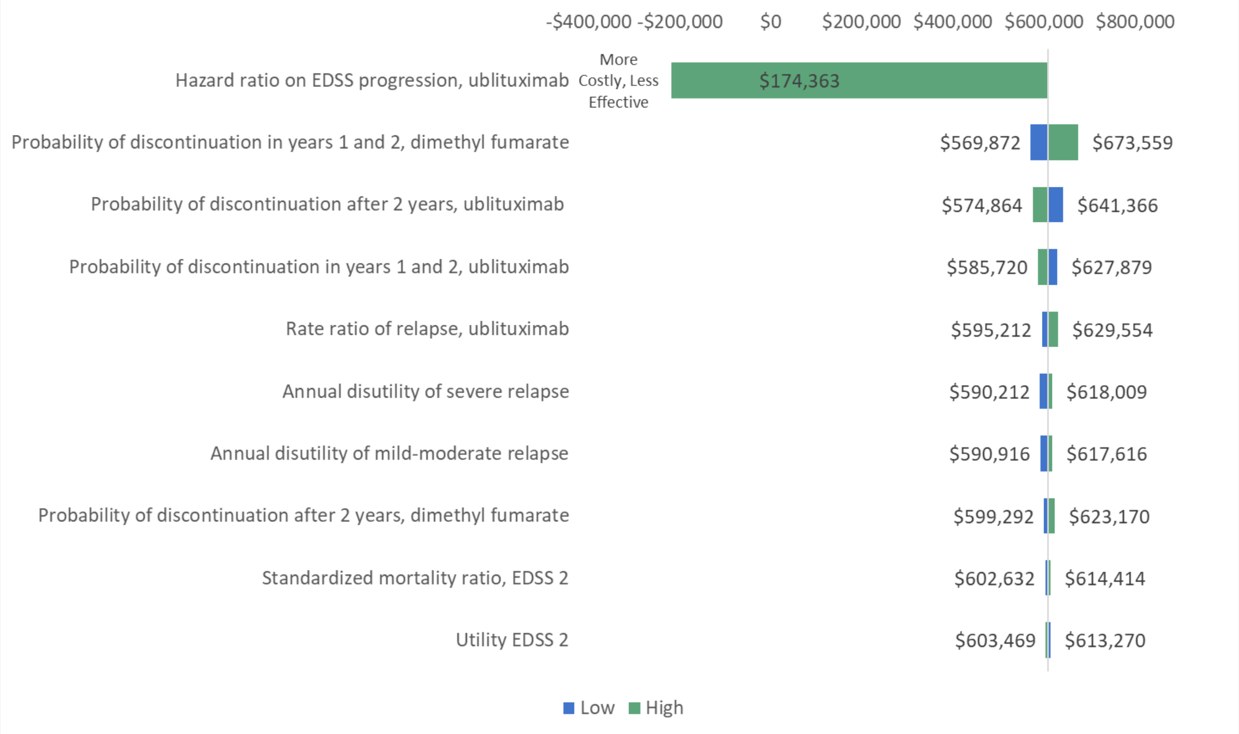
†As measured by time in EDSS health states less than 7.

‡Assuming a placeholder price for ublituximab equivalent to the net price of ocrelizumab.

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 where available or reasonable ranges) to evaluate changes in findings. Figure 4.1 presents the results from the one-way sensitivity analysis for ublituximab. Table 4.5 presents the inputs and results for each input that appeared in Figure 4.1. The incremental cost-effectiveness ratios for ublituximab ranged from approximately \$174,000 per QALY gained to more costly and less effective as compared to dimethyl fumarate. Notably, the most influential input on the cost effectiveness was the treatment's effectiveness on disease progression. Supplement Figures E2-E4 and Supplement Tables E22-24 present the results from the one-way sensitivity analysis for each of the other monoclonal antibodies as compared to dimethyl fumarate.

Figure 4.1. Tornado Diagram for Ublituximab versus Dimethyl Fumarate



EDSS: Expanded Disability Status Scale

Table 4.5. Tornado Diagram Inputs and Results for Ublituximab versus Dimethyl Fumarate

Input Name	Lower Input ICER	Upper Input ICER	Lower Input	Upper Input
HR on EDSS Progression, Ublituximab	$174,000	More costly, less effective	0.22	1.26
Probability of Discontinuation in Years 1 and 2, Dimethyl Fumarate	$569,000	$673,000	5.0%	13.6%
Probability of Discontinuation after 2 Years, Ublituximab	$641,000	$574,000	0.8%	2.3%
Probability of Discontinuation in Years 1 and 2, Ublituximab	$627,000	$585,000	2.2%	6.0%
Rate Ratio of Relapse, Ublituximab	$595,000	$629,000	0.19	0.46
Annual Disutility of Severe Relapse	$590,000	$618,000	-0.15	0.00
Annual Disutility of Mild-Moderate Relapse	$590,000	$617,000	-0.05	0.00
Probability of Discontinuation after 2 Years, Dimethyl Fumarate	$599,000	$623,000	0.8%	2.3%
Standardized Mortality Ratio, EDSS 2	$602,000	$614,000	1.30	1.93
Utility EDSS 2	$613,000	$603,000	0.76	0.80

EDSS: Expanded Disability Status Scale, HR: hazard ratio, ICER: incremental cost-effectiveness ratio

A probabilistic sensitivity analysis was conducted to vary all inputs with noted uncertainty simultaneously. Tables 4.6 and 4.7 present the percent of the 1,000 iterations that were beneath thresholds of $50,000, $100,000, $150,000, and $200,000 per QALY gained and evLY gained. The majority of the iterations were above thresholds of $200,000 per QALY gained or per evLY gained for all monoclonal antibody treatments. Additional results from the probabilistic sensitivity analyses can be found in Supplement Table E25.

Table 4.6. Probabilistic Sensitivity Analysis Cost per QALY Gained Results, versus Dimethyl Fumarate

Treatment	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
Ublituximab*	0%	0%	0%	8%
Natalizumab	0%	0%	0%	0%
Ofatumumab	0%	0%	0%	0%
Ocrelizumab	0%	0%	0%	13%

QALY: quality-adjusted life year

*Assuming a placeholder price for ublituximab equivalent to the net price of ocrelizumab.

Table 4.7. Probabilistic Sensitivity Analysis Cost Per evLY Gained Results, versus Dimethyl Fumarate

Treatment	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
Ublituximab*	0%	0%	0%	10%
Natalizumab	0%	0%	0%	0%
Ofatumumab	0%	0%	0%	0%
Ocrelizumab	0%	0%	0%	18%

evLY: equal value life year

*Assuming a placeholder price for ublituximab equivalent to the net price of ocrelizumab.

Scenario Analyses

We conducted numerous scenario analyses that are all detailed in Supplement E. We have chosen to present the following scenarios here:

1) Modified societal perspective that included components such as productivity losses, caregiver impact, and others as applicable.
2) Compared each intervention to a hypothetical monoclonal antibody biosimilar with treatment effectiveness equivalent to the average treatment effectiveness of the modeled interventions and cost equivalent to existing monoclonal antibody biosimilars (e.g., biosimilar rituximab with an average sales price of approximately $4,400 per year).
3) Stopped treatment when a patient reached an EDSS score higher than 7.

Details on the approach for each of the above scenario analyses as well as the approach and results for all scenario analyses conducted can be found in Supplement E. Table 4.8 presents the incremental cost per evLY gained for the base case as well as for the three selected scenarios. For all scenarios, the incremental cost-effectiveness ratios exceeded the upper bound of commonly used cost-effectiveness thresholds.

Table 4.8. Incremental Cost per evLY Gained for Select Scenario Analyses

Treatment	Base-Case Results ($/evLY Gained)	Modified Societal Perspective Scenario	Monoclonal Antibody Biosimilar Comparator Scenario	Treatment Stop after EDSS of 7 Scenario
Ublituximab*	$543,000	$524,000	More costly, less effective	$497,000
Natalizumab	$742,000	$722,000	>$1,000,000	$695,000
Ofatumumab	$727,000	$707,000	More costly, less effective	$663,000
Ocrelizumab	$288,000	$268,000	$826,000	$279,000

EDSS: Expanded Disability Status Scale, evLY: equal value life year gained

*Assuming a placeholder price for ublituximab equivalent to the net price of ocrelizumab.

Threshold Analyses

We performed threshold analyses for treatment costs across a range of incremental cost-effectiveness ratios ($50,000, $100,000, $150,000, and $200,000 per QALY and evLY gained). Table 4.9 presents the results from the threshold analyses based on the QALY outcome and Table 4.10 presents the results from the threshold prices based on the evLY outcome.

Table 4.9. QALY-Based Threshold Analysis Results*

	Ublituximab	Natalizumab	Ofatumumab	Ocrelizumab
Annual Price to Achieve $50,000/QALY Gained	$12,400	$14,900	$12,000	$16,200
Annual Price to Achieve $100,000/QALY Gained	$16,200	$20,500	$15,900	$23,600
Annual Price to Achieve $150,000/QALY Gained	$20,000	$26,100	$19,800	$30,900
Annual Price to Achieve $200,000/QALY Gained	$23,900	$31,600	$23,600	$38,200

QALY: quality-adjusted life year

*Rounded to three significant digits.

Table 4.10. evLY-Based Threshold Analysis Results*

	Ublituximab	Natalizumab	Ofatumumab	Ocrelizumab
Annual Price to Achieve $50,000/evLY Gained	$12,900	$15,500	$12,500	$16,900
Annual Price to Achieve $100,000/evLY Gained	$17,100	$21,700	$16,800	$24,900
Annual Price to Achieve $150,000/evLY Gained	$21,400	$27,800	$21,200	$33,000
Annual Price to Achieve $200,000/evLY Gained	$25,700	$34,000	$25,500	$41,000

evLY: equal-value life year

*Rounded to three significant digits.

Model Validation

We used several approaches to validate the model. First, we provided the preliminary model structure, methods and assumptions to manufacturers, patient groups, and clinical experts. Based on feedback from these groups, we refined data inputs used in the model as appropriate. Second, we varied model input parameters to evaluate the face validity of changes in results. We also performed model verification for model calculations using internal reviewers. As part of ICER's efforts in acknowledging model transparency, we will also share the model with the relevant manufacturers for external verification shortly after publishing the draft Evidence Report for this review. External reviewers provided comments on the model structure, inputs, assumptions, and findings. Finally, we compared results to other cost-effectiveness models in this therapy area.

Uncertainty and Controversies

The model structure is based on health states defined by EDSS, which is a widely used metric to assess and quantify the level of disability and severity of MS, and we heard from patients and patient advocacy groups that disability and disease progression are meaningful outcomes to patients with MS. Early levels of EDSS (EDSS <5) are based on measures of impairment in various functional systems, such as sensory and bladder functions. Later levels of EDSS (EDSS ≥5) are defined by physical disability and the impairment of walking. The EDSS metric has been critiqued in that later levels of EDSS focus too much on physical disability and not enough on upper body function and other functional systems, such as cognitive functions. Despite these critiques, EDSS remains the most commonly used measure for MS disease progression and is widely used in neurology clinical practice. Additionally, we are using natural history studies for progression rates that are more than 10 years old. These progression rates will likely make the treatments look more cost effective given that progression rates seem to be slower in more contemporary studies, likely due to differences in diagnostic criteria and increased use of MRI, allowing for earlier identification of mildly affected individuals. These limitations of the EDSS should be considered when interpreting the cost-effectiveness estimates given the cost-effectiveness model is driven by a treatment's effect on reducing EDSS progression.

Variation exists in the reported quality of life utility scores for people with MS at high levels of EDSS. Quality of life utility scores are relatively consistent across studies for EDSS 0 through 7, but estimates vary dramatically across sources for EDSS 8 and 9. The primary source we used in our modeling efforts to inform the quality-of-life utility scores for EDSS 0 through 7, selected based on sample size and methodology in alignment with our reference case, suggested a quality of life worse than death (i.e., quality of life less than 0) for people with MS at EDSS levels of 8 and 9. This contradicts the quality of life utility scores reported elsewhere for these two EDSS states.[59,60] One study by Kobelt and colleagues reported a utility of 0.533 for severe MS (EDSS 6.5 to 9.5) although an EDSS of 8 and 9 are likely underweighted in this estimate. Similarly, utilities derived from an MS specific survey in a study by Prosser and colleagues suggested a quality-of-life score between 0.49 and 0.70 for an EDSS of 8. Based on these studies, and our conversations with patients and other stakeholder groups, we did not model the utility of EDSS 8 and 9 as less than 0. Rather, we extrapolated a non-linear function between EDSS and the utilities reported from EDSS 0 to EDSS 7 to estimate a positive utility for EDSS 8 and 9.

Relatedly, the quality-of-life utility scores we used in our model were derived from community preferences based on the EQ-5D. We compared the findings from the generic EQ-5D to findings from an MS-specific survey, and the EQ-5D suggested a larger range in scores across the EDSS spectrum, potentially suggesting more sensitivity to EDSS changes than the MS survey. We elected to use the utilities from the EQ-5D in our modeling efforts. We tested this choice through scenario analyses.

As the scenario analysis suggests, the annualized net price range across monoclonal antibody treatments becomes much wider when including biosimilar rituximab. The estimated annual price for rituximab (biosimilar and branded forms) ranges between $4,000 and $9,000. These prices are below the draft threshold analysis annualized prices for the modeled monoclonal antibody treatments when referring to commonly cited threshold values versus generic dimethyl fumarate. As previously mentioned, rituximab does not have a labeled indication for treating people with relapsing forms of MS. When it comes to determining a fair price for new monoclonal antibody treatments, one may ask what evidence supports a comparative clinical advantage for the new monoclonal antibody treatment over the existing options and similarly at what cost tradeoff? If no known clinical advantages are demonstrated, one may also consider what price premium if any, is reasonable for labeled monoclonal antibody treatments over that of agents such as biosimilar rituximab. The present price premium between rituximab and the net price of ocrelizumab is between 600% and 1300%.

4.4. Summary and Comment

Our analyses suggest that each monoclonal antibody treatment produces improved clinical outcomes. At their estimated net prices including the placeholder price assumed for ublituximab, each intervention is expected to exceed standard cost-effectiveness levels in the US health care system. The cost-effectiveness findings are primarily driven by a treatment's ability to slow disability progression as well as the annualized net prices.

5. Contextual Considerations and Potential Other Benefits

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 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. Contextual Considerations

Contextual Consideration	Relevant Information
Acuity of need for treatment of individual patients based on short-term risk of death or progression to permanent disability	MS is a progressive disease that can result in permanent disability without treatment. There is a high need for effective treatments.
Magnitude of the lifetime impact on individual patients of the condition being treated	The onset of MS is typically in the third decade of life and symptoms are lifelong, and encompass years where education, work, and childbearing are important. Thus, effective treatments could have a large impact over a lifetime.
Other (as relevant)	People with MS may be treated by either general neurologists or MS specialists. The ability to access some treatments may depend on the patient's access to specialized care.

Table 5.2. Potential Other Benefits or Disadvantages

Potential Other Benefit or Disadvantage	Relevant Information
Patients' ability to achieve major life goals related to education, work, or family life	Because MS is a chronic disease that begins early in life, it can affect educational goals and ability to work including presenteeism, absenteeism, and premature exit from the workforce. Pregnancy must also be carefully considered given the potential toxicity of some DMTs during pregnancy.
Caregivers' quality of life and/or ability to achieve major life goals related to education, work, or family life	As MS progresses and people with MS have more mobility challenges, caregiver burden increases and can affect caregiver quality of life and ability to achieve major life goals.
Patients' ability to manage and sustain treatment given the complexity of regimen	Delivery of DMTs range from oral to injectable to intravenous infusions. Newer intravenous infusions, which are given less often than oral and injectable drugs, may improve adherence. Infusions and oral medications may also help people with MS avoid "needle fatigue" that comes from daily injections for years.
Society's goal of reducing health inequities	African Americans with MS may experience poorer outcomes and thus may have larger benefit from treatment with effective DMTs.
Other (as relevant)	The COVID-19 pandemic has affected care for people with MS in a couple ways. First, there may be delays in receiving infusions due to COVID-19-related shutdowns. Additionally, B-cell depleting therapies may impact a person's response to COVID-19 vaccines and put them at higher risk of COVID-19 infection.

6. Health-Benefit Price Benchmarks

ICER does not provide health-benefit price benchmarks as part of draft Evidence 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 Analysis section of this draft Evidence Report will match the health-benefit price benchmarks that will be presented in the next version of this Report.

7. Potential Budget Impact

7.1. Overview of Key Assumptions

Using results from the cost-effectiveness model, we estimated the potential total budgetary impact of ublituximab for patients with relapsing forms of MS. We used the treatment price from the base-case cost-effectiveness analysis, and the three threshold prices (at $50,000, $100,000, and $150,000 per QALY) in our estimates of budget impact. The aim of this potential budgetary impact analysis was to document the percentage of patients who could be treated at selected prices without crossing a potential budget impact threshold that is aligned with overall growth in the US economy. For 2022-2023, the five-year annualized potential budget impact threshold that should trigger policy actions to manage access and affordability is calculated to be approximately $777 million per year for new drugs.

Identifying the appropriate eligible population for the potential budget impact analysis was challenged by the number of existing treatments available, the different types of DMTs available, whether or not a patient is currently on a DMT or is new to treatment with a DMT, and whether or not a patient is stable on their DMT if currently taking a DMT. Further, given the widespread use of other active treatments in relapsing forms of MS with relatively similar efficacy, the potential budget impact analysis is likely predictable even without a potential budget impact analysis if one examines the differences in annual cost. If ublituximab is displacing treatments with similar efficacy and similar or higher prices, the budget impact is likely limited or slightly reduced. Conversely, if ublituximab is displacing treatments with similar efficacy but the displaced treatments are less costly, then ublituximab could have an increased and potentially large budget impact.

Considering these challenges, our objective was to develop a flexible framework for the potential budget impact analysis of ublituximab. The potential budget impact analysis will be available in ICER's Interactive Modeler for users to update key assumptions, including the eligible population size and comparator market basket. For the purposes of this report, we estimated the size of the potential eligible population for ublituximab treatment by applying prevalence estimates for MS (309.2 per 100,000 individuals: 0.309%)[34] to the 2022-2026 projected US population ages 18 years and older. We then applied the percent of those who have relapsing forms of MS (84.7%).[1] Lastly, we assumed that only patients who are currently being treated with another monoclonal antibody would switch to treatment with ublituximab, and thus we applied the percent of those who are currently taking a monoclonal antibody (56.5% based on market share information).[6161] Applying these estimates resulted in approximately 400,000 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 approximately 80,000 patients per year. Different assumptions can be made using ICER's Interactive Modeler.

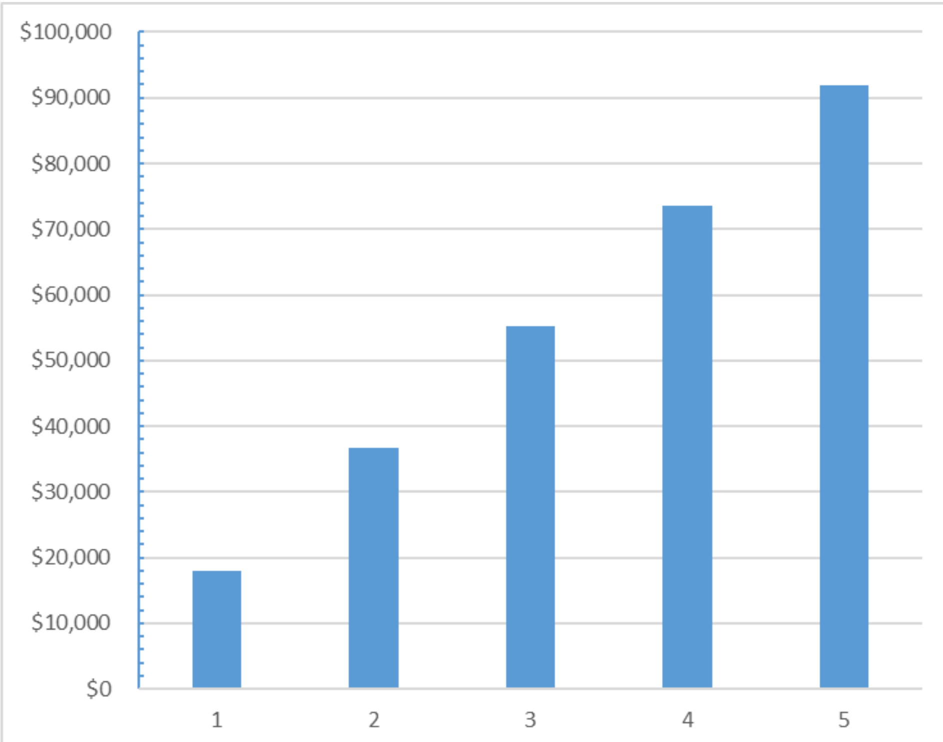
We assumed ublituximab uptake would displace market share from the other monoclonal antibodies in the cost-effectiveness analysis. The budget impact comparator market basket was assumed to be 82% ocrelizumab, 13% natalizumab, and 5% ofatumumab, calculated using market share data from Biomedtracker.[61] In a separate analysis, we assumed ublituximab uptake would displace market share from currently used monoclonal antibodies, including biosimilar rituximab. Market share data for rituximab was not available specific to its use in MS, thus we assumed it would have a similar market share to ocrelizumab. Thus the comparator basket in this scenario was 45% ocrelizumab, 45% rituximab, 7% natalizumab, and 3% ofatumumab. We assumed biosimilar rituximab would have clinical outcomes equivalent to the average clinical outcomes across the other monoclonal antibodies. Different assumptions can be made using ICER's Interactive Modeler.

7.2. Results

In the analysis that did not include biosimilar rituximab, and thus ublituximab uptake was assumed to displace market share from a market basket of the other monoclonal antibodies in the cost effectiveness analysis (82% ocrelizumab, 13% natalizumab, and 5% ofatumumab), all patients could be treated at the placeholder price and each of the threshold prices without crossing the potential budget impact threshold. Given the placeholder price for ublituximab was the lowest cost monoclonal antibody treatment in the comparator basket, displacing the other monoclonals would have a neutral or cost saving impact on the budget. Because the threshold prices for ublituximab were all less than the prices of current monoclonal antibody treatments, displacing the other monoclonals at each of the threshold prices would have a cost saving impact on the budget.

In the analysis that included biosimilar rituximab in the comparator basket, and thus ublituximab uptake was assumed to displace a market basket consisting of 45% ocrelizumab, 45% rituximab, 7% natalizumab, and 3% ofatumumab, only 17% of the population could initiate ublituximab before crossing the potential budget impact threshold. That is because biosimilar rituximab is priced considerably less than the placeholder price for ublituximab, and thus when included in the comparator market basket, the average price of comparator market basket is less costly than ublituximab. All patients could be treated with ublituximab without crossing the potential budget impact threshold if ublituximab was priced at any of the threshold prices. Figure 7.1 displays the cumulative annual budget impact per patient treated with ublituximab for this scenario that includes biosimilar rituximab at the placeholder price for ublituximab.

Figure 7.1. Cumulative Annual Budget Impact per Patient Treatment with Ublituximab with Comparator Basket Inclusive of Biosimilar Rituximab



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Supplemental Materials

A. Background: Supplemental Information

The following definitions are adapted from the 2017 and 2019 ICER MS reviews.

A1. Definitions

Commonly used Clinical Distinctions in MS

Active MS: MS is defined as active when there is clinical evidence of relapse or inflammatory activity (i.e., new or enlarging lesions or gadolinium-enhancing lesions) detected on MRI.

Clinically isolated syndrome: A monophasic clinical episode with patient-reported symptoms and objective findings reflecting a focal or multifocal inflammatory demyelinating event in the central nervous system, developing acutely or sub-acutely, with a duration of at least 24 hours, with or without recovery, and in the absence of fever or infection; similar to a typical MS relapse (attack and exacerbation) but in a patient not known to have MS.[62]

Relapsing-remitting MS (RRMS): MS with periods of partial or complete recovery between acute exacerbations and no significant disability progression between relapses; 85-90% of MS at onset.

Secondary-progressive MS (SPMS): Initial RRMS for several years that is followed by gradual disease progression with or without further relapses.

Primary-progressive MS (PPMS): Progressive accumulation of disability from disease onset, with few or no relapses. Approximately 10-15% of MS patients are diagnosed with PPMS.

Evolving Criteria for Diagnosis of MS

International Advisory Committee on Clinical Trials of MS Revisions (2013): A re-examination of the 1996 phenotype descriptions of MS defined by the US National MS Society Advisory Committee on Clinical Trials in MS. Activity was defined as clinical relapse and/or MRI activity. Progression was defined as the accumulation of disability measured by at least annual clinical evaluation. Relapsing disease was delineated as: 1) a clinically isolated syndrome that was active or not active, and 2) an RRMS classified as “not active” or “active.” Progressive disease was described as: 1) active with progression, 2) active without progression, 3) not active but with progression, and 4) not active without progression. PPMS was defined as the progressive accumulation of disability from onset and SPMS was defined the progressive accumulation of disability after an initial relapsing course.[63]

McDonald Criteria (2010 Revision): Allows the appearance of a new T2 and/or gadolinium-enhancing lesion on MRI at any time following an earlier baseline or reference scan, or the presence of both asymptomatic gadolinium-enhancing and non-enhancing lesions on a presenting patient's first scan for dissemination in time and/or space along with other simplifications.

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.[62]

Outcomes in MS Research

Annualized relapse rate (ARR): The per-person average number of relapses in one year for a group of patients. A relapse is usually defined by new or worsening neurologic symptoms that last at least 24-48 hours and that stabilize over days to weeks and resolve gradually, though not always completely. The definition of a relapse is not consistent across trials, which adds to the uncertainty when comparing results across trials. Experts consider the definitions used in the CombiRx trial to be the benchmark. The investigators carefully delineated protocol defined relapses, non-protocol relapses and suspected relapses.[64]

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. Six-month CDP is considered to be less-sensitive but a more robust outcome than three-month CDP.[35] Table A1 depicts the variations in definitions for CDP across the trials used in the NMA.

Confirmed disability improvement: Decreases of >1.0 or >0.5 points from baseline EDSS score if baseline ≤5.0 or >5.0, respectively, assessed at a scheduled or unscheduled visit, confirmed at six months at a scheduled visit in the absence of relapses.[65]

No Evidence of Disease Activity: Referring to stabilization of disease as evidenced by lack of clinical relapses, lack of disease progression measured by EDSS and absence of new disease activity (new T2 lesions/enhancing lesion) on MRI over a period of observation. No Evidence of Disease Activity-3 essentially measures clinical relapses, MRI evidence of disease activity and disability worsening, all of which are linked to the inflammatory phase of MS. It correlates less with the neurodegenerative process that starts early in the disease course and is ultimately responsible for disease progression. Some of the obvious draw backs of No Evidence Of Disease Activity-3 include the lack of inclusion of brain atrophy and cognitive dysfunction. Adding assessment parameters for cognition and tracking brain volume loss constitutes the basis for No Evidence of Disease Activity-4. Absence of clinical relapses, lack of new or enlarged T2W lesions, and disability progression in the previous six months and a mean annual brain volume loss rate of <0.4% was used to define No Evidence of Disease Activity-4.[66]

Table A1. Confirmed Disability Progression Definitions across Trials Included in NMA

Disability Progression Definition	Trial(s)
Baseline EDSS ≤5.5: Increase in EDSS of ≥1.0 points sustained for 3/6 months **Baseline EDSS >5.5**: Increase in EDSS of ≥0.5 points sustained for 3/6 months	ULTIMATE I and II, TRANSFORMS, FREEDOMS I, OPERA I and II, TEMSO, TOWER
Baseline EDSS 0: Increase in EDSS of ≥1.5 points sustained for 3/6 months **Baseline EDSS 1.0-5.0**: Increase in EDSS of ≥1.0 points sustained for 3/6 months **Baseline EDSS >5.5**: Increase in EDSS of ≥0.5 points sustained for 3/6 months	ASCLEPIOS I and II, OPTIMUM
Baseline EDSS ≤5.0: Increase in EDSS of ≥1.0 points sustained for 3/6 months **Baseline EDSS >5.0**: Increase in EDSS of ≥0.5 points sustained for 3/6 months	FREEDOMS II
Baseline EDSS 0: Increase in EDSS of ≥1.5 points sustained for 3/6 months **Baseline EDSS ≥1.0**: Increase in EDSS of ≥1.0 points sustained for 3/6 months	AFFIRM, CONFIRM, DEFINE
Baseline EDSS 0.0-5.0: Increase in EDSS of ≥1.0 points sustained for 3/6 months	SUNBEAM and RADIANCE
Baseline EDSS 0.0-5.0: Increase in EDSS of ≥1.0 points sustained for 3/6 months **Baseline EDSS 5.5**: Increase in EDSS of ≥0.5 points sustained for 3/6 months	BRAVO
Baseline EDSS 0: Increase in EDSS of ≥1.5 points sustained for 6 months **Baseline EDSS 0.5-4.5**: Increase in EDSS of ≥1.0 points sustained for 6 months **Baseline EDSS >5.0**: Increase in EDSS of ≥0.5 points sustained for 6 months	REGARD
Baseline EDSS 0: Increase in EDSS of ≥1.5 points sustained for 6 months **Baseline EDSS ≥1.0**: Increase in EDSS of ≥1.0 points sustained for 6 months	RIFUND-MS

EDSS: Expanded Disability Status Scale

Confirmed disability progression for EVIDENCE was not reported.

TENERE and HERMES did not report on confirmed disability progression, so it was not applicable.

Expanded Disability Status Scale (EDSS): The oldest and most commonly used measure of disability in MS. The EDSS ranges from 0 to 10 in increments of 0.5, where 0 is a normal examination and 10 is death from MS (see Table A2). Kurtzke first published the scale in 1983.[67] A clinician assigns an FS to a patient in eight neurologic systems (pyramidal, cerebellar, brainstem, sensory, bladder and bowel, vision, cerebral, other) based on a neurologic examination. Scores range from 0-6 with higher scores indicating greater disability. However, as shown in the table, the overall result is not a simple summation of the severity scores.

Table A2. EDSS Grading System*

Grade	Description
0	Normal neurologic examination (all grade 0 in FS, cerebral grade 1 acceptable)
1.0	No disability, minimal signs in one FS (i.e., grade 1 excluding cerebral grade 1)
1.5	No disability, minimal signs in more than 1 FS (more than one grade 1 excluding cerebral grade 1)
2.0	Minimal disability in one FS (one FS grade 2, others 0 or 1)
2.5	Minimal disability in one FS (two FS grade 2, others 0 or 1)
3.0	Moderate disability in one FS (one FS grade 3, others 0 or 1) or mild disability in three or four FS (three/four FS grade 2, others 0 or 1), though fully ambulatory
3.5	Fully ambulatory but with moderate disability in one FS (one grade 3) and one or two FS grade 2, or two FS grade 3, or five FS grade 2 (others 0 or 1)
4.0	Fully ambulatory without aid; self-sufficient; up and about some 12 hours a day despite relatively severe disability, consisting of one FS grade 4 (others 0 or 1) or combinations of lesser grades exceeding limits of previous steps; able to walk approximately 500 meters (m) without aid or resting
4.5	Fully ambulatory without aid; up and about much of the day; able to work a full day; may otherwise have some limitation of full activity or require minimal assistance; characterized by relatively severe disability, usually consisting of one FS grade 4 (others 0 or 1) or combinations of lesser grades exceeding limits of previous steps; able to walk approximately 300 m without aid or rest
5.0	Ambulatory without aid or rest for approximately 200 m; disability severe enough to impair full daily activities (e.g., to work full day without special provisions; usual FS equivalents are one grade 5 alone, others 0 or 1; or combinations of lesser grades usually exceeding specifications for step 4.0)
5.5	Ambulatory without aid or rest for approximately 100 m; disability severe enough to preclude full daily activities (usual FS equivalents are one grade 5 alone; others 0 or 1; or combinations of lesser grades usually exceeding those for step 4.0)
6.0	Intermittent or unilateral constant assistance (cane, crutch, or brace) required to walk approximately 100 m with or without resting (usual FS equivalents are combinations with more than two FS grade 3+)
6.5	Constant bilateral assistance (canes, crutches, or braces) required to walk approximately 20 m without resting (usual FS equivalents are combinations with more than two FS grade 3+)
7.0	Unable to walk beyond approximately 5 m even with aid; essentially restricted to wheelchair; wheels self in standard wheelchair and transfers alone; up and about approximately 12 hr/day (usual FS equivalents are combinations with more than one FS grade 4+; very rarely, pyramidal grade 5 alone)
7.5	Unable to take more than a few steps; restricted to wheelchair; may need aid in transfer; wheels self but cannot carry on in standard wheelchair a full day; may require motorized wheelchair (usual FS equivalents are combinations with more than one FS grade 4+)
8.0	Essentially restricted to bed or chair or perambulated in wheelchair but may be out of bed itself much of the day, retains many self-care functions; generally has effective use of arms (usual FS equivalents are combinations, generally grade 4+ in several systems)
8.5	Essentially restricted to bed much of the day; has some effective use of arms; retains some self-care functions (usual FS equivalents are combinations, generally 4+ in several systems)
9.0	Helpless bedridden patient; can communicate and eat (usual FS equivalents are combinations, mostly grade 4+)
9.5	Totally helpless bedridden patient; unable to communicate effectively or eat/swallow (usual FS equivalents are combinations, almost all grade 4+)
10.0	Death due to MS

*Reproduced from Kurtzke, 1983.[67]

The EDSS is frequently criticized for being insensitive to small changes, being heavily dependent on mobility, being subjective in some assessments with high intra- and inter-rater variability, and not capturing the full range of patient disability.

Timed 25-foot walk test: This test measures gait velocity by averaging the time it takes a patient to complete two 25-foot walks that are spaced less than five minutes apart. Patients may use assistive devices to complete the walk. A change of 20% or more has been identified as clinically significant.[68]

MS Functional Composite (MSFC): The MSFC summarizes the scores on a timed 25-foot walk, the nine-hole peg test, and the paced auditory serial addition test. The goal of this measure is to capture information on key functional measures affected by MS (leg, arm, and cognitive function). The scores are normalized and reported as the number of standard deviations from the mean with higher scores indicating better outcomes. The overall score is the average of the 3 standard deviation scores (z-scores).

Measures Using MRI: MRI technology has evolved significantly over the period that MS clinical trials have been performed. Stronger magnets and changing imaging protocols have improved the utility of MRI in the diagnosis and monitoring of patients with MS. However, these improvements lead to challenges in comparing results across studies. The primary outcomes evaluated in MRI studies of MS include:

T1-weighted images:

- Gadolinium-enhancing lesions that are thought to represent areas of active inflammation
- Hypointensities or "black holes" are thought to indicate areas of permanent nerve damage (axon loss)

T2-weighted images:

- Both the volume and number of T2-weighted lesions as well as the incidence of new and enlarging lesions are sometimes reported. The total volume of T2 lesions is used as a surrogate for the total amount of central nervous system disease, both old and new.

Brain volume:

- In MS, brain volume loss is correlated with the extent of disability and occurs early in the disease course. However, there are several techniques for measurement of brain volume, and it is not routinely measured.

A2. Potential Cost-Saving Measures in MS

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 MS (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 MS 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 MS that could be reduced, eliminated, or made more efficient. No suggestions were received.

B. Patient Perspectives: Supplemental Information

B1. Methods

Interviews with people with MS were conducted during the scoping phase of this review. We conducted interviews with a total of eight patients across the disease spectrum, from more recently diagnosed to non-ambulatory, and with different experiences with DMTs. We interviewed an additional five patients who were part of a patient group. The interview guide focused on three areas: 1) experience of living with MS, including past and current symptoms and how they affect daily life and functioning ; 2) experience with DMTs, including choice of therapy, efficacy, adverse events, and cost; and 3) future treatments and what people with MS would like to see from future treatments.

C. Clinical Guidelines

American Academy of Neurology, 2018[69]

The American Academy of Neurology issued practice guideline recommendations for DMTs for MS in 2018. The guideline recommends that DMT therapy be offered to those patients with relapsing forms of MS, particularly those with recent clinical relapses or MRI activity. Treatment may also be considered in patients who have single demyelinating events with two or more brain or spinal cord lesions. The choice of therapy should consider patient preferences in terms of safety, route of administration, lifestyle, cost, efficacy, and tolerability. Comorbidities such as depression, anxiety, vascular risk factors, and adverse behaviors should be assessed and treated before starting DMT therapy, as those may be associated with worse outcomes. Women of childbearing age should be counseled regarding the reproductive risks of taking DMTs, use of birth control, and plans for pregnancy should be discussed.

The guidelines offer the following recommendations for DMTs for these specific situations:

- For patients with highly active disease, preferred agents are alemtuzumab, fingolimod, and natalizumab.
- For patients with ≥1 relapse, ≥2 new lesions, or confirmed disability progression over one year, consider switching DMTs. Alemtuzumab, natalizumab, fingolimod, and ocrelizumab are preferred in this situation over injectable medications.
- For patients who plan to become pregnant, clinicians should counsel women to stop their DMT before conception for planned pregnancies, unless the risk of MS activity during pregnancy outweighs the risk associated with the DMT during pregnancy. DMTs should be discontinued during pregnancy if accidental exposure occurs, and DMTs should not be initiated during pregnancy unless the risk of MS activity during pregnancy outweighs the risk of DMTs.
- There are no data on stopping DMTs. DMTs in RRMS should be continued unless the patient and physician think stopping is needed. For SPMS, consider stopping DMTs when there have been no relapses or MRI activity for at least two years and EDSS is 7 or greater.

National Institute of Health and Care Excellence, 2022[70]

The National Institute of Health and Care Excellence issued updated guidelines covering the diagnosis and treatment of MS in 2022. The guidelines recommend comprehensive care for people with MS, including a comprehensive review of their care annually, ongoing information and support about the disease and referrals to social services for care needs, discussion about childbearing plans, and advance care planning. The guidelines further discuss assessment and pharmacologic and non-pharmacologic treatment for MS symptom such as fatigue, mobility problems, spasticity, pain, and cognitive problems. In terms of DMTs, the National Institute of Health and Care Excellence guideline refers to technology appraisals of individual drugs for guidance. For the DMTs covered in this review, the National Institute of Health and Care Excellence recommends:

- For patients who do not have highly active or rapidly evolving, severe RRMS, the following agents are recommended: diroximel fumarate, dimethyl fumarate, teriflunomide
- For patients with active disease defined by clinical or imaging features: ponesimod, ofatumumab, ocrelizumab (only if alemtuzumab is contraindicated)
- For patients with highly active or rapidly evolving RRMS: fingolimod, natalizumab, alemtuzumab
- For patients with SPMS: siponimod
- Not recommended: ozanimod (due to unclear effect on disease progression and higher cost-effectiveness estimates than what the National Institute of Health and Care Excellence normally considers reasonable)

Consortium of MS Centers, 2022[71]

The Consortium of MS Centers issued Best Practices in MS Therapies document in 2022. The document offers suggestions for best practices created by a group of MS specialists convened by the Consortium of MS Centers. In terms of therapeutic selection for MS, the best practices include offering a shared decision-making process that considers evidence-based information about the available options, the provider's knowledge and experience, and the patient's values and preferences. Multiple variables including patient-related factors (preferences, risk tolerance, comorbidities, reproductive status), disease-related factors (severity, phenotype, prognostic signs, risk of no treatment or under treatment), treatment-related factors (efficacy, safety, tolerability, monitoring, dosing route and frequency), and system-related factors (insurance coverage, access to services) must be considered when initiating DMTs. DMTs should be started once a patient is diagnosed with clinically isolated syndrome, RRMS or active SPMS. Clinicians should consider high-efficacy therapies in newly diagnosed patients with highly active MS and in patients experiencing breakthrough disease activity while on modestly effective therapies. Switching DMTs should be considered if there is suboptimal response to therapy (i.e., significant relapse, evidence of new activity on MRI, unexpected change in progression of disability, confirmed worsening on neurologic exam) or for patient-related factors (e.g., adherence, lifestyle or job-related issues, insurance issues, symptoms, or quality of life issues). Finally, there may be a subgroup of patients who can safely stop DMT without disease related consequences.

European Committee of Treatment and Research in MS/European Academy of Neurology, 2018[72]

The European Committee of Treatment and Research in MS and the European Academy of Neurology issued a joint guideline on the pharmacologic treatment of people with MS in 2018. The guidelines addressed questions about starting treatment in clinically isolated syndrome, RRMS/SPMS, and PPMS, as well as clinical management questions related to disease monitoring, DMT switching, benefit of long-term treatment with DMT, stopping DMT, and DMT during pregnancy. For RRMS, the guidelines recommend offering early treatment with DMTs in patients with active RRMS as defined by clinical relapses and/or MRI activity. Choosing between the available drugs will depend on patient characteristics and comorbidities, disease severity and activity, drug safety profile and accessibility of the drug, and for RRMS, there are no recommendations about choice of initial therapy. The guidelines recommend switching to another efficacious DMT if the first DMT is stopped and consider continuing DMT if a patient is stable clinically and on MRI and shows no safety or tolerability issues. In terms of patients who are planning a pregnancy, if there is high risk of disease activation, consider using interferon or glatiramer acetate; if a woman has persistently high disease activity, delaying pregnancy is advised; natalizumab or alemtuzumab can be used for these women who decide to get pregnant or have an unplanned pregnancy.

D. Comparative Clinical Effectiveness: Supplemental Information

D1. Detailed Methods

PICOTS

Population

Adults with relapsing forms of MS, including clinically isolated syndrome, RRMS, and active SPMS.

Data permitted, we examined the following subgroups including, but not limited to:

- Race/ethnicity
- Age
- Pregnant or planning a pregnancy
- Clinically isolated subgroup
- RRMS subgroup
- Active SPMS subgroup
- No previous use of DMT/treatment naïve.

Interventions and Comparators

The full list of interventions is as follows:

- Monoclonal antibodies
  - Natalizumab (Tysabri®, Biogen)
  - Ofatumumab (Kesimpta®, Novartis)
  - Ocrelizumab (Ocrevus®, Genentech)
  - Rituximab (Rituxan®, Genentech)
  - Ublituximab (TG Therapeutics)
- Oral therapies
  - Fumarates:
    - Dimethyl fumarate (Tecfidera®, Biogen, and generics)
    - Diroximel fumarate (Vumerity®, Biogen)
    - Monomethyl fumarate (Bafiertam®, Banner Life Sciences)
  - S1P receptor modulators:
    - Fingolimod (Gilenya®, Novartis)
    - Ozanimod (Zeposia®, Bristol Myers Squibb)

        - Ponesimod (Ponvory®, Janssen)
        - Siponimod (Mayzent®, Novartis)
    - Teriflunomide (Aubagio®, Sanofi)

Outcomes

The outcomes of interest are described in the list below. We recognize not all outcomes were measured consistently across disease-modifying therapy clinical trials.

- Patient-important outcomes
    - Disability improvement or progression as measured by:
        - EDSS
        - MSFC
    - Relapse
    - Cognitive function
    - Fatigue
    - Depression
    - Manual dexterity
    - Visual acuity
    - Health-related quality of life outcomes
    - Need for caretaker/health aide
    - Treatment adherence
    - Mobility
    - Ability to maintain employment
    - Adverse events including
        - Serious adverse events
        - Adverse events leading to discontinuation of therapy
        - Adverse events unique to specific drugs
- Other Outcomes
    - MRI outcomes (T2, T1, brain volume changes)
    - No Evidence of Disease Activity 3 and 4
    - Caregiver impact
        - Caregiver quality of life
        - Caregiver health
        - Caregiver productivity

Timing

Evidence on intervention effectiveness was derived from studies of at least one year's duration and evidence on harms from studies of at least three month's duration.

Settings

All relevant settings were considered, with a focus on outpatient settings in the US.

Study Design

RCTs and non-RCTs with any sample size were included. High quality comparative observational studies were also considered.

Table D1. 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, organisations, 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.
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.

Section and Topic	Item #	Checklist item
	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.
		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.

Section and Topic	Item #	Checklist item
	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.

Source: 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 new therapies for relapsing forms of multiple sclerosis followed established best research methods.[73,74] We conducted the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[75] The PRISMA guidelines include a checklist of 27 items.

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 https://icer.org/policy-on-inclusion-of-grey-literature-in-evidence-reviews/.

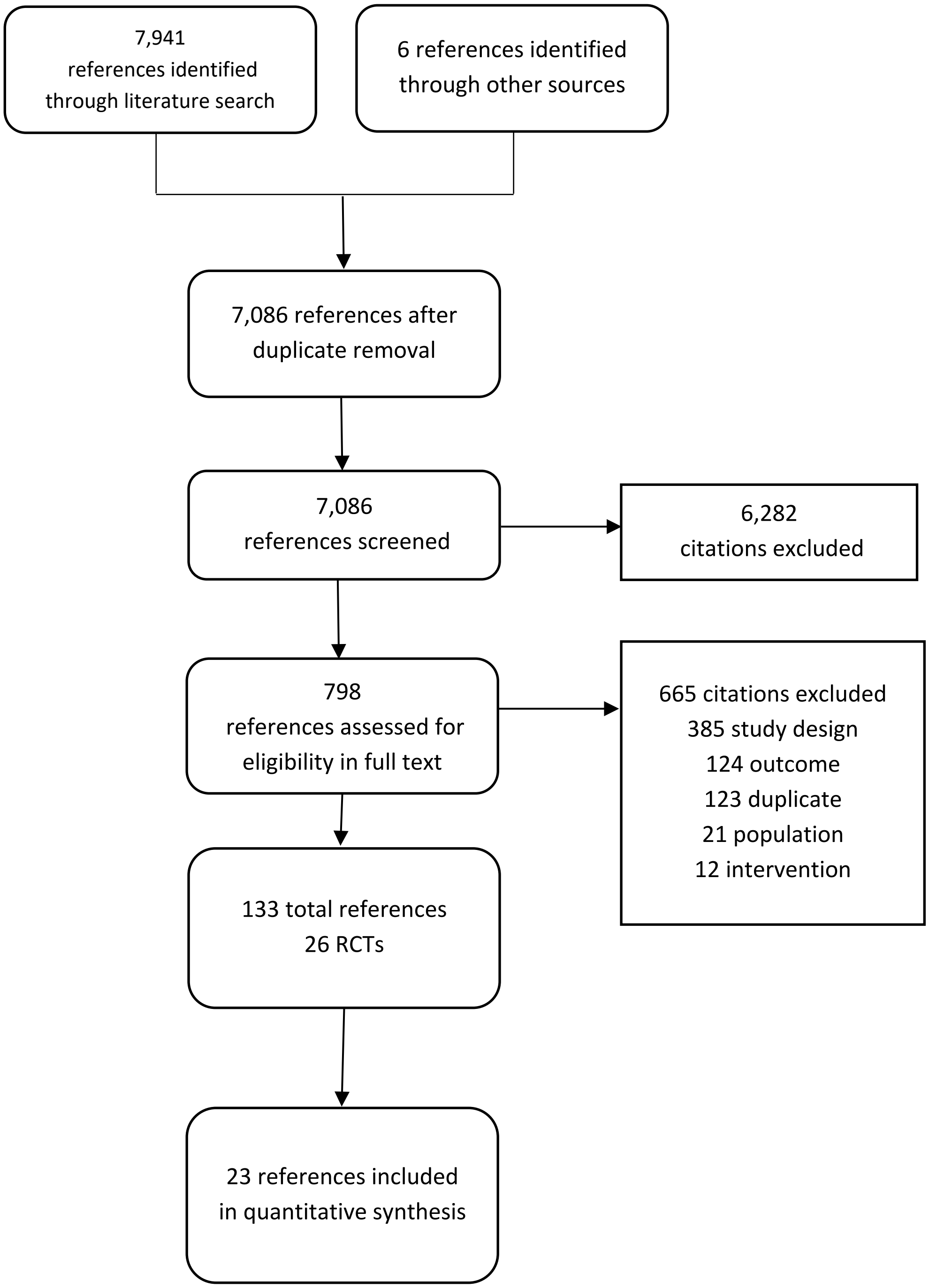
Table D2. Search Strategy of Medline 1996 to Present with Daily Update and Cochrane Central Register of Controlled Trials

1	(multiple sclerosis OR relapse remitting OR secondary progressive OR relapse-remitting multiple sclerosis OR secondary-progressive multiple sclerosis OR clinically isolated syndrome OR RRMS OR SPMS OR CIS).ti,ab
2	(natalizumab OR Tysabri OR ofatumumab OR Kesimpta OR ocrelizumab OR Ocrevus OR rituximab OR Rituxan OR ublituximab OR TG-1101 OR TG-20 OR dimethyl fumarate OR Tecfidera OR diroximel fumarate OR Vumerity OR monomethyl fumarate OR Bafiertam OR fingolimod OR Gilenya OR ozanimod OR Zeposia OR ponesimod OR Ponvory OR siponimod OR Mayzent OR teriflunomide OR Aubagio).ti,ab
3	1 AND 2
4	(addresses or autobiography or bibliography or biography or comment or congresses or consensus development conference or duplicate publication or editorial or guideline or in vitro or interview or lecture or legal cases or legislation or letter or news or newspaper article or patient education handout or periodical index or personal narratives or portraits or practice guideline or review or video audio media).pt.
5	(animals not (humans and animals)).sh.
6	4 OR 5
7	3 NOT 6
8	Limit 7 to English Language
9	Remove duplicates from 8

Table D3. Search Strategy of EMBASE SEARCH

#1	(multiple sclerosis OR relapse remitting OR secondary progressive OR relapse-remitting multiple sclerosis OR secondary-progressive multiple sclerosis OR clinically isolated syndrome OR RRMS OR SPMS OR CIS):ti,ab
#2	(‘natalizumab’ OR ‘Tysabri’ OR ‘ofatumumab’ OR ‘Kesimpta’ OR ‘ocrelizumab’ OR ‘Ocrevus’ OR ‘rituximab’ OR ‘Rituxan’ OR ‘ublituximab’ OR ‘TG-1101’ OR ‘TG-20’ OR ‘dimethyl fumarate’ OR ‘Tecfidera’ OR ‘diroximel fumarate’ OR ‘Vumerity’ OR ‘monomethyl fumarate’ OR ‘Bafiertam’ OR ‘fingolimod’ OR ‘Gilenya’ OR ‘ozanimod’ OR ‘Zeposia’ OR ‘ponesimod’ OR ‘Ponvory’ OR ‘siponimod’ OR ‘Mayzent’ OR ‘teriflunomide’ OR ‘Aubagio’):ti,ab
#3	#1 AND # 2
#4	('case report'/de OR 'practice guideline'/de OR 'questionnaire'/de OR 'chapter'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it)
#5	('animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp) NOT 'human'/exp
#6	#4 OR #5
#7	#3 NOT #6
#8	#7 AND [English]/lim
#9	#8 AND [medline]/lim
#10	#8 NOT #9

Figure D1. PRISMA Flowchart Showing Results of Literature Search for Relapsing Forms of MS



Study Selection

We performed screening at both the abstract and full-text level. Two investigators screened all abstracts identified through electronic searches according to the inclusion and exclusion criteria described earlier. 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.

We also included European Medical Agency regulatory documents related to teriflunomide, dimethyl fumarate, and natalizumab to supplement inputs for the NMA.

Data Extraction and Quality Assessment

We examined the risk of bias for each trial using criteria published in the Cochrane Risk of Bias Assessment Tool.[76,77] Risk of bias was assessed 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. To assess the risk of bias in trials in the report, 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.

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.[78,79]

Assessment of Bias

Table D4. Risk of Bias Assessment

Trial Name	Randomization Process	Deviation from the Intended Interventions	Missing Outcome Data	Measurement of the Outcome	Selection of the Reported Results	Overall Risk of Bias
Monoclonal Antibodies						
AFFIRM	Low	Low	Low	Low	Low	Low
OPERA I	Low	Low	Low	Low	Low	Low
OPERA II	Low	Low	Low	Low	Low	Low
ASCLEPIOS I	Low	Low	Low	Low	Low	Low
ASCLEPIOS II	Low	Low	Low	Low	Low	Low
HERMES	Low	Low	Low	Low	Low	Low
RIFUND-MS	Low	Some concerns	Low	Low	Low	Some concern
ULTIMATE I	Low	Low	Low	Low	Low	Low
ULTIMATE II	Low	Low	Low	Low	Low	Low
Oral Therapies						
CONFIRM	Some concern	Low	Some concern	Low	Low	Low
DEFINE	Low	Low	Some concern	Low	Low	Low
FREEDOMS I	Low	Low	Some concern	Low	Low	Low
FREEDOMS II	Low	Low	Some concern	Low	Low	Low
TRANSFORMS	Low	Low	Low	Low	Low	Low
RADIANCE	Low	Low	Low	Low	Low	Low
SUNBEAM	Low	Low	Low	Low	Low	Low
OPTIMUM	Low	Low	Low	Low	Low	Low
TOWER	Low	Low	Low	Low	Low	Low
TEMSO	Low	Low	Low	Low	Low	Low
TENERE	Low	Low	Low	Low	Low	Low
Interferons						
BRAVO	Some concern	Low	Some concern	Low	Low	Some concern
PRISMS	Low	Low	Low	Low	Low	Low
EVIDENCE	Low	Low	Low	Low	Low	Low

D2. NMA

NMA Methods

We evaluated the feasibility of conducting quantitative synthesis for ARR and CDP outcomes by exploring the differences in study populations, study design, analytic methods, and outcome assessment for each outcome of interest in the 22 RCTs evaluating the DMTs of interest. Trials deemed sufficiently similar in terms of population, intervention type, and outcome definitions were included in the NMAs. Of the 22 identified trials, two trials (ASCEND [natalizumab vs. placebo] and EXPAND [siponimod vs. placebo]) were conducted in SPMS patients, while the remaining 20 trials were conducted in majority RRMS patients (≥90% of the trial population). In addition, patients in ASCEND and EXPAND trials were older (mean age: 47-48 years) and had higher EDSS (mean EDSS: 5.4-6.5) compared to the other trials (mean age: 35-38; mean EDSS: 1.5-2.7). Therefore, we excluded these two trials from our NMAs. For the CDP NMAs, we had no data from two important trials (TENERE [teriflunomide vs. interferon beta-1a 44 mcg] and TRANSFORMS [fingolimod vs. interferon beta-1a 30 mcg]) that connected ocrelizumab (OPERA I and II: ocrelizumab vs. interferon beta-1a 44 mcg) and ozanimod (SUNBEAM: ozanimod vs. interferon beta-1a 30 mcg) to the rest of the network for the ARR NMA. As such, we introduced two trials of interferons (PRISMS: interferon beta-1a 44 mcg vs. placebo and BRAVO: interferon beta-1a 30 mcg vs. placebo) to allow us to connect ocrelizumab and ozanimod to the rest of the network via placebo for the CDP NMAs. See Figures D2-4 for the NMA figures. Patient characteristics and outcome definitions for all the trials included in the NMAs were considered sufficiently similar.

The NMAs combined data from trials comparing DMTs with placebo and direct comparative trials using a Bayesian Markov Chain Monte Carlo method. We used vague or noninformative prior distributions for all model parameters for all analyses. We assumed *a priori* that the random-effects model would be more appropriate because of the differences in patient population and cohort effects over the time period covered by the trials included in the NMA. However, given the sparse network, we explored both random- and fixed-effect models for each network. Posterior mean residual deviance and deviance information criterion values were calculated to assess the goodness of fit of the models to the data. All pairwise comparisons were estimated as medians with their 95% credible intervals.

For the ARR analyses, the primary inputs to the NMA were the number of relapses and the treatment exposure time in person-years. ARR was modeled as a Poisson distribution, using a generalized linear model with a log link. In general, the trials that reported ARRs adjusted for baseline characteristics of the participants rather than crude ARRs. To be faithful to the reported ARRs, we used the reported ARRs and person-years of follow-up to calculate the number of relapses in each arm of a trial. If the study did not report person-years of follow-up, we estimated it using the ARR and the number of relapses reported in the trial. Our preliminary inputs were provided to each manufacturer, and most provided additional data, primarily for the treatment exposure time in each arm of the respective trials. For CDP, we separately analyzed time to three-month CDP (CDP-3) and six-month CDP (CDP-6) as continuous survival models on a log hazard scale using a generalized linear model. The primary inputs to the models were the Log-HR and the associated standard error, derived from the mean HR for CDP-3 and CDP-6 and their associated 95% CIs that were reported in the studies. The Log-HR was calculated by taking the natural log of the mean HR. The standard error was derived from the width of the log of the 95% CIs divided by 3.92 (1.96 x 2). Input data for each NMA are provided in Tables D5-7.

Sensitivity analysis was performed for the 24-week CDP NMA, including one additional trial of interferon (EVIDENCE), which was omitted from the base-case network because of the short-follow up period (48 weeks). In general, a longer follow-up would be required to assess disability progression. The average follow-up duration for the other trials included in the base-case NMA on CDP outcomes ranged from approximately 18 months to two years.

NMA Limitations

Similar to other published NMAs of DMTs, our NMAs have certain limitations. First, due to data limitations, we had to introduce some older trials in our CDP NMA (PRISMS and BRAVO) to allow us to include ocrelizumab and ozanimod, which were only compared to interferon 44 mg and interferon 30 mg, respectively. The included placebo-controlled interferon 30 mg trial (BRAVO) was a single-blinded (rater-blinded) trial. Furthermore, there were slight variations in the definition of CDP across trials and in the proportion of patients who had received prior DMT. Trial heterogeneity was assessed with sensitivity analyses. Second, the network was relatively sparse compared to the number of included treatments. This precluded us from performing meta-regression to assess trial heterogeneity further. However, previously published NMAs in this space have shown that adjustment of the models for baseline risk based on trial-specific placebo arms had negligible impact on the results and therefore have all presented the unadjusted models as the base-case model. Finally, we compared our results to prior NMAs, and the relative ordering of drug effectiveness and magnitude of effectiveness were generally similar for all analyses.

Figure D2. ARR Network Diagram

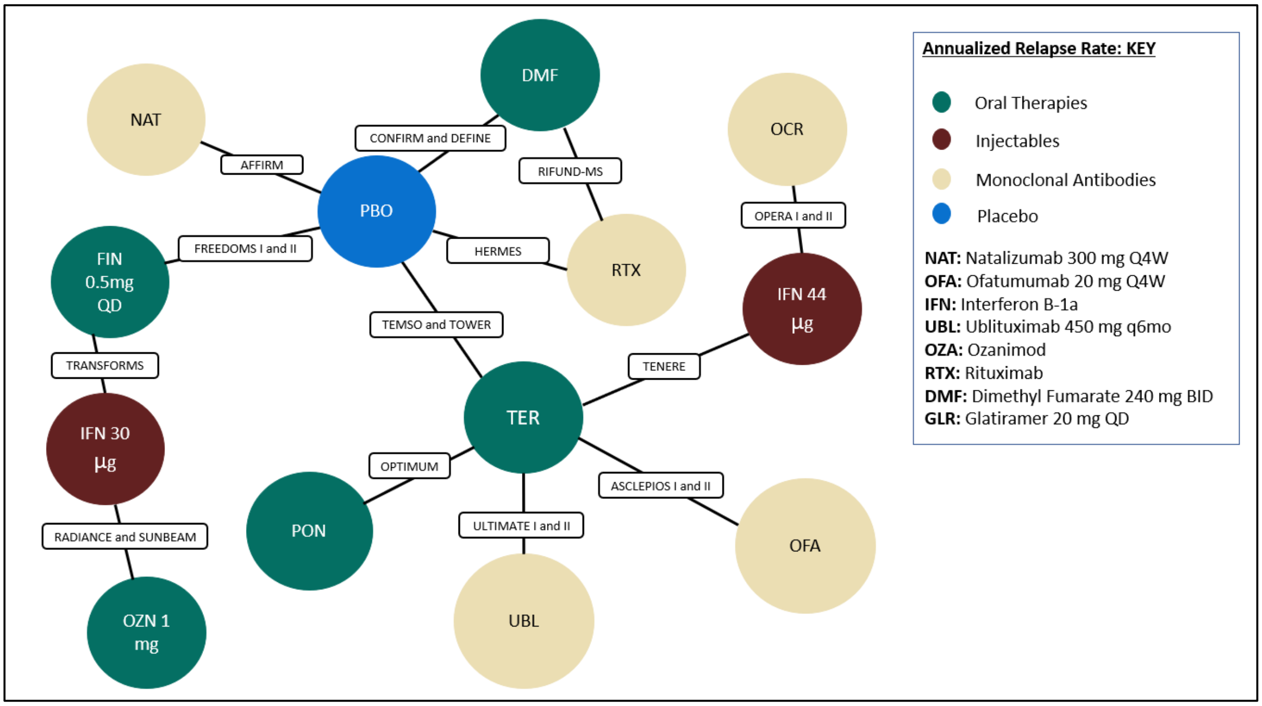


Figure D3. CDP-3 Network Diagram

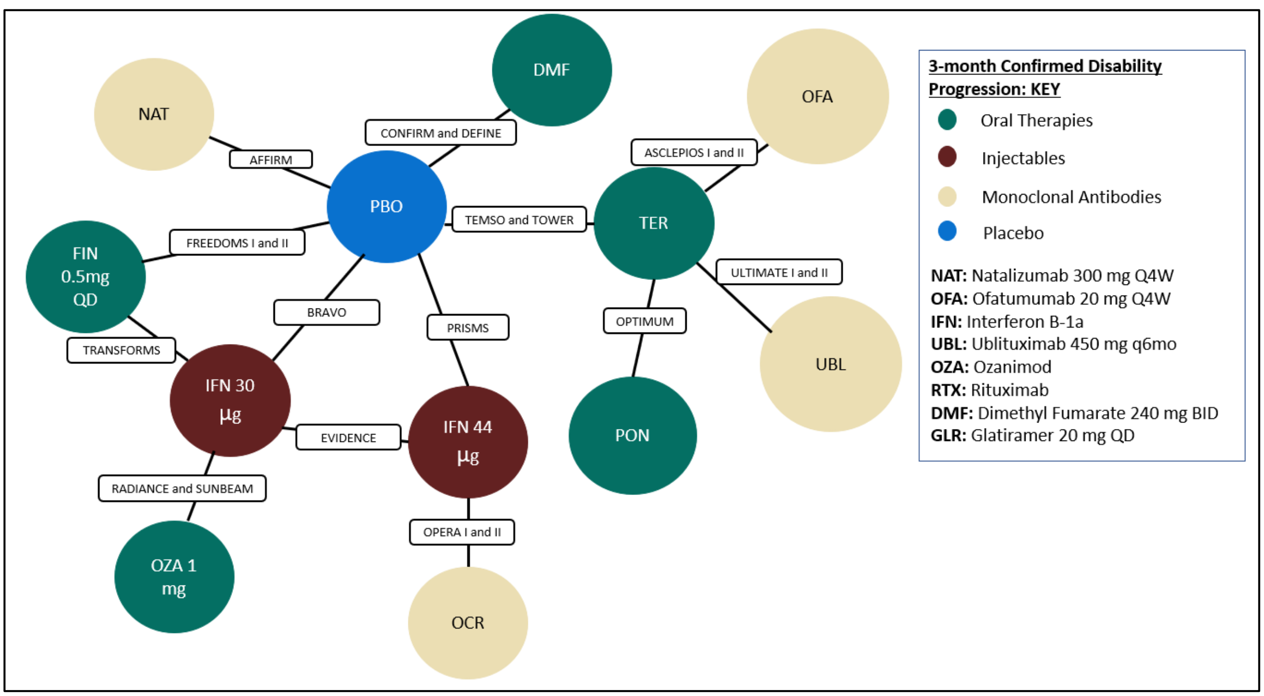


Figure D4. CDP-6 Network Diagram

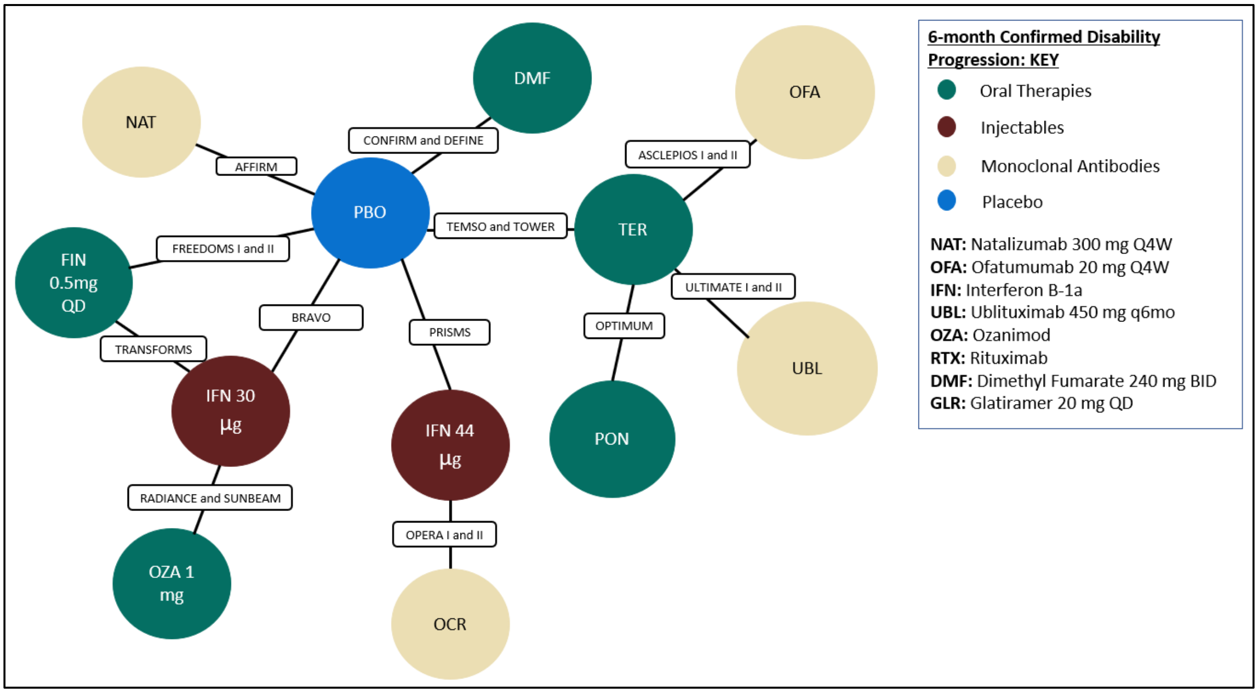


Table D5. Input Data for NMA: ARR (Number of Trials: 20)

Study	Arm	No. of Relapse	Person Years
AFFIRM	Natalizumab	288	1,254
AFFIRM	Placebo	460	630
ASCLEPIOS I	Ofatumumab	90	818.18
ASCLEPIOS I	Teriflunomide 14 mg	177	804.55
ASCLEPIOS II	Ofatumumab	95	950
ASCLEPIOS II	Teriflunomide 14 mg	198	792
CONFIRM	Dimethyl fumarate twice daily	122	553
CONFIRM	Placebo	225	561
DEFINE	Dimethyl fumarate twice daily	128	752.94
DEFINE	Placebo	246	683.33
FREEDOMS I	Fingolimod 0.5 mg	153	850
FREEDOMS I	Placebo	334	836
FREEDOMS II	Fingolimod 0.5 mg	131	623.81
FREEDOMS II	Placebo	246	615
OPERA I	Ocrelizumab	96	600
OPERA I	Interferon β-1a SC 44 µg	166	572.41
OPERA II	Ocrelizumab	98	612.5
OPERA II	Interferon β-1a SC 44 µg	168	579.31
OPTIMUM	Ponesimod 20 mg	242	1,210
OPTIMUM	Teriflunomide 14 mg	344	1,186.21
RADIANCE	Ozanimod 1 mg	143	841.18
RADIANCE	Interferon β-1a IM 30 µg	236	842.86
RIFUND-MS	Rituximab	3	200
RIFUND-MS	Dimethyl fumarate twice daily	17	195.4
SUNBEAM	Ozanimod 1 mg	97	538.89
SUNBEAM	Interferon β-1a IM 30 µg	184	525.71
TEMSO	Teriflunomide 14 mg	227	613.51
TEMSO	Placebo	335	620.37
TENERE	Teriflunomide 14 mg	26	100
TENERE	Interferon β-1a SC 44 µg	16	72.73
TOWER	Teriflunomide 14 mg	177	553.13
TOWER	Placebo	296	592
TRANSFORMS	Fingolimod 0.5 mg	69	429
TRANSFORMS	Interferon β-1a IM 30 µg	142	431
ULTIMATE I	Ublituximab	44	550
ULTIMATE I	Teriflunomide 14 mg	111	584.21
ULTIMATE II	Ublituximab	53	588.89
ULTIMATE II	Teriflunomide 14 mg	102	566.67
HERMES	Rituximab	21	52.5
HERMES	Placebo	19	27.14

ARR: annualized relapse rate, IM: intramuscular, mg: milligram, NMA: network meta analysis, SC: subcutaneous, µg: microgram

Table D6. Input Data for NMA: CDP-6 (Number of Trials: 18)

Study	Treatment	HR for Time to CDP-6	95% CI		Ln HR	SE
			Lower Bound	Upper Bound		
BRAVO	IFN β-1a IM 30 μg	0.73	0.47	1.14	-0.315	0.226
BRAVO	Placebo	Ref	Ref	Ref	N/A	N/A
PRISMS	IFN β-1a SC 44 μg	0.67	0.5	0.9	-0.400	0.150
PRISMS	Placebo	Ref	Ref	Ref	NA	NA
AFFIRM	Natalizumab	0.46	0.33	0.64	-0.777	0.169
AFFIRM	Placebo	Ref	Ref	Ref	N/A	N/A
ASCLEPIOS I	Ofatumumab	0.61	0.4	0.93	-0.494	0.215
ASCLEPIOS I	Teriflunomide 14 mg	Ref	Ref	Ref	N/A	N/A
ASCLEPIOS II	Ofatumumab	0.76	0.49	1.17	-0.274	0.222
ASCLEPIOS II	Teriflunomide 14 mg	Ref	Ref	Ref	N/A	N/A
CONFIRM	Dimethyl fumarate BID	0.62	0.37	1.03	-0.478	0.261
CONFIRM	Placebo	Ref	Ref	Ref	N/A	N/A
DEFINE	Dimethyl fumarate BID	0.77	0.52	1.14	-0.261	0.200
DEFINE	Placebo	Ref	Ref	Ref	N/A	N/A
FREEDOMS I	Fingolimod 0.5 mg	0.63	0.44	0.9	-0.462	0.183
FREEDOMS I	Placebo	Ref	Ref	Ref	N/A	N/A
FREEDOMS II	Fingolimod 0.5 mg	0.72	0.48	1.07	-0.329	0.204
FREEDOMS II	Placebo	Ref	Ref	Ref	N/A	N/A
OPERA I	Ocrelizumab	0.57	0.34	0.95	-0.562	0.262
OPERA I	IFN β-1a SC 44 μg	Ref	Ref	Ref	N/A	N/A
OPERA II	Ocrelizumab	0.63	0.4	0.98	-0.462	0.229
OPERA II	IFN β-1a SC 44 μg	Ref	Ref	Ref	N/A	N/A
OPTIMUM	Ponesimod 20 mg	0.84	0.57	1.24	-0.174	0.198
OPTIMUM	Teriflunomide 14 mg	Ref	Ref	Ref	N/A	N/A
RADIANCE & SUNBEAM	Ozanimod 1 mg	1.41	0.92	2.17	0.344	0.219
RADIANCE & SUNBEAM	IFN β-1a IM 30 μg	Ref	Ref	Ref	N/A	N/A
TEMSO	Teriflunomide 14 mg	0.749	0.505	1.11	-0.289	0.201
TEMSO	Placebo	Ref	Ref	Ref	N/A	N/A
TOWER	Teriflunomide 14 mg	0.843	0.533	1.334	-0.171	0.234
TOWER	Placebo	Ref	Ref	Ref	N/A	N/A
ULTIMATE I & II	Ublituximab	0.657	0.358	1.205	-0.420	0.310
ULTIMATE I & II	Teriflunomide 14 mg	Ref	Ref	Ref	N/A	N/A

BID: twice daily, CDP: confirmed disability progression, CI: confidence interval, HR: hazard ratio, IFN: interferon, IM: intramuscular, Ln: log, mg: milligram, N/A: not applicable, NMA: network meta-analysis, ref: reference, SC: subcutaneous, SE: standard error, μg: microgram

Table D7. Input Data for NMA: CDP-3 (Number of Trials: 18)

Study	Treatment	HR for Time to CDP3	95% CI		Ln HR	Standard Error
			Lower Bound	Upper Bound		
BRAVO	Placebo	Ref	Ref	Ref	N/A	N/A
BRAVO	IFN β-1a IM 30 µg	0.74	0.51	1.09	-0.301	0.194
PRISMS	Placebo	Ref	Ref	Ref	N/A	N/A
PRISMS	IFN β-1a SC 44 µg	0.62	0.43	0.91	-0.478	0.191
AFFIRM	Placebo	Ref	Ref	Ref	N/A	N/A
AFFIRM	Natalizumab	0.58	0.43	0.77	-0.545	0.149
ASCLEPIOS I	Teriflunomide 14 mg	Ref	Ref	Ref	N/A	N/A
ASCLEPIOS I	Ofatumumab	0.65	0.45	0.96	-0.431	0.193
ASCLEPIOS II	Teriflunomide 14 mg	Ref	Ref	Ref	N/A	N/A
ASCLEPIOS II	Ofatumumab	0.66	0.45	0.97	-0.416	0.196
CONFIRM	Placebo	Ref	Ref	Ref	N/A	N/A
CONFIRM	Dimethyl fumarate BID	0.79	0.52	1.19	-0.236	0.211
DEFINE	Placebo	Ref	Ref	Ref	N/A	N/A
DEFINE	Dimethyl fumarate BID	0.62	0.44	0.87	-0.478	0.174
FREEDOMS I	Placebo	Ref	Ref	Ref	N/A	N/A
FREEDOMS I	Fingolimod 0.5 mg	0.7	0.52	0.96	-0.357	0.156
FREEDOMS II	Placebo	Ref	Ref	Ref	N/A	N/A
FREEDOMS II	Fingolimod 0.5 mg	0.83	0.61	1.12	-0.186	0.155
OPERA I	IFN β-1a SC 44 µg	Ref	Ref	Ref	N/A	N/A
OPERA I	Ocrelizumab	0.57	0.37	0.9	-0.562	0.227
OPERA II	IFN β-1a SC 44 µg	Ref	Ref	Ref	N/A	N/A
OPERA II	Ocrelizumab	0.63	0.42	0.92	-0.462	0.200
OPTIMUM	Teriflunomide 14 mg	Ref	Ref	Ref	N/A	N/A
OPTIMUM	Ponesimod 20 mg	0.83	0.58	1.18	-0.186	0.181
RADIANCE & SUNBEAM	IFN β-1a IM 30 µg	Ref	Ref	Ref	N/A	N/A
RADIANCE & SUNBEAM	Ozanimod 1 mg	0.95	0.68	1.33	-0.051	0.171
TEMSO	Placebo	Ref	Ref	Ref	N/A	N/A
TEMSO	Teriflunomide 14 mg	0.7	0.51	0.97	-0.357	0.164
TOWER	Placebo	Ref	Ref	Ref	N/A	N/A
TOWER	Teriflunomide 14 mg	0.68	0.47	1	-0.386	0.193
ULTIMATE I and II	Teriflunomide 14 mg	Ref	Ref	Ref	N/A	N/A
ULTIMATE I and II	Ublituximab	0.84	0.5	1.41	-0.174	0.264

BID: twice daily, CDP: confirmed disability progression, CI: confidence interval, HR: hazard ratio, IFN: interferon, IM: intramuscular, Ln: log, mg: milligram, N/A: not applicable, NMA: network meta-analysis, ref: reference, SC: subcutaneous, µg: microgram

Figure D5. League Table: ARR Base Case

Ofatumumab												
0.97 (0.66, 1.43)	**Ublituximab**											
0.94 (0.61, 1.45)	0.97 (0.6, 1.54)	**Natalizumab**										
0.96 (0.46, 2.09)	0.99 (0.46, 2.21)	1.03 (0.46, 2.33)	**Ocrelizumab**									
0.87 (0.46, 1.71)	0.9 (0.47, 1.8)	0.93 (0.5, 1.79)	0.91 (0.35, 2.34)	**Rituximab**								
0.65 (0.44, 0.95)	0.67 (0.44, 1.01)	0.69 (0.43, 1.1)	0.67 (0.3, 1.44)	0.74 (0.37, 1.42)	**Ponesimod**							
0.61 (0.41, 0.9)	**0.63 (0.41, 0.97)**	**0.65 (0.45, 0.94)**	0.63 (0.28, 1.37)	0.7 (0.37, 1.26)	0.95 (0.61, 1.45)	**Fingolimod 0.5 mg**						
0.55 (0.36, 0.8)	**0.57 (0.36, 0.85)**	**0.59 (0.39, 0.82)**	0.57 (0.25, 1.22)	0.63 (0.34, 1.1)	0.86 (0.53, 1.27)	0.91 (0.63, 1.21)	**DMF**					
0.53 (0.26, 1.1)	0.55 (0.26, 1.16)	0.57 (0.27, 1.23)	**0.55 (0.43, 0.71)**	0.61 (0.24, 1.51)	0.82 (0.4, 1.74)	0.87 (0.42, 1.85)	0.96 (0.47, 2.09)	**IFN 44 µg**				
0.53 (0.29, 0.95)	0.54 (0.29, 1.01)	0.56 (0.32, 1)	0.55 (0.22, 1.34)	0.6 (0.28, 1.25)	0.82 (0.44, 1.51)	0.86 (0.55, 1.35)	0.96 (0.57, 1.7)	0.99 (0.41, 2.34)	**Ozanimod 1 mg**			
0.44 (0.35, 0.57)	**0.46 (0.34, 0.61)**	**0.47 (0.33, 0.68)**	**0.46 (0.22, 0.93)**	**0.51 (0.27, 0.91)**	**0.69 (0.51, 0.93)**	0.73 (0.53, 1)	0.8 (0.61, 1.15)	0.84 (0.42, 1.62)	0.84 (0.49, 1.45)	**Teriflunomide 14 mg**		
0.3 (0.17, 0.51)	**0.31 (0.17, 0.54)**	**0.32 (0.19, 0.53)**	**0.31 (0.13, 0.73)**	**0.34 (0.16, 0.68)**	**0.46 (0.26, 0.81)**	**0.49 (0.33, 0.71)**	**0.54 (0.34, 0.91)**	**0.56 (0.24, 1.27)**	**0.56 (0.44, 0.71)**	0.67 (0.41, 1.08)	**IFN 30 µg**	
0.29 (0.21, 0.41)	**0.3 (0.21, 0.44)**	**0.31 (0.23, 0.42)**	**0.31 (0.14, 0.64)**	**0.34 (0.19, 0.58)**	**0.46 (0.32, 0.66)**	**0.48 (0.39, 0.6)**	**0.53 (0.44, 0.7)**	0.56 (0.27, 1.11)	**0.56 (0.34, 0.92)**	**0.66 (0.53, 0.82)**	0.99 (0.64, 1.55)	**PBO**

DMF: dimethyl fumarate, IFN: interferon, mg: milligram, PBO: placebo, µg: microgram

The DMTs are arranged from most effective (top left) to least effective (bottom right). Each box represents the estimated median rate ratio and 95% credible interval. Estimates in bold signify that the 95% credible interval does not contain 1.

Figure D6. League Table: CDP-6 Base Case

Ocrelizumab											
0.88 (0.41, 1.86)	**Natalizumab**										
0.75 (0.34, 1.68)	0.86 (0.42, 1.74)	**Ofatumumab**									
0.77 (0.28, 2.06)	0.88 (0.35, 2.18)	1.02 (0.47, 2.23)	**Ublituximab**								
0.61 (0.25, 1.45)	0.69 (0.32, 1.51)	0.81 (0.43, 1.52)	0.78 (0.34, 1.84)	**Ponesimod**							
0.61 (0.29, 1.21)	0.69 (0.38, 1.23)	0.81 (0.42, 1.51)	0.79 (0.33, 1.82)	1 (0.48, 2.02)	**Fingolimod 0.5 mg**						
0.6 (0.4, 0.9)	0.69 (0.36, 1.31)	0.81 (0.4, 1.62)	0.78 (0.32, 1.96)	1 (0.46, 2.13)	1 (0.57, 1.8)	**IFN 44 µg**					
0.58 (0.28, 1.19)	0.66 (0.36, 1.21)	0.77 (0.39, 1.49)	0.75 (0.31, 1.78)	0.95 (0.45, 1.99)	0.95 (0.57, 1.62)	0.95 (0.53, 1.72)	**DMF**				
0.56 (0.24, 1.26)	0.63 (0.31, 1.3)	0.74 (0.34, 1.58)	0.72 (0.28, 1.87)	0.92 (0.4, 2.1)	0.92 (0.48, 1.77)	0.92 (0.45, 1.85)	0.97 (0.49, 1.88)	**IFN 30 µg**			
0.51 (0.25, 1.03)	0.58 (0.32, 1.05)	0.68 (0.46, 1)	0.66 (0.33, 1.32)	0.84 (0.51, 1.4)	0.84 (0.51, 1.42)	0.84 (0.48, 1.51)	0.89 (0.52, 1.54)	0.92 (0.47, 1.79)	**Teriflunomide 14 mg**		
0.39 (0.14, 1.04)	0.45 (0.18, 1.09)	0.52 (0.2, 1.32)	0.5 (0.17, 1.54)	0.65 (0.24, 1.74)	0.64 (0.28, 1.51)	0.64 (0.26, 1.56)	0.68 (0.29, 1.61)	0.7 (0.41, 1.21)	0.76 (0.33, 1.82)	**Ozanimod 1 mg**	
0.41 (0.22, 0.74)	**0.46 (0.29, 0.73)**	**0.54 (0.31, 0.91)**	0.52 (0.24, 1.15)	0.67 (0.36, 1.26)	**0.67 (0.47, 0.96)**	0.67 (0.43, 1.04)	0.7 (0.48, 1.04)	0.73 (0.42, 1.27)	0.79 (0.55, 1.15)	1.03 (0.48, 2.24)	**PBO**

DMF: dimethyl fumarate, IFN: interferon, mg: milligram, PBO: placebo, µg: microgram

The DMTs are arranged from most effective (top left) to least effective (bottom right). Each box represents the estimated median rate ratio and 95% credible interval. Estimates in bold signify that the 95% credible interval does not contain 1.

Figure D7. League Table: CDP-3 Base Case

Ocrelizumab											
0.83 (0.39, 1.8)	**Ofatumumab**										
0.64 (0.31, 1.31)	0.78 (0.42, 1.43)	**Natalizumab**									
0.64 (0.29, 1.49)	0.78 (0.45, 1.38)	1 (0.51, 2.01)	**Ponesimod**								
0.64 (0.26, 1.56)	0.79 (0.39, 1.53)	1.01 (0.46, 2.18)	1.01 (0.47, 2.07)	**Ublituximab**							
0.6 (0.42, 0.86)	0.73 (0.37, 1.41)	0.95 (0.51, 1.73)	0.94 (0.44, 1.93)	0.94 (0.41, 2.13)	**IFN 44 µg**						
0.53 (0.22, 1.28)	0.64 (0.28, 1.43)	0.83 (0.39, 1.8)	0.82 (0.34, 1.92)	0.82 (0.32, 2.11)	0.88 (0.39, 1.98)	**Ozanimod 1 mg**					
0.54 (0.27, 1.06)	0.65 (0.37, 1.15)	0.84 (0.5, 1.41)	0.84 (0.43, 1.58)	0.84 (0.4, 1.78)	0.9 (0.5, 1.58)	1.03 (0.49, 2.12)	**DMF**				
0.54 (0.28, 1.07)	**0.65 (0.47, 0.92)**	0.84 (0.5, 1.4)	0.84 (0.53, 1.3)	0.84 (0.47, 1.51)	0.89 (0.51, 1.59)	1.02 (0.49, 2.15)	1 (0.63, 1.6)	**Teriflunomide 14 mg**			
0.5 (0.23, 1.08)	0.61 (0.31, 1.18)	0.79 (0.42, 1.46)	0.79 (0.36, 1.6)	0.78 (0.34, 1.82)	0.83 (0.42, 1.63)	0.95 (0.61, 1.47)	0.93 (0.52, 1.65)	0.93 (0.52, 1.65)	**IFN 30 µg**		
0.48 (0.25, 0.93)	0.59 (0.34, 1.02)	0.75 (0.46, 1.25)	0.75 (0.39, 1.4)	0.75 (0.37, 1.57)	0.8 (0.47, 1.4)	0.91 (0.45, 1.89)	0.9 (0.58, 1.4)	0.9 (0.58, 1.4)	0.96 (0.56, 1.7)	**Fingolimod 0.5 mg**	
0.37 (0.21, 0.67)	**0.45 (0.28, 0.72)**	**0.58 (0.39, 0.87)**	0.58 (0.32, 1)	0.57 (0.3, 1.13)	**0.62 (0.39, 0.99)**	0.7 (0.36, 1.36)	**0.69 (0.5, 0.96)**	**0.69 (0.5, 0.95)**	0.74 (0.46, 1.21)	0.77 (0.57, 1.02)	PBO

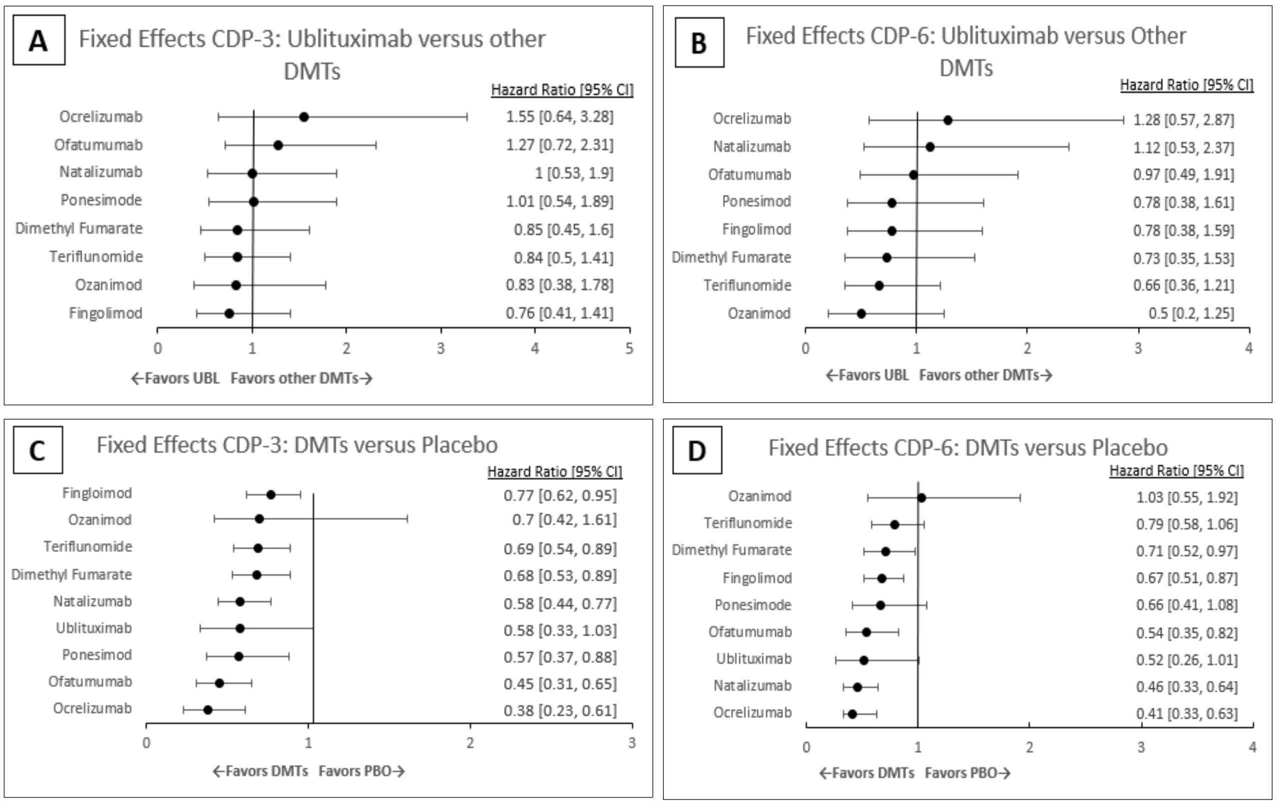
DMF: dimethyl fumarate, IFN: interferon, mg: milligram, PBO: placebo, µg: microgram

The DMTs are arranged from most effective (top left) to least effective (bottom right). Each box represents the estimated median hazard ratio and 95% credible interval. Estimates in bold signify that the 95% credible interval does not contain 1.

Sensitivity Analysis

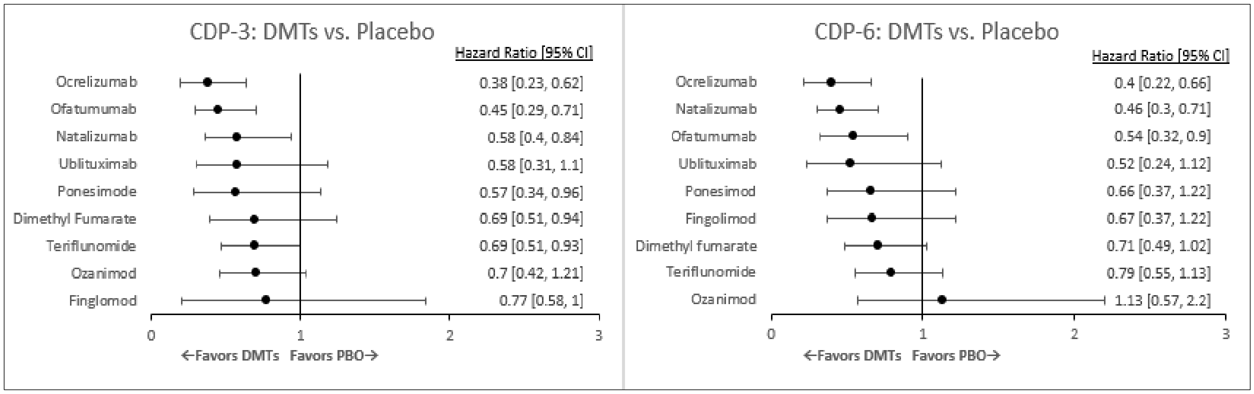
The fixed effect NMA models and the sensitivity analysis models (which included an additional interferon trial (EVIDENCE) that was excluded from the base-case model) provided a similar fit to the data compared with the base-case model. Results of fixed effect models and sensitivity analyses for the CDP NMAs are presented below.

Figure D8. Fixed Effect NMAs: Time to Sustained Disability Progression (CDP-3 and CDP-6)



CDP: confirmed disability progression, CI: confidence interval, DMT: disease-modifying therapy, PBO: placebo, UBL: ublituximab
Forest plot shows the estimated HRs and 95% CIs.

Figure D9. Additional Sensitivity Analyses (Includes EVIDENCE Trial Excluded from Base-Case Analysis)



CDP: confirmed disability progression, CI: confidence interval, DMT: disease-modifying therapy, PBO: placebo, UBL: ublituximab

Forest plot shows the estimated HRs and 95% CIs.

D3. Evidence Tables

Table D8. Study Design

Title	Study Design	Population	Dosing Regimen	Entry Criteria	Primary Outcome	MS Criteria Used
AFFIRM Polman 2006[80] NCT00027300	Phase III double-blind, PBO-controlled, parallel-group multicenter RCT Trial duration: 2 years	Patients with RMS	**Arm I:** natalizumab 300 mg IV every 4 weeks up to 116 weeks **Arm II:** matched PBO	**Inclusion:** -Age 18 and 50 -EDSS of 0 to 5.0 -Diagnosis of RMS (McDonalds Criteria 2001) -At least one medically documented relapse within 12 months before the study began **Exclusion:** -PP, SP, or progressive relapsing -Relapse within 50 days before the administration of first dose of study drug -Treatment with cyclophosphamide or mitoxantrone within previous year, or treatment with IFN beta, glatiramer acetate, cyclosporine, azathioprine, methotrexate, or IVIG within previous 6 months	Cumulative probability of sustained progression of disability at 2 years	2001 McDonald Criteria
OPERA I & II Hauser 2017[81] NCT01412333 & NCT01247324	Phase III double-blind, parallel-group, RCT Trial duration: 96 weeks	Patients with RMS	**Arm I:** OCR 600 mg IV every 24 weeks (2 300-mg infusions on days 1 and 15 for the first dose and a single 600 mg infusion thereafter) + matching SC PBO up to 96 weeks **Arm II:** IFN beta-1a at a dose of 44 µg SC three times weekly + matching IV PBO up to 96-	**Inclusion:** -Age 18 to 55 -EDSS of 0-5.5 at screening -Diagnosis of MS (revised McDonald criteria 2010) -At least 2 documented clinical relapses within previous 2 years or 1 clinical relapse within year before screening -MRI of brain showing abnormalities consistent with MS **Exclusion:** -Diagnosis of PPMS -Previous treatment with any B-cell targeted therapy or other immunosuppressive medication as defined in protocol	ARR	2010 McDonald Criteria

Title	Study Design	Population	Dosing Regimen	Entry Criteria	Primary Outcome	MS Criteria Used
			weeks All patients received one 100 mg dose of IV methylprednisolone before each infusion	-Disease duration of more than 10 years in combination with EDSS of 2.0 or less at screening		
ASCLEPIOS I & II Hauser 2020[82] NCT02792218 & NCT02792231	Double-blind, double-dummy, Phase III trial Trial duration: 1.6 years	Patients with RMS	**Arm I:** OFA 20 mg SC subcutaneously every 4 weeks after 20 mg loading doses at days 1, 7, and 14 + oral PBO **Arm II:** Oral TER at dose of 14 mg once daily, for up to 30 months + SC PBO	**Inclusion:** -Age 18 to 55 -EDSS of 0 to 5.5 -Diagnosis of MS with a RMS or SPMS course (2010 revised McDonald criteria) -At least 1 relapse in year before screening, at least two relapses in 2 years before screening, or; at least one lesion detected with the use of gadolinium enhancement (gadolinium-enhancing lesion) on MRI in year before randomization **Exclusion:** -Diagnosed with PPMS or SPMS without disease activity -Disease duration of more than 10 years with EDSS of 2.0 or less -Pregnant or lactating -Neurological findings consistent with PML or confirmed PML -Treated with medications as specified or within timeframes (e.g., corticosteroids, ofatumumab, rituximab, ocrelizumab, alemtuzumab, natalizumab, cyclophosphamide, teriflunomide, leflunomide, etc.)	ARR	2010 McDonald Criteria

Title	Study Design	Population	Dosing Regimen	Entry Criteria	Primary Outcome	MS Criteria Used
HERMES Hauser 2008[83] NCT00097188	Phase II randomized, double-blind, PBO-controlled study Trial duration: 48 weeks	Patients with RRMS	Arm I: Rituximab 1000 mg IV on days 1 and 15 Arm II: Matched IV PBO	**Inclusion:** -Age 18 to 55 -EDSS of 0 to 5.0 -Diagnosis of RRMS -2005 McDonalds Criteria -At least 1 relapse during preceding year **Exclusion:** -Disease categorized as SP, PS, or progressive relapsing disease -Relapse within 30 days -Cyclophosphamide or mitoxantrone treatment within 12 months -Systemic corticosteroid therapy within 30 days; treatment with IFN beta, glatiramer acetate, natalizumab, plasmapheresis, or IVIG within 60 days; or non-lymphocyte-depleting immunosuppressive therapies within 90 days	Total count of gadolinium-enhancing lesions detected on MRI scans of brain	2005 McDonald Criteria
RIFUND-MS Svenningsson 2022[84] NCT02746744	Phase III multicenter, rater-blinded, active-comparator RCT Trial duration: 24 months	Patients with RRMS	**Arm I:** IV Rituximab 1000 mg followed by 500 mg every 6 months **Arm II:** Oral dimethyl fumarate 240 mg BID	**Inclusion:** -Aged 18-50 -Diagnosis of RRMS (prevailing McDonald Criteria) or with demyelinating episode in conjunction with at least 1 asymptomatic lesion compatible with MS -10 years or less since diagnosis (initially ≤5 years but increased in April 2017 to ≤10 years to expand recruitment base) -Treatment naive or had exposure only to beta IFNs or glatiramer acetate -EDSS of 0-5.5 -Documented evidence of disease activity (minimum of 1 relapse, 2 new enlarged T2 lesions, or 1 contrast-enhancing lesion) in preceding year	Proportion of patients with at least 1 relapse	2010/ 2017 McDonald Criteria

Title	Study Design	Population	Dosing Regimen	Entry Criteria	Primary Outcome	MS Criteria Used
				Exclusion: -Diagnosis of progressive multiple sclerosis -Pregnant or breastfeeding -Contraindications for MRI -Receiving simultaneous treatment with other immunosuppressive drugs -Severe cardiac disorder		
ULTIMATE I & II Steinman 2022[23] NCT03277248 & NCT03277261	Phase III double-blind, active-controlled, multi-center RCT Trial duration: 96 weeks	Adults with RMS with active disease	**Arm I:** UBL 150 mg IV (over 4 hours on day 1 followed by 450 mg over 1 hour on days 15, 168, 336, and 504 (week 72) + oral PBO once daily up to week 95 **Arm II:** TER 14 mg tablet orally once daily from day 1 up to week 95 + PBO IV infusion on days 1, 15, 168, 336, and 504 (week 72)	**Inclusion:** -Age 18-55 -EDSS of 0-5.5 at screening -Diagnosis of RMS and active disease -McDonald Criteria 2010 **Exclusion:** -Treatment with prior anti-CD20 or other B-cell directed treatment, alemtuzumab, natalizumab, teriflunomide, leflunomide and stem cell transplantation -Diagnosis with PPMS -Pregnant or nursing	ARR	2010 McDonald Criteria
CONFIRM Fox 2012[85] NCT00451451	Phase III randomized study Trial duration: 104 weeks	Adults with RRMS	**Arm I:** BG-12 240 mg BID **Arm II:** BG-12 240 mg 3 times daily **Arm III:** glatiramer acetate 20 mg SC daily **Arm IV:** daily oral PBO	**Inclusion:** -Age 18-55 -Diagnosis of RRMS -McDonald Criteria 2005 -EDSS of 0-5.0 -At least 1 clinically documented relapse in previous 12 months or at least 1 gadolinium enhancing lesions 0 to 6 weeks before randomizations **Exclusion:** -Progressive forms of MS	ARR	2005 McDonald Criteria

Title	Study Design	Population	Dosing Regimen	Entry Criteria	Primary Outcome	MS Criteria Used
				-Other clinically significant illness -Prespecified laboratory abnormalities -Prior exposure to glatiramer acetate or contraindicated medications		
DEFINE Gold 2012[86] NCT00420212	Phase III double-blind, PBO-controlled RCT Trial duration: 104 weeks	Adults with RRMS	**Arm I:** BG-12 240 mg two times daily **Arm II:** BG-12 240 mg three times daily **Arm III:** matched placebo	**Inclusion:** -Age 18-55 -Diagnosis of RRMS -McDonald Criteria 2005 -EDSS of 0-5.0 -Disease activity as evidenced by at least 1 clinically documented relapse within 12 months before randomization or a brain MRI scan obtained 6 weeks before randomization showing at least 1 gadolinium-enhancing lesion **Exclusion:** -Progressive forms of MS -Another major disease that would preclude participation -Abnormal results on prespecified laboratory tests -Recent exposure to contraindicated medications	ARR	2005 McDonald Criteria
FREEDOMS I Kappos 2010[87] NCT0028997	Phase III, double-blind, PBO-controlled RCT Trial duration: 104 weeks	Adults with RRMS	**Arm I:** oral FIN 0.5 mg daily for 24 months **Arm II:** oral FIN 1.0 mg daily for 24 months **Arm III:** oral PBO daily for 24 months	**Inclusion:** -Age 18-55 -EDSS of 0-5.5 -Diagnosis of RMS -2005 revised McDonalds Criteria -1 or more documented relapses in the previous year or 2 or more in the previous 2 years **Exclusion:** -Relapse or corticosteroid treatment within 30 days before randomization, active	ARR	2005 McDonald Criteria

Title	Study Design	Population	Dosing Regimen	Entry Criteria	Primary Outcome	MS Criteria Used
				infection, macular edema, diabetes, immune suppression (drug- or disease-induced), or clinically significant systemic disease; IFN-beta or glatiramer acetate therapy had to have been stopped 3 or more months before randomization		
FREEDOMS II Calabresi 2014[88] NCT00355134	Phase III double-blind, PBO-controlled, parallel-group, multicenter RCT Trial duration: 104 weeks	Adults with RRMS	**Arm I:** oral FIN 0.5 mg daily for 24 months **Arm II:** oral FIN 1.25 mg daily for 24 months **Arm III:** oral PBO daily for 24 months	**Inclusion:** -Age 18-55 -EDSS of 0-5.5 -Diagnosed with RRMS -2005 revised McDonald criteria -Had 1 or more confirmed relapses during preceding year (or 2 or more confirmed relapses during previous 2 years), -Both treatment-naive and previously treated patients included in study **Exclusion:** -Clinically significant systemic disease or immune suppression (drug-induced or disease-induced) -Active infection or macular oedema, diabetes, or history of malignancy (apart from successfully treated basal or squamous-cell skin carcinoma) -Specific cardiac, pulmonary, or hepatic disorders excluded	ARR	2005 McDonald Criteria
TRANSFORMS Cohen 2010[36] NCT00340834	Phase III, multicenter, double-blind, double-dummy, parallel-group RCT	Patients with RRMS	**Arm I:** oral FIN 0.5 mg daily for 24 months **Arm II:** oral FIN 1.25 mg daily for 24 months	**Inclusion:** -Age 18-55 -EDSS of 0-5.5 -Diagnosis of MS with RR course -Had had at least 1 documented relapse during previous year or at least 2 documented relapses during previous 2 years	ARR	2005 McDonald Criteria

Title	Study Design	Population	Dosing Regimen	Entry Criteria	Primary Outcome	MS Criteria Used
	Trial duration: 52 weeks		**Arm III:** IM IFN beta-1a (Avonex®), at weekly dose of 30 µg	**Exclusion:** -Documented relapse or corticosteroid treatment within 30 days before randomization -Active infection, macular edema, immunosuppression (either drug- or disease-induced) -Clinically significant coexisting systemic disease -Previous recent therapy with either any type of IFN beta or glatiramer acetate was not criterion for exclusion		
SUNBEAM Comi 2019[34] NCT02047734	Phase III double-blind, double-dummy, active-controlled RCT Trial duration: 52 weeks	Patients with RRMS	**Arm I:** once daily oral ozanimod 1 mg **Arm II:** once daily oral ozanimod 0.5 mg **Arm III:** weekly IM injections of IFN beta-1a 30 µg An initial 7-day dose escalation was used for ozanimod and oral PBO	**Inclusion:** -Age 18-55 -EDSS of 0-5.0 -RRMS, PRMS, or SPMS diagnosis -McDonald Criteria 2010 -Either at least 1 relapse in 12 months before screening or at least one relapse in the 24 months before screening + at least 1 gadolinium-enhancing lesion in 12 months before randomization -History of brain MRI lesions consistent with MS -No history of relapse or systemic corticosteroid or adrenocorticotrophic hormone use from 30 days before screening up to randomization **Exclusion:** -Diagnosis of PPMS -Disease duration more than 15 years -EDSS of 2.0 or less -Contraindications to MRI or gadolinium contrast	ARR	2010 McDonald Criteria

Title	Study Design	Population	Dosing Regimen	Entry Criteria	Primary Outcome	MS Criteria Used
				-Previous inability to tolerate IFN beta -Specific cardiac conditions (e.g., recent MI, stroke) -Previous treatment with lymphocyte-depleting therapies or lymphocyte trafficking blockers; or active infections excluded		
RADIANCE Cohen 2019[89] NCT02047734	Phase III multicenter, double-blind RCT Trial duration: 104 weeks	Adults with RR, PR, or SPMS	**Arm I:** once daily oral ozanimod 1·0 mg **Arm II:** once daily oral ozanimod 0·5 mg **Arm III:** weekly IM injections of IFN beta-1a 30 µg An initial 7-day dose escalation was used for ozanimod and oral PBO	**Inclusion:** -Age 18-55 -EDSS of 0-5.50 -Diagnosis of RRMS, PRMS, or SPMS -McDonald Criteria 2010 -Either at least 1 relapse within 12 months before screening or at least 1 relapse within 24 months before screening plus at least 1 gadolinium-enhancing lesion within 12 months before randomization -Brain MRI lesions consistent with MS **Exclusion:** -Diagnosis of PPMS -Disease duration greater than 15 years -EDSS of 2.0 or less -Previous inability to tolerate IFN beta -Specific CV conditions (e.g., recent MI) -Previous treatment with lymphocyte-depleting therapies or lymphocyte-trafficking blockers	ARR	2010 McDonald Criteria
OPTIMUM Kappos 2021[90] NCT02425644	Phase III multicenter, double-blind, active-comparator RCT	Adults with RRMS, SPMS	**Arm I:** Ponesimod 20 mg qd **Arm II:** Teriflunomide 14 mg qd	**Inclusion:** -Age 18-55 -EDSS of 0-5.5 -RRMS or SPMS -McDonald 2010 Diagnostic Criteria -Recent clinical or MRI activity, 1 or more MS attacks within 1-12 months of	ARR	2010 McDonald Criteria

Title	Study Design	Population	Dosing Regimen	Entry Criteria	Primary Outcome	MS Criteria Used
	Trial duration: 108 weeks			assessment, or two or more attacks within 1-24 months, or with one or more Gd+ lesions of brain from MRI within 6 months -May be treatment naive or previously treated **Exclusion:** -Pregnant and breastfeeding -MS relapse within 1 month of baseline assessment -Progressive MS at onset (PPMS or PRMS) -No previous treatment with S1P modulators or teriflunomide		
TEMSO O'Connor 2011[91] NCT00134563	Phase IIII Double-blind, PBO-controlled, parallel-group RCT Trial duration: 108 weeks	Adults with RMS, with or without progression	**Arm I:** Oral teriflunomide 7mg once daily **Arm II:** Oral teriflunomide 14mg once daily **Arm III:** Oral PBO once daily	**Inclusion:** -Age 18-55 -EDSS of 5.5 or lower -Diagnosis of RMS with or without progression -McDonald Criteria 2001 -At least 2 clinical relapses in previous 2 years or 1 relapse during preceding year, but no relapses in 60 days before randomization **Exclusion:** -Other systemic diseases -Pregnant or planned to conceive during trial period	ARR	2001 McDonald Criteria
TOWER Confavreux 2014[92] NCT00751881	Phase III Double-blind, PBO-controlled RCT Trial duration: 48 weeks	Adults with RMS	**Arm I:** Oral teriflunomide 7mg once daily **Arm II:** Oral teriflunomide 14mg once daily	**Inclusion:** -Age 18-55 -EDSS of 5.5 or less -Diagnosis of RMS with or without progression -McDonald Criteria 2005 -At least 1 relapse in previous year or at least 2 relapses in previous 2 years, and no relapse in 30 days before randomization	ARR	2005 McDonald Criteria

Title	Study Design	Population	Dosing Regimen	Entry Criteria	Primary Outcome	MS Criteria Used
			Arm III: Oral PBO once daily	**Exclusion:** -Other relevant diseases -Pregnant, breastfeeding, or planned to conceive or father a child during study -Previously or concomitantly received cytokine therapy, IFN beta, or glatiramer acetate within 3 months of randomization -Had ever used natalizumab or other immunosuppressive agents		
TENERE Vermersch 2014[93] NCT00883337	Phase III Multicenter, Parallel-group, Rater-blinded, RCT Trial duration: 48 weeks	Adults with RRMS with or without progression	**Arm I:** Oral teriflunomide 7 mg once daily **Arm II:** Oral teriflunomide 14 mg once daily **Arm III:** SC IFN beta-1a 44 µg	**Inclusion:** -Adults 18 years and older -EDSS of less than 5.5 -Diagnosis of RMS with or without progression -McDonald Criteria 2005 **Exclusion:** -Use of SC IFN-1a, teriflunomide, or leflunomide -Prior or ongoing use of natalizumab, cladribine, mitoxantrone, or other immunosuppressants; or use of other IFNs, glatiramer acetate, IVIG, or cytokine therapy within 3 months -Other relevant systemic illnesses -Pregnant and/or breast-feeding, or planning to conceive	Time to failure (first occurrence of confirmed relapse or permanent treatment discontinuation for any cause)	2005 McDonald Criteria
BRAVO Vollmer 2014[20] NCT00605215	Parallel-group, PC RCT Trial duration: 104 weeks	Adults with RRMS	**Arm I:** Laquinimod 0.6 mg oral once daily **Arm II:** oral placebo	**Inclusion:** -Adults aged 18-55 -Diagnosis of RRMS (revised McDonald criteria) -EDSS of 0-5.5 -At least 1 relapse in previous 12 months, 2 relapses in previous 24 months, or 1 relapse	ARR	2005 McDonald Criteria

Title	Study Design	Population	Dosing Regimen	Entry Criteria	Primary Outcome	MS Criteria Used
			Arm III: IFN β-1a 30µg IM weeky	in previous 12-24 months + 1 GdE lesion in previous 12 months **Exclusion:** -Progressive forms of MS -Corticosteroid use for relapses in previous 30 days -Use of experimental drugs, investigational drugs, or immunosuppressive therapy (including mitoxantrone) in previous 6 months, use of glatiramer acetate in previous 2 months, and prior use of natalizumab, laquinimod, cladribine or any IFN-beta 1a at any time		
EVIDENCE Panitch 2007[22]	Multicenter, assessor-blinded RCT Trial duration: 48 weeks	Adults with relapsing MS	**Arm I:** IFN β-1a 44 µg TIW **Arm II**: IFN β-1a 30 µg QW	**Inclusion:** -Adults aged 18-55 years -Clinically-confirmed relapsing MS -EDSS TM of 0-5.5 -Experienced ≥2 exacerbations in 2 years before inclusion in study -Never treated with IFN β-1a **Exclusion:** -Previous use of IFN, cladribine, or total lymphoid irradiation; use of glatiramer acetate or cytokine therapy in prior 3 months -Use of IVIG in prior 6 months -Use of other immunomodulatory agents in prior 12 months	Proportion of patients who remained free from relapses	NR

Title	Study Design	Population	Dosing Regimen	Entry Criteria	Primary Outcome	MS Criteria Used
REGARD Mikol 2008[94] NCT00078338	Multicenter, parallel-group, open-label RCT Trial duration: 96 weeks	Adults with RRMS	**Arm I:** IFN β-1a 44 µg TIW **Arm II:** glatiramer acetate 20 mg SC once daily up to 96 weeks	**Inclusion**: -Adults with 18-60 -Diagnosis of RRMS -IFN beta and glatiramer acetate naive -EDSS of 0-5.5 -At least 1 attack in preceding 12 months -Clinical stable or neurologically improving during 4 weeks before randomization **Exclusion:** -Progressive MS -Treatment with steroids or adrenocorticotrophic hormone within previous 4 weeks -Previous treatment with IFN beta, glatiramer acetate, or cladribine, plasma exchange within 3 months, IV gamma globulin within 6 months	Time to first relapse (up to 96 weeks)	2001 McDonald Criteria
PRISMS PRISMS Study Group 1998[21]	Double-blind, PBO-controlled RCT Trial Duration: 96 weeks	Adults with RRMS	**Arm I:** IFN β-1a 44 µg **Arm II:** IFN β-1a 22 µg **Arm III:** PBO	**Inclusion:** -Adults with RRMS -At least 2 relapses in preceding 2 years -EDSS of 0-5.0 **Exclusion:** -Previous systemic treatment with interferons, lymphoid irradiation, cyclophosphamide, or with other immunomodulatory or immunosuppressive treatments in preceding 12 months	Relapse count over course of study	NR

ARR: annualized relapse rate, BG-12: dimethyl fumarate, BID: twice daily, CV: cardiovascular, EDSS: expanded disability status scale, FIN: fingolimod, IFN: interferon, IM: intramuscular, IV: intravenous, IVIG: intravenous immunoglobulin, mg: milligram, MI: myocardial infarction, MRI: magnetic resonance imaging, MS: multiple sclerosis, OCR: ocrelizumab, OFA: ofatumumab, PBO: placebo, PML: progressive multifocal leukoencephalopathy, PPMS: primary progressive multiple sclerosis, RCT: randomized controlled trial, RMS: relapsing multiple sclerosis, RRMS: relapse remitting multiple sclerosis, SC: subcutaneous, SPMS: secondary progressive multiple sclerosis, µg: microgram

Table D9. Baseline Characteristics for Interferon Trials[21,22,94]

Trial	Arm	Arm Size	Trial Duration, Weeks	Age, Mean (SD)	RRMS, %	EDSS Score, Mean (SD)	Relapses in Previous 12 Months, Mean (SD)	No Previous DMT, %
Interferons								
BRAVO	IFN β-1a IM 30 µg	447	104	38.5 (30.3-45.9)†	100	2.5 (1.5-3.5)	1.0 (1.0-2.0)	90.60
	Placebo	450		37.5 (30.3-45.4)†	100	2.5 (1.5-3.5)	1.0 (1.0-2.0)	94
EVIDENCE	IFN β-1a SC 44 µg	339	48	38.3 (18-55)	100	2.0 (NR)	1.3 (NR)ǂ	NR
	IFN β-1a IM 30 µg	338		37.4 (18-55)	100	2.0 (NR)	1.3 (NR)ǂ	NR
PRISMS	Placebo	187	96	34.6 (28.8-40.4)*	100	2.4 (1.2)	1.5 (NR)ǂ	100
	IFN β-1a SC 44 µg	184		35.6 (28.4-41.0)*	100	2.5 (1.3)	1.5 (NR)ǂ	100

EDSS: expanded disability status scale, IFN β-1a: interferon beta-1a, IM: intramuscular, NR: not reported, SC: subcutaneous, SD: standard deviation, µg: microgram

*Median (IQR). †Median (P25, P75). ǂOriginally reported as number of relapses in previous 24 months, one year data estimated.

Table D10. Key Safety Outcomes in Pivotal Trials

Intervention	Safety Concerns (Adverse Events >10% and Greater than Comparator)
Monoclonal Antibodies	
Natalizumab	Abdominal discomfort, arthralgia, depression, diarrhea, gastroenteritis, headache, fatigue, infection (lower respiratory tract, urinary tract), rash
Ocrelizumab	Infection (nasopharyngitis, upper respiratory tract), infusion-related reaction, system organ class infection or infestation
Ofatumumab	Headache, infection (nasopharyngitis, upper respiratory tract infection), injection-related reaction
Rituximab	Infection (upper respiratory tract), infusion-related reaction
Ublituximab	Headache, infection (nasopharyngitis, respiratory tract), infusion-related reaction, nausea, pyrexia
Oral Therapies	
Dimethyl Fumarate	Back pain, diarrhea, fatigue, flushing, infection (nasopharyngitis, urinary tract infection) nausea, pruritus, upper abdominal pain, vomiting
Fingolimod	Abdominal pain, abnormal lab liver-function test, back pain, cough, diarrhea, infection, influenza, headache, hypertension, fatigue, nausea
Ozanimod	Infection (nasopharyngitis)
Ponesimod	Hepatobiliary disorder or liver test abnormality, hypertension, upper respiratory tract infection
Siponimod	Fall, headache, infections and infestations, liver-related investigations, hypertension
Teriflunomide	Alanine transaminase increase, diarrhea, hair thinning, headache, nasopharyngitis, nausea

D4. Ongoing Studies

Table D11. Ongoing Studies

Title/Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Date
Determining the Effectiveness of Early Intensive Versus Escalation Approaches for RRMS (DELIVER-MS) NCT03535298	Phase IV, randomized, open-label	High Efficacy Therapies Group: - Lemtrada - Ocrevus - Tysabri - Rituxan - Kesimpta Drug Escalation Therapies Group: - Betaseron - Copaxone - Aubagio - Extavia - Gilenya - Glatopa - Plegridy - Rebif - Tecfidera - Avonex - Mavenclad - Mayzent - Vumerity - Zeposia - Bafiertam - Ponvory	Inclusion Criteria: -Adults 18 to 60 years -Diagnosis of RRMS -Ambulatory with disease onset ≤5 years and treatment-naïve -Eligible to receive DMT -EDSS ≤6.5 Exclusion Criteria: -Contraindication to all forms of DMTs -Contraindication or inability to under MRI	Brain volume loss (at 36 months)	December 3, 2025
Traditional Versus Early Aggressive Therapy for Multiple Sclerosis Trial (TREAT-MS)	Randomized, parallel assignment, single masking	Early Aggressive Therapy: - Tysabri - Lemtrada - Ocrevus	Inclusion Criteria: -Adults aged 18 to 60 years -Diagnosis of MS -HIV negative	Time to sustained disability progression (up to 75 months)	August 1, 2025

Title/Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Date
NCT03500328		- Rituxan - Mavenclad - Kesimpta Traditional Therapy: - Glatiramer acetate - Avonex - Subcutaneous interferon - Plegridy - Aubagio - Tecfidera - Vumerity - Bafiertam - Gilenya - Mayzent - Zeposia - Ponvory	-JC antibody negative or low positive -No chemotherapy in past year Exclusion Criteria: -Prior treatment with DMTs -Prior treatment with experimental aggressive therapies -Treatment with teriflunomide in past 2 years	Change in overall burden of MS (up to 48 weeks)	
Disease Modifying Therapies Withdrawal in Inactive Secondary Progressive Multiple Sclerosis Patients Older Than 50 Years (STOP-I-SEP) (STOP-I-SEP) NCT03653273	Phase 3, randomized, open-label, parallel assignment	Arm 1: DMT withdrawal Arm 2: DMT continuation	Inclusion criteria: - Adults 50 and older - SPMS for at least 3 years - No clinical relapse or gadolinium enhancement on MRI scan for at least 3 years - EDSS >3 Exclusion criteria: - On mitoxanthrone or almetuzumab - Natalizumab in the past year - Other neurological or systemic disease - Contraindication to MRI	Disability Progression measured by EDSS (24 months)	Primary completion: July 2026 Study Completion: January 2028

Title/Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Date
Discontinuation of Disease Modifying Therapies (DMTs) in Multiple Sclerosis (MS) (DISCOMS) NCT03073603	Phase 4, single arm	Arm 1: drug continuation Arm 2: drug discontinuation	Inclusion criteria: - Patients with RRMS, SPMS, or PPMS - 55 years of age or older - No evidence of recent MRI activity - Using any of the FDA approved MS DMTs - Taking the approved DMT for at least two years - Able to undergo MRI Exclusion criteria: -Any MS relapse in the past 5 years - Significant intolerance of presently-used DMT - More than two courses of acute, systemic steroids in the last 5 years or any use within the last year - Prior use of experimental agent	Safety (18 to 24 months)	August 31, 2021
Discontinuing Disease-modifying Therapies in Stable Relapsing - Onset Multiple Sclerosis (DOT-MS) NCT04260711	Randomized, parallel assessment	Arm 1: Discontinuation of DMT Arm 2: continuation of DMT	Inclusion criteria: -Adults 18 and older Treatment with first-line DMTs - Definite diagnosis of relapse-onset MS - No inflammatory activity Exclusion criteria:	New clinically confirmed releases (2 years) New lesions on MRI (2 years)	Primary completion: August 2023 Study completion: January 2024

Title/Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Date
			- A switch between first-line DMT over two years prior to inclusion - Pregnancy - Used an interferon-beta and have tested positive for neutralizing antibodies		

DMT: disease modifying therapy, EDSS: expanded disability status scale, HIV: human immunodeficiency virus, JC: John Cunningham, MRI: magnetic resonance imaging, MS: multiple sclerosis, RRMS: relapse remitting multiple sclerosis

Source: www.ClinicalTrials.gov (NOTE: studies listed on site include both clinical trials and observational studies)

D5. Previous Systematic Reviews and Technology Assessments

We compared the results of our three NMAs to five previously published health technology assessments, including our 2017 MS review.[25,26,54,95,96] Our review included two agents that have not been previously studied for RMS: rituximab and ublituximab. Rituximab is not approved for RMS but frequently used off-label. Ublituximab is slated for FDA decision by Dec 28, 2022. Broadly, the magnitude of the relative risk and ordering of DMTs by efficacy reported by other NMAs were consistent with our results.

Table D12. NMA Comparison for ARR: DMT versus Placebo – Risk Ratio (95% CI)

Drug	Lucchetta 2018	McCool 2019	Samjoo 2020	Hennessy 2022	2017 ICER	2022 ICER
Ofatumumab 20 mg	N/A	N/A	**0.27 (0.20, 0.35)**	N/A	N/A	**0.29 (0.21, 0.44)**
Ublituximab 450 mg	N/A	N/A	N/A	N/A	N/A	**0.3 (0.21, 0.44)**
Natalizumab 300 mg	**0.31 (0.27, 0.36)**	**0.32 (0.26, 0.39)**	**0.31 (0.24, 0.42)**	**0.38 (0.34, 0.41)**	**0.31 (0.25, 0.4)**	**0.31 (0.23, 0.42)**
Ocrelizumab 600 mg	**0.37 (0.31, 0.46)**	**0.34 (0.26, 0.39)**	**0.33 (0.25, 0.44)**	**0.36 (0.30, 0.44)**	**0.35 (0.27, 0.44)**	**0.31 (0.14, 0.64)**
Rituximab 500 mg	N/A	N/A	N/A	N/A	**0.51 (0.27, 0.93)**	**0.34 (0.19, 0.58)**
Ponesimod 20 mg	N/A	N/A	N/A	**0.47 (0.39, 0.58)**	NA	**0.46 (0.32, 0.66)**
Fingolimod 0.5 mg	**0.47 (0.41, 0.53)**	**0.46 (0.40, 0.54)**	**0.46 (0.37, 0.55)**	**0.46 (0.42, 0.51)**	**0.46 (0.39, 0.55)**	**0.48 (0.39, 0.6)**
Dimethyl Fumarate 240 mg BID	**0.48 (0.42, 0.55)**	**0.50 (0.42, 0.59)**	**0.50 (0.40, 0.62)**	NA	**0.53 (0.43, 0.63)**	**0.53 (0.44, 0.7)**
Ozanimod 1 mg	N/A	N/A	N/A	**0.47 (0.38, 0.59)**	N/A	**0.56 (0.34, 0.92)**
Teriflunomide 14 mg	**0.69 (0.58, 0.81)**	**0.66 (0.58, 0.76)**	**0.79 (0.62, 0.97)**	**0.68 (0.60, 0.76)**	**0.67 (0.56, 0.79)**	**0.66 (0.53, 0.82)**

BID: twice daily, ICER: Institute for Clinical and Economic Review, mg: milligram, N/A: intervention not included in NMA

Note: Estimates in bold signify that the 95% credible interval does not contain 1.

Table D13. NMA Comparison for Three-Month CDP: DMT versus Placebo – HR (95% CI)

Drug	Lucchetta 2018	McCool 2019	Samjoo 2020	Hennessy 2022	2022 ICER
Ocrelizumab 600 mg	**0.39 (0.2, 0.75)**	**0.38 (0.24, 0.61)**	**0.39 (0.25, 0.62)**	**0.48 (0.36, 0.66)**	**0.37 (0.21, 0.67)**
Ofatumumab 20 mg	N/A	N/A	**0.46 (0.3, 0.68)**	**0.41 (0.31, 0.54)**	**0.45 (0.28, 0.72)**
Natalizumab 300 mg	**0.55 (0.41, 0.72)**	**0.58 (0.41, 0.81)**	**0.58 (0.41, 0.81)**	**0.59 (0.48, 0.71)**	**0.58 (0.39, 0.87)**
Ublituximab 450 mg	N/A	N/A	N/A	N/A	0.57 (0.3, 1.13)
Ponesimod 20 mg	N/A	N/A	N/A	**0.61 (0.44, 0.82)**	0.58 (0.32, 1.0)
Dimethyl Fumarate 240 mg BID	**0.61 (0.48, 0.77)**	**0.66 (0.5, 0.89)**	**0.67 (0.45, 0.97)**	N/A	**0.69 (0.5, 0.96)**
Teriflunomide 14 mg	N/A	**0.69 (0.53, 0.92)**	**0.7 (0.53, 0.92)**	**0.69 (0.58, 0.82)**	**0.69 (0.5, 0.95)**
Ozanimod 1 mg	N/A	N/A	N/A	0.72 (0.52, 1.01)	0.7 (0.36, 1.36)
Fingolimod 0.5 mg	**0.75 (0.61, 0.91)**	**0.73 (0.57, 0.91)**	**0.73 (0.58, 0.91)**	**0.73 (0.61, 0.87)**	0.77 (0.57, 1.02)

ARR: annualized relapse rate, BID: twice daily, ICER: Institute for Clinical and Economic Review, mg: milligram, N/A: intervention not included in NMA

Note: Estimates in bold signify that the 95% credible interval does not contain 1.

Table D14. NMA Comparison for Six-Month CDP: DMT versus Placebo – HR (95% CI)

Drug	Lucchetta 2018	McCool 2019	Samjoo 2020	2022 ICER
Ocrelizumab 600 mg	**0.51 (0.29, 0.89)**	**0.45 (0.23, 0.84)**	**0.47 (0.25, 0.89)**	**0.41 (0.22, 0.74)**
Natalizumab 300 mg	**0.46 (0.38, 0.57)**	**0.46 (0.3, 0.71)**	**0.46 (0.30, 0.70)**	**0.46 (0.29, 0.73)**
Ofatumumab 20 mg	N/A	N/A	**0.54 (0.33, 0.86)**	**0.54 (0.31, 0.91)**
Ublituximab 450 mg	N/A	N/A	N/A	0.52 (0.24, 1.15)
Ponesimod 20 mg	N/A	N/A	N/A	0.67 (0.36, 1.26)
Fingolimod 0.5 mg	**0.68 (0.52, 0.87)**	**0.67 (0.48, 0.93)**	**0.67 (0.49, 0.92)**	**0.67 (0.47, 0.96)**
Dimethyl Fumarate 240 mg BID	**0.56 (0.35, 0.88)**	**0.68 (0.47, 0.97)**	**0.68 (0.48, 0.95)**	0.7 (0.48, 1.04)
Teriflunomide 14 mg	N/A	0.79 (0.55, 1.13)	0.79 (0.57, 1.10)	0.79 (0.55, 1.15)
Ozanimod 1 mg	N/A	N/A	N/A	1.03 (0.48, 2.24)

BID: twice a day, ICER: Institute for Clinical and Economic Review, mg: milligram, N/A: intervention not included in NMA

Note: Estimates in bold signify that the 95% credible interval does not contain 1.

D6. Subgroup Analyses

Natalizumab

Available subgroup analyses of natalizumab were limited to one population of interest: patients of African descent. However, the pooled post-hoc analysis of AFFIRM and SENTINEL trial data was limited to 49 trial participants.[97] Of these participants, 39 had received supplemental therapy of interferon β-1a intramuscular 30 µg in both study arms, making it difficult to attribute any clinical benefit to natalizumab alone. We chose to not report on the results of this analysis due to the low certainty of evidence.

Ofatumumab

A post-hoc analysis of ASCLEPIOS I and II evaluated the treatment difference between ofatumumab and teriflunomide 14 mg on the outcomes of ARR, confirmed disability progression at three and six months, Gd+ T1 lesions, new/enlarging T2 lesions, and safety across one subgroup of interest: patients who were diagnosed with MS within three years and were treatment naïve.[98] Ofatumumab was superior to teriflunomide 14 mg in treatment naïve patients on the following outcomes: ARR, confirmed disability progression at six months, both MRI lesion counts, Gd+ T1 lesions, and new/enlarging T2 lesions. Patients treated with ofatumumab had higher rates of serious adverse events and adverse events that led to treatment discontinuation than teriflunomide 14 mg. The clinical benefit and safety results of this post hoc analysis were largely consistent with overall ASCLEPIOS I and II findings.

Ocrelizumab

A pooled post-hoc analysis of OPERA I and II evaluated the treatment difference between ocrelizumab and interferon β-1a SC 44 ug on the outcomes of ARR, CDP-3, Gd+ T1 lesions, and new/enlarging T2 lesions at week 96 across three subgroups of interest: age (<40 and ≥40), race (African descent), and patients with no DMT use within two years of study inclusion.[99,100]

Among patients ages 40 and above, ocrelizumab was superior to interferon β-1a subcutaneous 44 ug on all described outcomes except ARR. Older patients (age 40 and above) did not experience a treatment difference between study arms in the reduction of relapse. Patients under 40 had a significant treatment difference in ARR that was in favor of ocrelizumab.

Patients with no prior use of DMT within two years of study enrollment received a greater treatment benefit from ocrelizumab than interferon β-1a subcutaneous 44 ug on the outcomes of ARR and MRI lesions; ocrelizumab was not statistically superior to interferon β-1a subcutaneous 44 ug in slowing disease progression (CDP-3) in patients with prior DMT use within two years of study enrollment.

Only 4.3% of OPERA trial participants were of African descent. Results in this subgroup were similar to the overall trial population for the outcomes of ARR and MRI lesions. However, ocrelizumab treatment appeared to be less efficacious in terms of slowing progression; participants of African descent had a higher of rate of CDP-3 and CDP-6 compared to the rest of the ASCLEPIOS study population. Furthermore, ocrelizumab was not statistically superior to interferon β-1a subcutaneous 44 ug on either disability outcomes in patients of African descent, a contrast to the findings of the ASCLEPIOS study.

Rituximab

There was no available evidence on differences in efficacy and safety of rituximab treatment across any subgroups of interest.

Ublituximab

A pooled post-hoc analysis of ULTIMATE I and II evaluated the treatment difference between ublituximab and teriflunomide 14 mg on the outcomes of ARR, Gd+ T1 lesions, and new/enlarging T2 lesions at week 96 across two subgroups of interest: age (<38 and ≥38) and previous use of DMT.[101] There was no treatment benefit of ublituximab over teriflunomide 14 mg on the outcome of ARR in patients 38 years and older. Ublituximab was superior to teriflunomide 14 mg on ARR and both MRI outcomes among treatment naïve patients.

Ozanimod

In analyses of ARR stratified by baseline age (≤40 or >40) in both the RADIANCE and SUNBEAM trials, the treatment difference between ozanimod 1 mg and interferon β-1a was statistically significant in patients under 40 and there was a trend towards benefit but no significant difference in ozanimod versus interferon β-1a 30µg in those over 40. In both the RADIANCE and SUNBEAM trials, subgroup analyses on use of prior DMT showed statistically significant treatment differences in the reduction of ARR of ozanimod 1 mg compared to interferon β-1a regardless of prior DMT status.[34,89] Data for subgroups on race/ethnicity or clinically isolated syndrome, RRMS, or active SPMS populations were not reported.

Dimethyl Fumarate

Subgroup analyses from the CONFIRM and DEFINE trials shows dimethyl fumarate twice daily was statistically significantly superior in lowering ARR compared to placebo regardless of age subgroup (<40, ≥ 40). For three month CDP, the treatment difference between dimethyl fumarate twice daily and placebo was statistically significant in patients under 40 but no significant in those over 40.[102] In an integrated analysis of CONFIRM and DEFINE across racial/ethnic subgroups, the treatment difference for both ARR and CDP at three months between dimethyl fumarate twice daily and placebo was statistically significant for Hispanic patients and among Black and Asian patients, there was a trend towards benefit, but no significant difference was observed.[103] For ARR, there was no difference in the treatment effect of patients who had or had not previously received MS treatment. For confirmed disability progression at three months, there was a significant reduction in patients receiving dimethyl fumarate twice daily versus placebo who had no prior MS treatment but not in patients who had used prior MS treatment.[102]

Fingolimod

Two integrated analyses of the FREEDOMS I, FREEDOMS II, and TRANSFORMS trials reported the ARR treatment difference between patients receiving fingolimod 0.5 mg or placebo was statistically significant, regardless of age (≤40 or >40), treatment history (naïve or previously treated), or ethnicity (Hispanic or non-Hispanic).[104,105]

Teriflunomide

Several subgroup analyses evaluating patients previously enrolled in the TEMSO, TOWER, and TENERE trials, were stratified by age (38 or >38 years), race (Chinese descent or Asian descent), or prior treatment with a DMT (naïve, previously treated, or recently treated).[46,106-108] Across all subgroups, patients stratified to 14 mg Teriflunomide had a greater reduction in ARR versus placebo. The proportion of patients free from disability worsening at three and six months was similar regardless of race subgroup,[106] however the percentage of patients achieving three-month CDP was lower for recently treated patients than naïve and previously treated patients.[46]

Ponesimod

A subgroup analysis was conducted on patients in the OPTIMUM trial with an EDSS score ≤3 and/or who were treatment naïve at baseline.[109] Among patients randomized to ponesimod 20 mg, those with an EDSS score of ≤3 saw the greatest benefit from treatment on ARR with a 47% reduction compared to teriflunomide (RR: 0.530; P<0.001) as well as greater improvement on the MS-fatigue questionnaire (mean difference: -4.31; P=0.0017). Treatment-naïve patients on ponesimod also saw a greater improvement on the MS-fatigue questionnaire versus teriflunomide (mean difference: -5.30; P=0.0004).

Siponimod

The efficacy and safety of siponimod in the treatment of SPMS have been reported previously.[53] Here, we report on the efficacy of siponimod stratified by age and previous treatment regimen. SPMS patients were stratified by mean baseline age (<50 or ≥50) and analyzed post-hoc on three- and six-month CDP and adverse events. Overall, siponimod had similar clinical benefits for patients regardless of baseline age in three-month CDP (HR: 0.69 vs. 0.70 vs. 0.62, respectively) and six-month CDP (HR: 0.63 vs. 0.62 vs. 0.63, respectively). Serious adverse events occurred at a similar rate for the overall population (17.9%), <50 (14.1%), and ≥50 (16.9%) on siponimod versus placebo (15.2-20.3% respectively).[110]

In treatment-naïve patients, patients on siponimod gained more clinical benefit on three-month CDP compared to placebo (HR: 0.69 vs. 0.82) though it was not statistically significant. This trend continued for six-month CDP (HR: 0.58 vs. 0.79).[35]

Secondary Progressive Multiple Sclerosis

Three DMTs in our review have available evidence for patients with SPMS.

EXPAND was a Phase III RCT that evaluated the efficacy and safety of siponimod in adults with SPMS and a baseline EDSS score of 3-6.5.[35] Patients were randomized 2:1 to siponimod (n=1,105) or placebo (n=546) for a follow-up period of up to 37 months. Siponimod met its primary endpoint of time to CDP-3 and reduced the risk of disability progression by 21% against placebo. Significant treatment differences in favor of siponimod were also observed on time to CDP-6 and ARR. The safety profile of siponimod was in line with other S1P receptor modulators with an improved cardiac safety profile due to dose-titration strategies.

ASCEND was a Phase III RCT that evaluated the efficacy and safety of natalizumab in adults with SPMS and baseline EDSS score of 3-6.5.[111] Patients were randomized to natalizumab (n=440) or placebo (n=449) for a follow up period of up to two years. The primary endpoint of the study was a multicomponent measure of sustained disability progression that incorporated changes in at least one of the following components: EDSS score, timed 25-foot walk, and a nine-hole peg test. Natalizumab was not superior to placebo on its primary endpoint but did achieve a significant treatment benefit on the nine-hole peg test.

A subgroup analysis of the Phase III RCT, TEMSO, demonstrated that teriflunomide 14 mg was superior to placebo on ARR and CDP-3 outcomes in patients with RRMS, but not in SPMS patients who made up 8% of the study population.[108]

E. Long-Term Cost-Effectiveness: Supplemental Information

E1. Detailed Methods

Table E1. Impact Inventory

Sector	Type of Impact (Add Additional Domains, as Relevant)	Included in This Analysis from [...] Perspective?		Notes on Sources (if Quantified), Likely Magnitude and 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	☐	X	
	Future related medical costs	X	X	
	Future unrelated medical costs	X	X	
Informal Health Care Sector				
Health-Related Costs	Patient time costs	NA	X	
	Unpaid caregiver-time costs	NA	X	
	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	X	
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	X	
Environment	Production of toxic waste pollution by intervention	NA	☐	
Other	Other impacts (if relevant)	NA	☐	

NA: not applicable

Adapted from Sanders et al.[112]

Description of evLY Calculations

The 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.[113]
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.

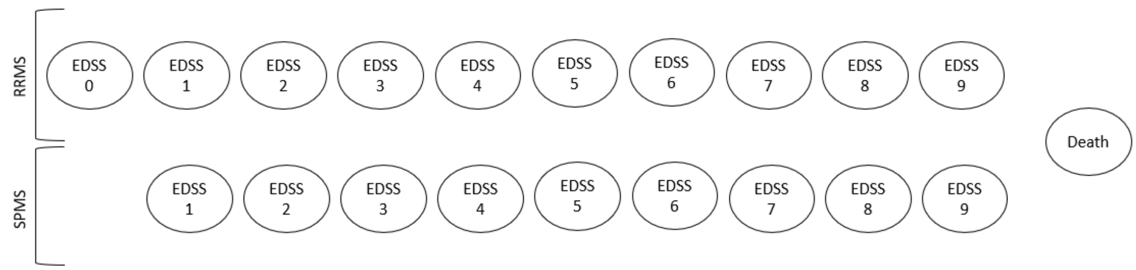
Model Structure

The model consisted of health states defined by the EDSS, a commonly used scale to describe MS disease progression (Figure E1). The model included 20 health states, including EDSS 0-9 during RRMS, EDSS 1-9 during SPMS, and death. The model structure collapsed EDSS scores into whole unit increments. Patients transitioned between these health states during cycles of one year and over a lifetime time horizon.

Arrows for the possible transitions among health states are not depicted in Figure E1 for simplicity purposes. During RRMS, a patient could transition to any higher or any lower EDSS health state or stay in the same EDSS health state. Patients with RRMS could also convert from RRMS to SPMS. During SPMS, a patient could transition to any higher EDSS health state or stay in the same EDSS health state. EDSS regression to a lower EDSS health state was not possible once a patient had reached SPMS.

A relapse could occur in any of the alive health states and was modeled as an event within a health state rather than as a separate health state. Patients remained in the model until they died. All patients could transition to the death health state due to all-cause or disease-specific mortality from any of the alive health states. This proposed model structure aligns with the most commonly used structure for MS modeling from a recent systematic literature review.[114]

Figure E1. Model Health States*



EDSS: Expanded Disability Status Scale, RRMS: relapsing-remitting multiple sclerosis, SPMS: secondary-progressive multiple sclerosis

*Arrows for the transitions among health states are not depicted in Figure E1. In RRMS, transitions to more severe and to less severe EDSS health states are possible. In SPMS, transitions to more severe EDSS health states are possible. The health states are collapsed into whole unit increments for EDSS health states.

Target Population

The target population consisted of adults ages 18 years and older in the US with relapsing forms of MS. Table E2 presents the baseline population characteristics based on evidence from the pivotal trials. At baseline, the cohort was distributed among the RRMS health states using baseline EDSS data from the pivotal trials for DMTs that reported these data.

Table E2. Baseline Population Characteristics

	Value	Source
Mean Age at Baseline	38 years	Weighted average (by sample size) from MS DMT RCTs that reported these data[80-82,85,86,111,115]
Percent Female	68%	
Percent RRMS EDSS 0 at Baseline	4.5%	Weighted average (by sample size) from MS DMT RCTs that reported these data[80,81,85,86,91]
Percent RRMS EDSS 1 at Baseline	22.7%	
Percent RRMS EDSS 2 at Baseline	30.1%	
Percent RRMS EDSS 3 at Baseline	23.0%	
Percent RRMS EDSS 4 at Baseline	13.8%	
Percent RRMS EDSS 5 at Baseline	5.6%	
Percent RRMS EDSS 6 at Baseline	0.3%	
Percent RRMS EDSS 7 at Baseline	0.0%	
Percent RRMS EDSS 8 at Baseline	0.0%	
Percent RRMS EDSS 9 at Baseline	0.0%	

DMT: disease-modifying therapy, EDSS: Expanded Disability Status Scale, MS: multiple sclerosis, RCT: randomized controlled trial, RRMS: relapsing-remitting multiple sclerosis

Treatment Strategies

The list of interventions was developed with input from patient organizations, clinicians, manufacturers, and payers on which treatments to include. The full list of interventions is as follows:

- Ublituximab
- Natalizumab (Tysabri®)
- Ofatumumab (Kesimpta®)
- Ocrelizumab (Ocrevus®)

Although included in the comparative clinical assessment, rituximab was not modeled as an intervention in the comparative value analysis due to insufficient evidence on disease progression at this time. Oral therapies for relapsing forms of MS were not evaluated as interventions within the comparative value section of this review.

We compared treatment initiation of each modeled intervention to dimethyl fumarate. Dimethyl fumarate was selected as the comparator following numerous conversations with stakeholders suggesting it is a market leader, effective, and currently the lowest cost oral DMT.

E2. Model Inputs and Assumptions

The model was informed by several key assumptions described in Table E3.

Table E3. Key Model Assumptions

Assumption	Rationale
The model structure was collapsed into whole unit increments for EDSS.	Data for transition probabilities, costs, and other consequences by EDSS health state were available at the whole unit level. This structure and assumption aligns with other published cost-effectiveness analyses in MS.
Cost and mortality inputs for each EDSS state were assumed to be the same for RRMS and SPMS.	Little evidence exists to suggest these would differ between RRMS and SPMS and the available evidence was largely in RRMS.
In a cycle where a conversion from RRMS to SPMS occurred, we assumed a one level increase in EDSS, except when the transition occurred from RRMS EDSS 9.	Clinical opinion supported the increase in disease progression alongside the conversion from RRMS to SPMS.
Patients continued treatment after transitioning to SPMS.	Clinical opinion supported the continued use of treatment even after transitioning to SPMS.
Trial-reported discontinuation was annualized and applied over the first two years after initiating treatment. Discontinuation after two years was assumed to be related to serious adverse events only and did not vary by treatment.	We had trial evidence that approximated a two-year duration, so we annualized the trial data and applied that evidence over two years. Literature and clinical expert opinion suggested that discontinuation decreases over time,[58] and thus after two years on treatment, the only discontinuation that occurred was assumed to be related to serious adverse events. Discontinuation was widely varied through the sensitivity analyses.
PML was assumed to be minimized by way of JCV testing for applicable DMTs and therefore was not modeled separately from serious infections.	PML is a very rare event given repeated JCV virus testing and the research conducted to minimize the impact of PML with the use of DMTs. We considered it to be consistent in terms of costs and health consequences to other serious infections.
Separate from the modeled discontinuation, patients remained on treatment over their lifetime.	There is no clinical consensus as to when treatment should stop, but we heard from clinical experts that they would be unlikely to remove a patient from treatment if the patient was tolerating it. We conducted a scenario analysis where treatment stopped when a patient reached an EDSS of 7 or higher.
If a patient discontinued the initial therapy (either intervention or comparator), they transitioned to a subsequent treatment with cost and effectiveness similar to the monoclonal antibody market leader. A patient did not discontinue this subsequent treatment basket until death.	Utilization data and clinical opinion suggested that most RRMS and SPMS patients initiate subsequent treatment upon discontinuation. The specific subsequent treatment would vary in the real world. But, for the purposes of the model, it was important to hold this subsequent treatment fixed to emphasize the potential differences in the initial treatment. Our approach standardized the treatment switch across the modeled arms and ensured the cost and effectiveness of the subsequent treatment did not drive the results. The characteristics of the subsequent treatment were varied through scenario analyses.
A DMT is not associated with any EDSS improvement (i.e., moving to a lower EDSS state) than what was observed in the transitions for best supportive care.	Currently, there is weak evidence to support a benefit of the modeled interventions on EDSS improvement. Further, additional research is needed to understand the competing risks of how an observed EDSS improvement may impact the findings for EDSS delayed progression. Our base-case analysis only applies a treatment's effect to EDSS progression (i.e., moving to a higher EDSS state). This assumption was examined in a scenario analysis.

DMT: disease-modifying therapy, EDSS: Expanded Disability Status Scale, JCV: John Cunningham polyomavirus, PML: progressive multifocal leukoencephalopathy, RRMS: relapsing-remitting multiple sclerosis, SPMS: secondary-progressive multiple sclerosis

Model Inputs

Clinical Inputs

Key clinical inputs include disease progression, relapse rates, serious adverse events, discontinuation, and mortality. Treatment effectiveness, measured by disease progression and ARRs, was estimated using NMA.

Disease Progression

We used transition probabilities derived in the absence of treatment with a DMT and applied a treatment effect for each intervention and comparator to derive DMT-specific transition probabilities for each arm of our model. Transition probabilities between EDSS states for patients with RRMS in the absence of treatment with DMTs are provided in Table E4. These transition probabilities were used in the prior RRMS ICER review and were based on a previous study[56] that used data from the placebo arms of two MS clinical trials[116,117] (for EDSS states up to 7) supplemented with cohort data from a large London, Ontario MS registry[118] (for EDSS states 8 and 9 because of limited observations beyond EDSS 7 in the trials). This approach of supplementing clinical trial data and cohort data is the most common approach in MS health technology assessment models, with the London, Ontario MS dataset being the most commonly used natural history dataset.[114] The placebo arms of the two MS clinical trials indicated EDSS regression as well as progression in EDSS states among those with RRMS, and thus regression and progression are both possible in our model for patients with RRMS up to EDSS 7. A limitation of the London, Ontario dataset is that improvement in EDSS is not possible and thus in our model, EDSS regression (i.e., improvement) is not possible for patients with RRMS in the EDSS 8 or 9 health states. We used trial data for EDSS 0-7 that did suggest regression was possible, thereby minimizing the concern with the London, Ontario dataset. There are other natural history datasets available, such as the British Columbia MS database, [119] that were not selected due to the bundling of SPMS and RRMS transitions and the lack of evidence on the probability of converting from RRMS to SPMS.

Table E4. Annual Probabilities of EDSS Transitions in the Absence of Treatment with a DMT, RRMS[52,56,118]

EDSS at Cycle Start	EDSS at Cycle End									
	0	1	2	3	4	5	6	7	8	9
0	0.312	0.289	0.312	0.070	0.016	0.001	0.000	0.000	0.000	0.000
1	0.178	0.232	0.419	0.127	0.039	0.004	0.001	0.000	0.000	0.000
2	0.06	0.130	0.494	0.215	0.088	0.011	0.002	0.000	0.000	0.000
3	0.019	0.055	0.299	0.322	0.241	0.044	0.013	0.003	0.004	0.000
4	0.005	0.017	0.127	0.251	0.410	0.121	0.048	0.014	0.007	0.000
5	0.001	0.004	0.033	0.096	0.252	0.295	0.211	0.085	0.023	0.000
6	0.000	0.001	0.009	0.034	0.123	0.257	0.329	0.190	0.056	0.001
7	0.000	0.000	0.003	0.013	0.057	0.169	0.309	0.256	0.189	0.004
8	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.995	0.005
9	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	1.000

EDSS: Expanded Disability Status Scale

Transition probabilities between EDSS states for patients with SPMS in the absence of treatment with DMTs are provided in Table E5. These values were used in the prior ICER MS review and were based on a previous study[56] that calculated the transition probabilities among patients with SPMS using data from the London, Ontario MS dataset.[118]

Table E5. Annual Probabilities of EDSS Transitions in the Absence of Treatment with a DMT, SPMS[52,56,118]

EDSS at Cycle Start	EDSS at Cycle End								
	1	2	3	4	5	6	7	8	9
1	0.769	0.154	0.077	0.000	0.000	0.000	0.000	0.000	0.000
2	0.000	0.636	0.271	0.062	0.023	0.008	0.000	0.000	0.000
3	0.000	0.000	0.629	0.253	0.077	0.033	0.003	0.005	0.000
4	0.000	0.000	0.000	0.486	0.350	0.139	0.007	0.018	0.000
5	0.000	0.000	0.000	0.000	0.633	0.317	0.022	0.026	0.002
6	0.000	0.000	0.000	0.000	0.000	0.763	0.19	0.045	0.002
7	0.000	0.000	0.000	0.000	0.000	0.000	0.805	0.189	0.006
8	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.926	0.074
9	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	1.000

EDSS: Expanded Disability Status Scale

Probabilities for the conversion from RRMS to SPMS in the absence of treatment with DMTs are provided in Table E6. These values were used in the prior ICER MS review and were based on a previous study[56] that calculated the probability of converting from RRMS to SPMS using the time-to-SPMS data from the London, Ontario MS dataset.[52,56,118]

Table E6. Annual Probabilities of Converting from RRMS to SPMS in the Absence of Treatment with a DMT[56,118]

RRMS EDSS State	Probability of Transitioning to SPMS
0	0.000
1	0.003
2	0.032
3	0.117
4	0.210
5	0.299
6	0.237
7	0.254
8	0.153
9	1.000

EDSS: Expanded Disability Status Scale, RRMS: relapsing-remitting multiple sclerosis, SPMS: secondary-progressive multiple sclerosis

For RRMS, the order for estimating those at risk for transitions was first to identify those who died within a cycle, then those who converted to SPMS, and then for all others (i.e., those who did not die or convert to SPMS), they were assigned baseline risks equivalent to those reported in Table E4. For SPMS, the order for estimating those at risk for transitions was first to identify those who died within a cycle, and then for all others, they were assigned baseline risks equivalent to those reported in Table E5.

The DMT-specific disease progression HRs, as estimated from our NMA, for each comparator and intervention was then applied to these transition probabilities in the absence of treatment with a DMT to estimate disease progression for each intervention and comparator. Table E7 presents the results from ICER's NMA of the HR for disease progression for each intervention and comparator that was included in the model. The HRs for disease progression were applied to increasing EDSS transitions (for both RRMS and SPMS) and for the conversion from RRMS to SMPS. The HR is assumed to be the same for both RRMS and SPMS.

Table E7. DMT-Specific HR of Disease Progression

Treatment	Base Case*	Credible Interval†	Source
Ublituximab	0.53	0.22-1.26	ICER NMA
Natalizumab	0.46	0.25-0.85	
Ofatumumab	0.54	0.28-1.06	
Ocrelizumab	0.41	0.20-0.84	
Dimethyl Fumarate	0.70	N/A	

DMT: disease-modifying therapy, ICER: Institute for Clinical and Economic Review, NMA: network meta-analysis
*Calculated by multiplying the HR of the monoclonal antibody vs. dimethyl fumarate by the HR of dimethyl fumarate vs. best supportive care.
†Calculated based on the 95% CI of the monoclonal antibody vs. dimethyl fumarate.

ARRs

We used ARRs in the absence of treatment with a DMT and applied a treatment effect for each intervention and comparator to derive DMT-specific relapse rates. ARRs in the absence of treatment with a DMT, reported separately for RRMS and SPMS, are provided in Table E8. These estimates were used in the 2017 MS ICER review and were based on work from prior studies.[56,120] These estimates were selected as they represent a mid-range given the substantial variation in relapse rates that exists.

Table E8. ARRs in the Absence of Treatment with a DMT[56,120]

EDSS State	RRMS	SPMS
0	0.71	N/A
1	0.73	0.00
2	0.68	0.47
3	0.72	0.88
4	0.71	0.55
5	0.59	0.52
6	0.49	0.45
7	0.51	0.34
8	0.51	0.34
9	0.51	0.34

EDSS: Expanded Disability Status Scale, MS: multiple sclerosis, N/A: not applicable

For patients who experienced a relapse in a given cycle, 25% of the relapses were assumed to be severe and 75% were assumed to be mild/moderate.[121] A disutility and cost of relapse was assigned based on severity, with more detail provided in the sections below.

The DMT-specific rate ratios for relapse rates, as estimated from the NMA, for each comparator and intervention were then applied to the ARRs in the absence of treatment with a DMT to estimate relapse rates for each intervention and comparator. Table E9 presents the rate ratio for relapse rates for each intervention and comparator that will be included in the model. The rate ratio is assumed to be the same for both RRMS and SPMS.

Table E9. DMT-Specific Rate Ratio for Relapse Rate

Treatment	Base Case*	Range†	Source
Ublituximab	0.30	0.19-0.46	ICER NMA
Natalizumab	0.31	0.22-0.44	
Ofatumumab	0.29	0.20-0.43	
Ocrelizumab	0.30	0.13-0.67	
Dimethyl Fumarate	0.53	N/A	

DMT: disease-modifying therapy, ICER: Institute for Clinical and Economic Review, NMA: network meta-analysis
*Calculated by multiplying the HR of the monoclonal antibody vs. dimethyl fumarate by the HR of dimethyl fumarate vs. best supportive care.
†Calculated based on the 95% CI of the monoclonal antibody vs. dimethyl fumarate.

Adverse Events

Serious adverse events for each modeled intervention and comparator were included in the model with the rationale that serious adverse events would be most likely to influence costs and/or health outcomes. To estimate the serious adverse events for each included DMT, we calculated annual serious adverse event rates from each available clinical trial for any serious adverse event that occurred in at least 1% of the trial population. Based on the review of the evidence for the included treatments, serious infection was modeled as a serious adverse event. PML was assumed to be minimized by way of JCV testing for applicable DMTs (e.g., natalizumab) and therefore was not modeled separately from serious infections. Table E10 reports the serious adverse events for each intervention and comparator. Costs and disutilities were applied to each serious adverse event occurrence, with more detail provided in the sections below.

Table E10. Annual Probability of Serious Adverse Events

Serious Adverse Event	Ublituximab	Natalizumab	Ofatumumab	Ocrelizumab	Dimethyl Fumarate
Serious Infection	2.2%	1.4%	1.6%	0.7%	1.2%
Source	ULTIMATE I and II[122]	AFFIRM[80], ICER 2017 Report[52]	ASCLEPIOS I and II[82]	OPERA I and II[81]	DEFINE[86]

ICER: Institute for Clinical and Economic Review, RRMS: relapsing-remitting multiple sclerosis

Discontinuation

Trial-reported discontinuation was annualized and applied over the first two years. We had trial evidence that approximated a two-year duration, so we annualized the trial data and applied that evidence for two years. The annual discontinuation was calculated for each intervention and comparator in the economic model using discontinuation evidence reported in the pivotal trials. For each intervention and comparator, we abstracted the total number of study participants, the total number of study participants who discontinued, and the follow-up time for discontinuation. Reasons for discontinuation that were excluded from our discontinuation probability estimates included withdrawing consent, protocol violation, and noncompliance. All other reasons for discontinuation were included. We then calculated the annual rate and probability of discontinuation. Table E11 reports the annual discontinuation probabilities for each intervention and comparator that was applied during the first two years of the model.

Table E11. Annual Discontinuation Probability, First Two Years on Treatment

Treatment	Annual Discontinuation Probability	Source
Ublituximab	3.9%	ULTIMATE I and II[122]
Natalizumab	2.5%	AFFIRM[80]
Ofatumumab	4.9%	ASCLEPIOS I and II[82]
Ocrelizumab	4.7%	OPERA I and OPERA II[81]
Dimethyl Fumarate	8.8%	CONFIRM and DEFINE[86]

Literature and clinical expert opinion suggested that discontinuation decreases over time,[58] and thus after two years on treatment, the only discontinuation that occurred in the model was assumed to be the result of a serious adverse event. Discontinuation after two years on treatment was consistent over time and across DMTs and was set at 1.5% per year, calculated based on the average annual serious adverse event occurrence across the modeled DMTs.

If a patient discontinued the initial modeled treatment for any reason, they transitioned to a subsequent treatment with cost and effectiveness similar to the market leading monoclonal antibody treatment. A patient did not discontinue this subsequent treatment until death.

Mortality

All-cause mortality based on age- and sex-adjusted US Life Tables was multiplied by MS-specific mortality using a standardized mortality ratio that increased with EDSS. These mortality multipliers were used in the 2017 MS ICER review and were calculated using the following equation from a prior study:[123]

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

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.[114] The mortality multipliers are reported in Table E12. We assumed mortality by EDSS state did not differ between RRMS and SPMS.

Table E12. Mortality Inputs

EDSS State	Base Case	Range
0	1.00	0.81-1.21
1	1.43	1.16-1.72
2	1.60	1.30-1.93
3	1.64	1.33-1.98
4	1.67	1.36-2.01
5	1.84	1.50-2.22
6	2.27	1.85-2.74
7	3.10	2.52-3.74
8	4.45	3.62-5.36
9	6.45	5.25-7.77

EDSS: Expanded Disability Status Scale

Utility Inputs

Health state utilities were derived from publicly available literature and were applied to each health state. We used consistent health state utility values across treatments evaluated in the model. Health state utilities are reported in Table E13. For EDSS 0 to 7, we used utility estimates from a previously published study that were derived from patient responses to the EQ-5D using DEFINE and CONFIRM trial data for RRMS values and a United Kingdom survey for SPMS values.[56,124] This previously published study reported a dramatic reduction in utility score after EDSS 7, whereas the decline was gradual from EDSS 0 to 7. Therefore, to estimate utility scores for EDSS 8 and 9 in our model, instead of using the estimates reported in this previously published study, we used a non-linear extrapolation with EDSS and EDSS^2 as predictors to estimate the utility values for EDSS 8 and EDSS 9 using the reported utility scores for 0 to 7, and a utility of 10 for death (i.e., EDSS 10). This produced utility scores for EDSS 8 and 9 greater than zero. Utility estimates greater than zero for EDSS 8 and 9 have been reported by other sources as well.[59,60]

Table E13. Health State Utility Values

EDSS State	Utility, RRMS	Utility, SPMS
0	0.8752	N/A
1	0.8342	0.7905
2	0.7802	0.7365
3	0.6946	0.6509
4	0.6253	0.5816
5	0.5442	0.5005
6	0.4555	0.4118
7	0.3437	0.3000
8	0.2433	0.2095
9	0.1267	0.1034
10	0.0000	0.0000

EDSS: Expanded Disability Status Scale, MS: multiple sclerosis, N/A: not applicable

Additional decrements in quality of life associated with serious adverse events and relapses were applied for each occurrence. Table E14 reports the annual disutility for each of these occurrences. We assumed no cycle utility could drop beneath zero.

Table E14. Other Disutility Values

	Annual Disutility	Source
Serious Infection	-0.005	Jakubowiak 2016[125]
Mild/Moderate Relapse	-0.016	Monthly disutility from Prosser 2004[126] applied for two months based on the average relapse duration;[127] also supported by Kobelt 2006[59]
Severe Relapse	-0.05	

Treatment Utilization

The following inputs were used to model treatment utilization and associated costs:

- Dosage for the indication
- Route of administration
- Frequency of administration.

Table E15 reports the modeled treatment regimen for each intervention and comparator.

Table E15. Recommended Treatment Regimen

Treatment	Route of Administration	Dosing Schedule	Monitoring
Ublituximab	IV	150 mg infused over 4 hours on day 1, 450 mg infused over 1 hour on day 15 and every 6 months thereafter	Monitoring for 1 hour post-infusion for the first 2 infusions
Natalizumab (Tysabri®)	IV	300 mg infused over 1 hour every 4 weeks	Provider visit with JCV test at 3 and 6 months, and every 6 months thereafter
Ofatumumab (Kesimpta®)	SC	20 mg at weeks 0, 1, and 2, followed by 20 mg every 4 weeks thereafter starting at week 4	Hepatitis B test and quantitative serum immunoglobulin test at time 0
Ocrelizumab (Ocrevus®)	IV	300 mg infused over 2 hours at time 0, 300 mg infused over 2 hours at week 2, followed by 600 mg infused over 2 hours every 6 months	Monitoring for 1 hour post-infusion
Dimethyl Fumarate	Oral	120 mg twice a day for the first 7 days, 240 mg twice a day thereafter	CBC at time 0 and time 6 months

CBC: complete blood count, IV: intravenous, JCV: John Cunningham polyomavirus, mg: milligram, SC: subcutaneous

Economic Inputs

All costs used in the model were inflated to 2021 US dollars.

Treatment-Related Costs

Acquisition Costs

Table E16 reports the treatment price per unit and per year for each of the modeled interventions and comparator. At this time, a price has not been set for ublituximab and thus we assumed a placeholder price for ublituximab equivalent to the net price of ocrelizumab. For IV-administered treatments with a price available (i.e., natalizumab and ocrelizumab), we identified the WAC from REDBOOK and net price data from SSR Health, LLC, or based on net price data submitted directly from the manufacturer. In the case of ocrelizumab, the manufacturer provided us the average net price (net of all discounts, rebates, patient assistance programs, and concessions to wholesalers and distributors, both statutory [i.e., 340B statutory discount] and voluntary) and thus this net price was used in our analyses. A discount from SSR Health was assumed for natalizumab. We estimated net prices by comparing the four-quarter averages of both net prices and WAC per unit to arrive at a mean discount from WAC for the drug. Finally, we applied this average discount to the most recent available WAC to arrive at an estimated net price per unit. The net price was used in the modeling efforts. The IV-administered treatments included an additional 6% mark-up to reflect the provider-administered nature of these treatments.

For subcutaneously-administered treatments (i.e., ofatumumab), we identified the WAC from REDBOOK and we obtained net pricing estimates from either SSR Health, LLC, or directly from the manufacturer. A discount from SSR Health was assumed for ofatumumab. We estimated net prices by comparing the four-quarter averages of both net prices and WAC per unit to arrive at a mean discount from WAC for the drug. Finally, we applied this average discount to the most recent available WAC to arrive at an estimated net price per unit. The net price was used in the modeling efforts.

For dimethyl fumarate, generic versions are available. In alignment with the ICER Reference Case, we used the generic version to estimate the price used in the model. No further discounts were applied.

Table E16. Drug Costs

Drug	Unit Size	WAC per Unit	WAC per Year	Net Price per Unit	Net Price per Year	Source
Ublituximab	Unknown	N/A	$71,187	N/A	$55,081	Placeholder based on ocrelizumab[128], 6% provider administered mark-up not included
Natalizumab	300 mg	$7,856	$102,128	$7,762	$100,902	Redbook[129], SSR Health[130], 6% provider administered mark-up not included
Ofatumumab	20 mg	$7,480	Year 1: $119,686 Years 2+: $97,245	$5,483	Year 1: $87,730 Years 2+: $71,281	Redbook[129], SSR Health[130]
Ocrelizumab	300 mg	$17,797	$71,187	$13,770	$55,081	Redbook[129], Manufacturer provided net price*, 6% provider administered mark-up not included
Dimethyl Fumarate	120 mg/ 240 mg	$5.36/$3.75	Year 1: $2,762 Years 2+: $2,739	$5.36/$3.75	Year 1: $2,762 Years 2+: $2,739	Redbook[129]

ASP: average sales price, mg: milligram, WAC: wholesale acquisition cost

*Annual price net of all discounts, rebates, patient assistance programs, and concessions to wholesalers and distributors, both statutory (i.e., 340B statutory discount) and voluntary.

Administration Costs

Administration costs were included for IV-administered treatments. Treatments that are infused over one hour or less had an infusion cost of $78 per administration (CPT 96365).[131] Each additional hour (i.e., after one hour) required for an infusion received an additional administration cost of $24 per hour (CPT 96366).[131] No administration costs were included for treatments that were self-administered (e.g., subcutaneous and oral treatments). Refer to Table E15 for the administration requirements for each treatment.

Monitoring Costs

Unit costs associated with monitoring requirements are presented in Table E17. Refer to Table E15 for the monitoring requirements for each treatment.

Table E17. Drug Monitoring Unit Costs

Category	Unit Cost	Source
Post-Infusion Monitoring	Included in infusion administration charge	Physician fee and lab schedule 2022[131,132]
CBC (CPT 85025)	$8	
JCV Test (CPT 86711)	Paid for by manufacturer	
Hepatitis B Test (CPT 87340)	$10	
Quantitative Serum Immunoglobulin Test (CPT 82784)	$9	
Provider Visit (CPT 99215)	$164	

CBC: complete blood count, CPT: Current Procedural Terminology, JCV: John Cunningham polyomavirus

Non-Treatment-Related Costs

MS Direct Health Care Costs

The model assigned annual MS health care costs based on EDSS state, with costs consistent between RRMS and SPMS. The annual health care costs used in this analysis were estimated from two sources, a study by Kobelt and colleagues published in 2006 that reported direct costs by different levels of EDSS,[59] and a more recent source by Bebo and colleagues published in 2022 that reported direct costs for the average MS patient but without stratifications based on different levels of EDSS.[8] First, the costs from both sources were inflated to 2021 US dollars. Then the average cost from the Bebo source was adjusted based on the relationship between cost and EDSS as observed in the Kobelt source. Therefore, the Bebo source was the primary source for direct cost inputs for this model given it was the more recent source, but the relationship between direct cost and EDSS from the Kobelt source was used to adjust the costs from the Bebo source for various levels of EDSS. This approach assumed the EDSS distribution was the same between both sources. Direct MS costs included hospital inpatient care, non-acute institutional care, outpatient facility care, physician office care, durable medical equipment use, other ancillary costs, and non-DMT prescription medications. Outpatient medication administration (assumed to be related to DMT use) and DMT prescription medications were not included in the direct costs as they were modeled separately in this analysis. Table E18 reports the annual MS direct health care costs modeled for each EDSS state. For patients who experienced a mild/moderate relapse, an additional $1,223 of annual direct costs were included. For patients who experienced a severe relapse, an additional $3,576 of annual direct costs were included. The additional cost for a relapse was retrieved from ICER's 2017 MS review, adjusted for inflation, and then adjusted for severity using the relationship reported in a study that examined cost differences among patients without a relapse, patients with a mild/moderate relapse, and patients with a severe relapse.[121]

Table E18. Annual MS Direct Costs

EDSS State	Annual MS Direct Cost	Source
0	$5,771	Kobelt et al., 2006 and Bebo et al., 2022[8,59]
1	$9,920	
2	$14,070	
3	$18,217	
4	$22,365	
5	$26,515	
6	$30,664	
7	$34,812	
8	$38,960	
9	$43,109	

EDSS: Expanded Disability Status Scale, ICER: Institute for Clinical and Economic Review, RRMS: relapsing-remitting multiple sclerosis

Unrelated Direct Health Care Costs

The MS direct health care costs presented in the previous section do not include health care costs unrelated to MS. Therefore, unrelated direct health care costs were applied over the lifetime time horizon. Treatment costs and condition-related care costs were in addition to these unrelated direct health care costs. Table E19 reports the value and source of these costs.

Table E19. Unrelated Health Care Costs

Age	Annual Cost	Source
19-64 Years	$8,083	CMS National Health Expenditure Data[133]
65 Years and Older	$21,581	

CMS: Centers for Medicare and Medicaid Services

Adverse Event Costs

Additional costs associated with the occurrence of a serious adverse event were applied. The unit costs were the same as those used in ICER's 2017 MS review but inflated to 2021 US dollars. Table E20 reports the cost for each serious adverse event included in the model.

Table E20. Serious Adverse Event Unit Costs

Serious Adverse Event	Unit Cost	Source
Serious Infection, DRG 177	$12,406	ICER's 2017 Review[124]

DRG: diagnosis-related group, ICER: Institute for Clinical and Economic Review, RRMS: relapsing-remitting multiple sclerosis

Indirect Costs

In the modified societal perspective, the model assigned annual indirect costs based on EDSS state, with costs consistent between RRMS and SPMS. The approach to estimating annual indirect costs by EDSS was the same as the approach detailed above for direct costs. The model assigned annual indirect costs based on EDSS state, with costs consistent between RRMS and SPMS. The annual indirect costs used in this analysis were estimated from two sources, a study by Kobelt and colleagues published in 2006 that reported indirect costs by different levels of EDSS,[59] and a more recent source by Bebo and colleagues published in 2022 that reported indirect costs for the average MS patient but without stratifications based on different levels of EDSS.[8] First, the costs from both sources were inflated to 2021 US dollars. Then the average cost from the Bebo source was adjusted based on the relationship between indirect costs and EDSS as observed in the Kobelt source. Therefore, the Bebo source was the primary source for indirect cost inputs for this model given it was the more recent source, but the relationship between indirect cost and EDSS from the Kobelt source was used to adjust the costs from the Bebo source for various levels of EDSS. This approach assumed the EDSS distribution was the same between both sources. Indirect costs included absenteeism, presenteeism, early retirement, premature death, social productivity loss in volunteer work, nonmedical costs, paid daily nonmedical care, home modification, special equipment, and health care services not covered by insurance. These costs were sourced from the patient with MS, the primary caregiver, and the secondary caregiver. Table E21 reports the annual indirect costs modeled for each EDSS state. For patients who experienced a mild/moderate relapse, an additional $1,550 of annual indirect costs were included. For patients who experienced a severe relapse, an additional $2,944 of annual indirect costs were included. These additional costs for a relapse were retrieved from ICER's 2017 MS review, adjusted for inflation, and then adjusted for severity using the relationship reported in a study that examined indirect cost differences among patients without a relapse, patients with a mild/moderate relapse, and patients with a severe relapse.[121]

Table E21. Annual Indirect Costs

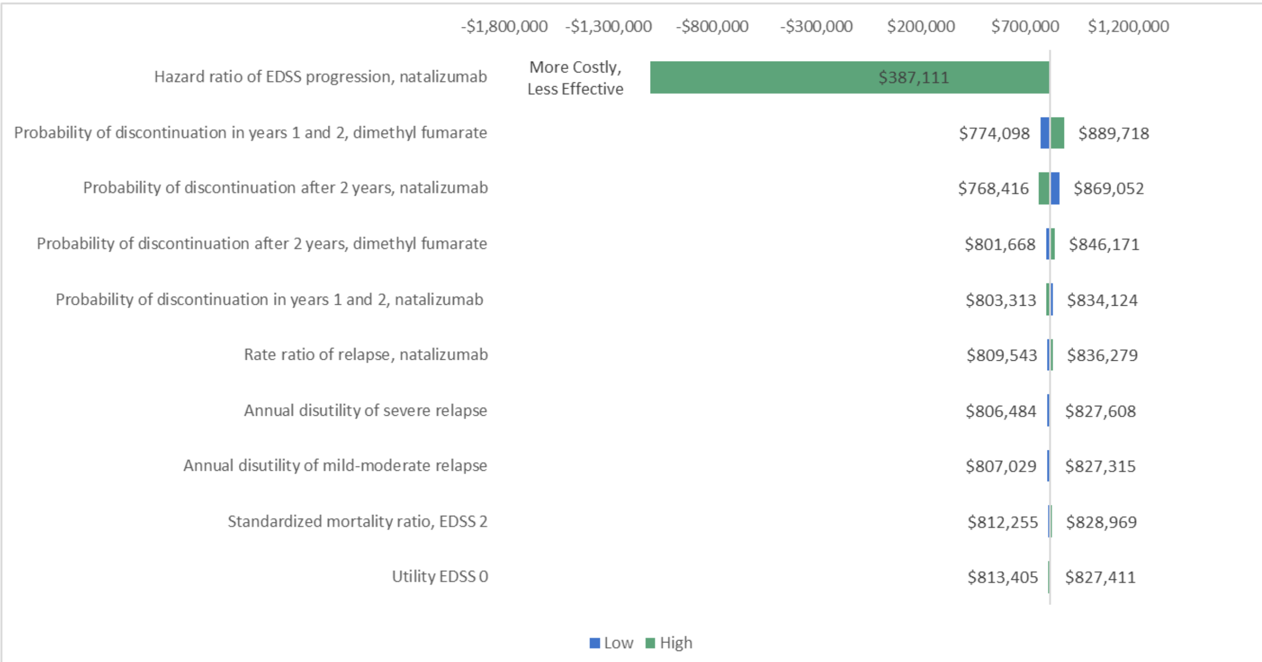
EDSS State	Annual Indirect Cost	Source
0	$9,027	Kobelt et al., 2006 and Bebo et al., 2022[8,59]
1	$12,349	
2	$15,672	
3	$18,994	
4	$22,317	
5	$25,639	
6	$28,962	
7	$32,284	
8	$35,607	
9	$38,930	

EDSS: Expanded Disability Status Scale, ICER: Institute for Clinical and Economic Review, RRMS: relapsing-remitting multiple sclerosis

E4. Sensitivity Analyses

Figures E2-E4 report the tornado diagrams for natalizumab, ofatumumab, and ocrelizumab. The tornado diagram for ublituximab is presented in the Report. Tables E22-24 provide the specific input values and corresponding outcomes for each of the inputs that appeared in the tornado diagram.

Figure E2. Tornado Diagram, Natalizumab versus Dimethyl Fumarate



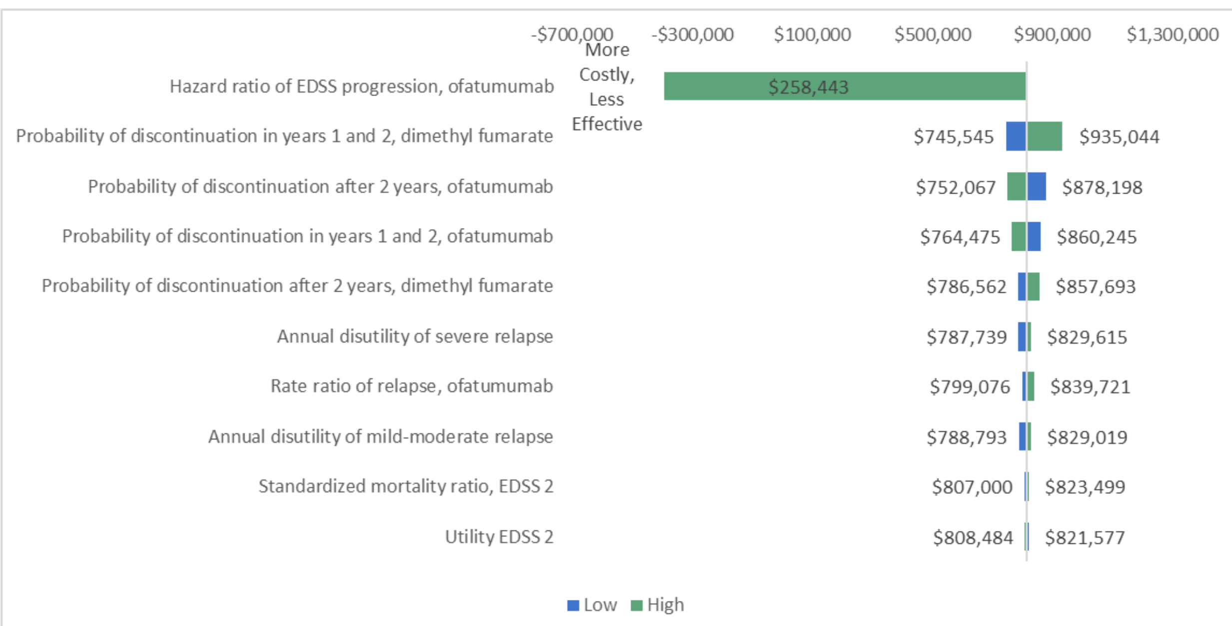
EDSS: Expanded Disability Status Scale

Table E22. Tornado Diagram Inputs and Results for Natalizumab versus Dimethyl Fumarate

	Lower Input ICER	Upper Input ICER	Lower Input	Upper Input
HR of EDSS Progression, Natalizumab	$387,000	More costly, less effective	0.25	0.85
Probability of Discontinuation in Years 1 and 2, Dimethyl Fumarate	$774,000	$890,000	5.0%	13.6%
Probability of Discontinuation after 2 Years, Natalizumab	$869,000	$768,000	0.8%	2.3%
Probability of Discontinuation after 2 Years, Dimethyl Fumarate	$802,000	$846,000	0.8%	2.3%
Probability of Discontinuation in Years 1 and 2, Natalizumab	$834,000	$803,000	1.4%	3.9%
Rate Ratio of Relapse, Natalizumab	$810,000	$836,000	0.22	0.44
Annual Disutility of Severe Relapse	$806,000	$828,000	-0.15	0.00
Annual Disutility of Mild-Moderate Relapse	$807,000	$827,000	-0.05	0.00
Standardized Mortality Ratio, EDSS 2	$812,000	$829,000	1.30	1.93
Utility EDSS 0	$827,000	$813,000	0.86	0.89

EDSS: Expanded Disability Status Scale, HR: hazard ratio, ICER: incremental cost-effectiveness ratio

Figure E3. Tornado Diagram, Ofatumumab versus Dimethyl Fumarate



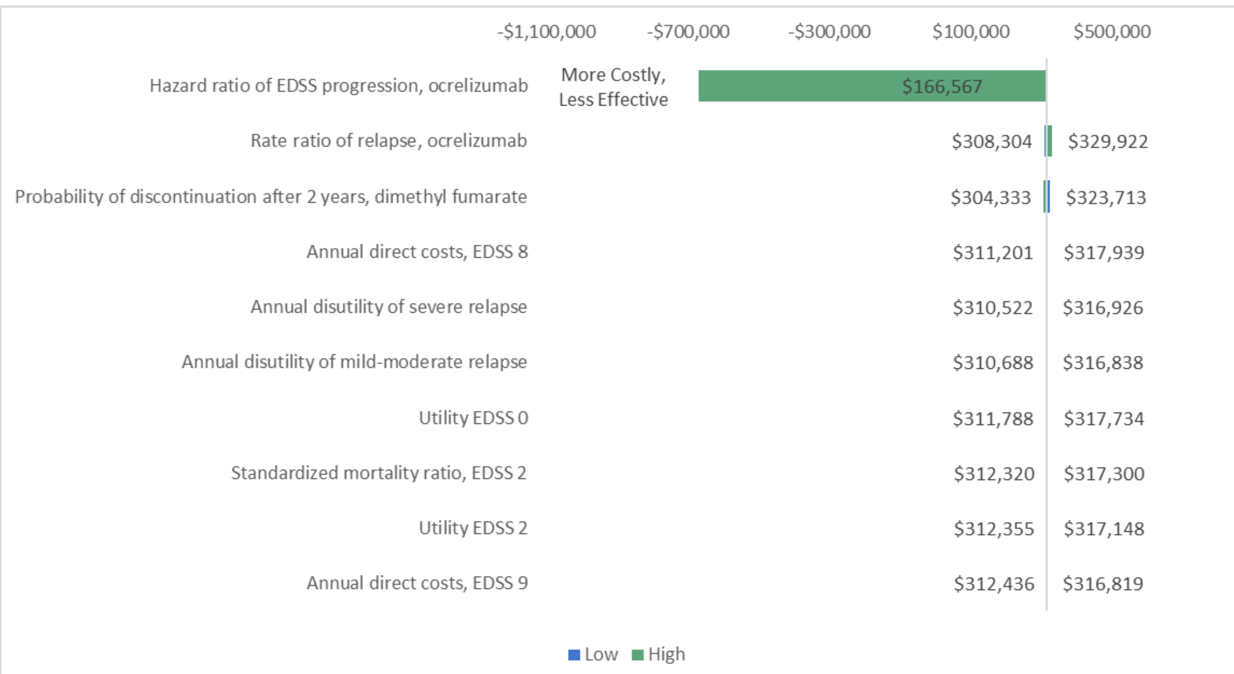
EDSS: Expanded Disability Status Scale

Table E23. Tornado Diagram Inputs and Results for Ofatumumab versus Dimethyl Fumarate

	Lower Input ICER	Upper Input ICER	Lower Input	Upper Input
HR of EDSS Progression, Ofatumumab	$258,000	More costly, less effective	0.28	1.06
Probability of Discontinuation in Years 1 and 2, Dimethyl Fumarate	$746,000	$935,000	5.0%	13.6%
Probability of Discontinuation after 2 Years, Ofatumumab	$878,000	$752,000	0.8%	2.3%
Probability of Discontinuation in Years 1 and 2, Ofatumumab	$860,000	$764,000	2.8%	7.6%
Probability of Discontinuation after 2 Years, Dimethyl Fumarate	$787,000	$858,000	0.8%	2.3%
Annual Disutility of Severe Relapse	$788,000	$830,000	-0.15	0.00
Rate Ratio of Relapse, Ofatumumab	$799,000	$840,000	0.20	0.43
Annual Disutility of Mild-Moderate Relapse	$789,000	$829,000	-0.05	0.00
Standardized Mortality Ratio, EDSS 2	$807,000	$823,000	1.30	1.93
Utility EDSS 2	$822,000	$808,000	0.76	0.80

EDSS: Expanded Disability Status Scale, HR: hazard ratio, ICER: incremental cost-effectiveness ratio

Figure E4. Tornado Diagram, Ocrelizumab versus Dimethyl Fumarate



EDSS: Expanded Disability Status Scale

Table E24. Tornado Diagram Inputs and Results for Ocrelizumab versus Dimethyl Fumarate

	Lower Input ICER	Upper Input ICER	Lower Input	Upper Input
HR of EDSS Progression, Ocrelizumab	$167,000	More costly, less effective	0.20	0.84
Rate Ratio of Relapse, Ocrelizumab	$308,000	$330,000	0.13	0.67
Probability of Discontinuation after 2 Years, Dimethyl Fumarate	$324,000	$304,000	0.8%	2.3%
Annual Direct Costs, EDSS 8	$318,000	$311,000	$31,700	$46,959
Annual Disutility of Severe Relapse	$311,000	$317,000	-0.15	0.00
Annual Disutility of Mild-Moderate Relapse	$311,000	$317,000	-0.05	0.00
Utility EDSS 0	$318,000	$312,000	0.86	0.89
Standardized Mortality Ratio, EDSS 2	$312,000	$317,000	1.30	1.93
Utility EDSS 2	$317,000	$312,000	0.76	0.80
Annual Direct Costs, EDSS 9	$317,000	$312,000	$35,075	$51,959

EDSS: Expanded Disability Status Scale, HR: hazard ratio, ICER: incremental cost-effectiveness ratio

Table E25 reports the results of the probabilistic sensitivity analyses. The mean probabilistic incremental cost-effectiveness ratios are higher than the deterministic incremental cost-effectiveness ratios. This is largely driven by the deterministic incremental cost effectiveness ratio using the median HR for the key model input. The median HR is the traditional metric outcome from an NMA; however, a decision-analytic model traditionally uses means as the deterministic point estimates.

Table E25. Results of Probabilistic Sensitivity Analysis

	Ublituximab Mean	Dimethyl Fumarate Mean
Costs	$1,900,000	$1,100,000
QALYs	13.15 (95% CI: 8.46, 16.70)	12.10 (95% CI: 11.76, 12.43)
evLYs	13.29 (95% CI: 8.46, 16.93)	12.10 (95% CI: 11.76, 12.43)
ICER ($/QALY)	$762,000	
ICER ($/evLY)	$672,000	
	Natalizumab Mean	**Dimethyl Fumarate Mean**
Costs	$2,800,000	$1,100,000
QALYs	13.94 (95% CI: 10.64, 16.40)	12.10 (95% CI: 11.76, 12.43)
evLYs	14.11 (95% CI: 10.64, 16.67)	12.10 (95% CI: 11.76, 12.43)
ICER ($/QALY)	$924,000	
ICER ($/evLY)	$846,000	
	Ofatumumab Mean	**Dimethyl Fumarate Mean**
Costs	$2,100,000	$1,100,000
QALYs	13.17 (95% CI: 9.41, 16.12)	12.10 (95% CI: 11.76, 12.43)
evLYs	13.30 (95% CI: 9.41, 16.39)	12.10 (95% CI: 11.76, 12.43)
ICER ($/QALY)	$935,000	
ICER ($/evLY)	$833,000	
	Ocrelizumab Mean	**Dimethyl Fumarate Mean**
Costs	$1,900,000	$1,100,000
QALYs	14.39 (95% CI: 10.73, 16.70)	12.10 (95% CI: 11.76, 12.43)
evLYs	14.59 (95% CI: 10.73, 16.94)	12.10 (95% CI: 11.76, 12.43)
ICER ($/QALY)	$349,000	
ICER ($/evLY)	$321,000	

CI: credible interval, evLYs: equal-value life year, ICER: incremental cost-effectiveness ratio, QALY: quality-adjusted life year

E5. Scenario Analyses

We conducted a number of scenario analyses to assess the robustness of results and test structural assumptions. The scenario analyses included:

1) Modified societal perspective that includes components such as productivity losses, informal care, or others as applicable.
2) Compared each intervention to a hypothetical monoclonal antibody biosimilar with treatment effectiveness equivalent to the average treatment effectiveness of the modeled interventions and cost equivalent to existing monoclonal antibody biosimilars.
3) Stopped treatment after a patient reached an EDSS higher than 7.
4) Modified the subsequent treatment to a) best supportive care and b) a generic oral DMT.
5) Changed the health state utility evidence source to reflect an MS utility survey using patient weights.
6) Modeled the cost effectiveness of natalizumab assuming administration every six weeks.
7) Included a treatment effect on EDSS improvement (i.e., increasing the probability of transitions from a higher to a lower EDSS health state).

Scenario Analysis 1: Modified Societal Perspective

In this scenario analyses, we expanded the perspective to that of a modified societal perspective. Additional costs included absenteeism, presenteeism, early retirement, premature death, social productivity loss in volunteer work, nonmedical costs, paid daily nonmedical care, home modification, special equipment, and health care services not covered by insurance. Table E26 reports the findings from this scenario analysis. Cost-effectiveness estimates for all interventions still exceeded upper bounds of commonly used thresholds.

Table E26. Incremental Cost-Effectiveness Ratios, Modified Societal Perspective

Treatment	Cost per Additional Year without Ambulatory Restrictions*	Cost per Additional Year without a Wheelchair†	Cost per QALY Gained	Cost per Life Year Gained	Cost per evLY Gained
Ublituximab‡	$386,000	$430,000	$587,000	$1,500,000	$524,000
Natalizumab	$515,000	$596,000	$799,000	$2,100,000	$722,000
Ofatumumab	$524,000	$583,000	$793,000	$2,100,000	$707,000
Ocrelizumab	$187,000	$223,000	$293,000	$772,000	$268,000

evLY: equal-value life year, QALY: quality-adjusted life year

*As measured by time in EDSS health states less than 5

†As measured by time in EDSS health states less than 7

‡Assuming a placeholder price for ublituximab equivalent to the net price of ocrelizumab.

Scenario Analysis 2: Monoclonal Antibody Biosimilar Comparator

In this scenario analyses, we compared each intervention to a hypothetical monoclonal antibody biosimilar with treatment effectiveness equivalent to the average treatment effectiveness of the modeled interventions and cost equivalent to existing monoclonal antibody biosimilars (e.g., biosimilar rituximab with an annual average sales price of approximately $4,400 per year). Table E27 reports the findings from this scenario analysis. Cost-effectiveness estimates for all interventions were either dominated (more costly, less effective) by the comparator or far exceeded upper bounds of commonly used thresholds.

Table E27. Incremental Cost-Effectiveness Ratios, Monoclonal Antibody Biosimilar Comparator

Treatment	Cost per Additional Year without Ambulatory Restrictions*	Cost per Additional Year without a Wheelchair†	Cost per QALY Gained	Cost per Life Year Gained	Cost per evLY Gained
Ublituximab‡	More costly, less effective	More costly, less effective	More costly, less effective	More costly, less effective	More costly, less effective
Natalizumab	>$1 million	>$1 million	>$1 million	>$1 million	>$1 million
Ofatumumab	More costly, less effective	More costly, less effective	More costly, less effective	More costly, less effective	More costly, less effective
Ocrelizumab	$662,000	$865,000	>$1 million	>$1 million	$826,000

evLY: equal-value life year, QALY: quality-adjusted life year

*As measured by time in EDSS health states less than 5.

†As measured by time in EDSS health states less than 7.

‡Assuming a placeholder price for ublituximab equivalent to the net price of ocrelizumab.

Scenario Analysis 3: Treatment Stop after EDSS of 7

In this scenario analyses, we stopped all DMT treatment once a patient reached an EDSS higher than 7. Therefore, for EDSS 8 and 9, transition probabilities were equivalent to those for best supportive care, and no treatment costs or treatment consequences were assigned. Table E28 reports the findings from this scenario analysis. Cost-effectiveness estimates for all interventions still exceeded upper bounds of commonly used thresholds.

Table E28. Incremental Cost-Effectiveness Ratios, Treatment Stop after EDSS of 7

Treatment	Cost per Additional Year without Ambulatory Restrictions*	Cost per Additional Year without a Wheelchair†	Cost per QALY Gained	Cost per Life Year Gained	Cost per evLY Gained
Ublituximab‡	$367,000	$409,000	$557,000	$1,500,000	$497,000
Natalizumab	$497,000	$576,000	$769,000	$2,000,000	$695,000
Ofatumumab	$492,000	$547,000	$743,000	$1,900,000	$663,000
Ocrelizumab	$196,000	$234,000	$305,000	$796,000	$279,000

evLY: equal-value life year, QALY: quality-adjusted life year

*As measured by time in EDSS health states less than 5.

†As measured by time in EDSS health states less than 7.

‡Assuming a placeholder price for ublituximab equivalent to the net price of ocrelizumab.

Scenario Analysis 4: Different Subsequent Treatment

In this scenario analyses, we varied the subsequent treatment assumed, while keeping the subsequent treatment the same across all interventions and the comparator. Table E29 reports the findings assuming a subsequent treatment of best supportive care and Table E30 reports the findings assuming a subsequent treatment of a generic oral DMT. Cost-effectiveness estimates for all interventions still exceeded upper bounds of commonly used thresholds for each subsequent treatment scenario. Notably, these estimates are not drastically different from our base-case estimates given the change in subsequent treatment assumption occurred in both the intervention and comparator.

Table E29. Incremental Cost-Effectiveness Ratios, Best Supportive Care Subsequent Treatment

Treatment	Cost per Additional Year without Ambulatory Restrictions*	Cost per Additional Year without a Wheelchair†	Cost per QALY Gained	Cost per Life Year Gained	Cost per evLY Gained
Ublituximab‡	$350,000	$380,000	$525,000	$1,400,000	$455,000
Natalizumab	$466,000	$521,000	$711,000	$1,900,000	$626,000
Ofatumumab	$475,000	$515,000	$710,000	$1,900,000	$614,000
Ocrelizumab	$202,000	$233,000	$311,000	$820,000	$277,000

evLY: equal-value life year, QALY: quality-adjusted life year

*As measured by time in EDSS health states less than 5.

†As measured by time in EDSS health states less than 7.

‡Assuming a placeholder price for ublituximab equivalent to the net price of ocrelizumab.

Table E30. Incremental Cost-Effectiveness Ratios, Generic Oral DMT Subsequent Treatment

Treatment	Cost per Additional Year without Ambulatory Restrictions*	Cost per Additional Year without a Wheelchair†	Cost per QALY Gained	Cost per Life Year Gained	Cost per evLY Gained
Ublituximab‡	$378,000	$419,000	$574,000	$1,500,000	$503,000
Natalizumab	$497,000	$568,000	$767,000	$2,000,000	$682,000
Ofatumumab	$506,000	$559,000	$764,000	$2,000,000	$668,000
Ocrelizumab	$206,000	$241,000	$320,000	$842,000	$287,000

evLY: equal-value life year, QALY: quality-adjusted life year

*As measured by time in EDSS health states less than 5.

†As measured by time in EDSS health states less than 7.

‡Assuming a placeholder price for ublituximab equivalent to the net price of ocrelizumab.

Scenario Analysis 5: Alternate Utility Source

In this scenario analyses, we used utility evidence from an MS survey with community preferences. Table E31 reports the findings from this scenario analysis. Cost-effectiveness estimates for all interventions were higher than the base-case results given the smaller spread in utility estimates observed in the MS survey.

Table E31. Incremental Cost-Effectiveness Ratios, Alternate Utility Source

Treatment	Cost per QALY Gained	Cost per evLY Gained
Ublituximab*	$623,000	$597,000
Natalizumab	$852,000	$826,000
Ofatumumab	$833,000	$798,000
Ocrelizumab	$330,000	$324,000

EDSS: Expanded Disability Status Scale

*Assuming a placeholder price for ublituximab equivalent to the net price of ocrelizumab.

Scenario Analysis 6: Frequency of Administration for Natalizumab

In this scenario analyses, we reduced the frequency of administration to once every six weeks, rather than once every four weeks as assumed in our base-case analysis. Reducing the frequency of natalizumab to every six months reduced the annual cost of natalizumab to approximately $67,000. Table E32 reports the incremental cost-effectiveness ratios from this scenario analysis for natalizumab. The cost-effectiveness estimate for natalizumab remained higher than commonly used thresholds even under this scenario.

Table E32. Incremental Cost-Effectiveness Ratios, Reduced Frequency of Administration

Treatment	Cost per Additional Year without Ambulatory Restrictions*	Cost per Additional Year without a Wheelchair†	Cost per QALY Gained	Cost per Life Year Gained	Cost per evLY Gained
Natalizumab	$332,000	$385,000	$516,000	$1,400,000	$467,000

evLY: equal-value life year, QALY: quality-adjusted life year

*As measured by time in EDSS health states less than 5.

†As measured by time in EDSS health states less than 7.

Scenario Analysis 7: Treatment Effect on EDSS Improvement

In this scenario analyses, we modeled the potential for a DMT to influence EDSS improvement. In the base-case analysis, the HR for disease progression was only applied to transitions moving to more severe health states. In this scenario analysis, we allow for the potential for a DMT to increase the probability of moving to a less severe health state. Evidence on a treatment's effect on EDSS improvement at 24 weeks is not available for all modeled interventions, or is not statistically significant for a modeled intervention, and thus we present this scenario only for ublituximab, but the implications of this scenario on the results could be extrapolated to other treatments if evidence suggests. In a tertiary analysis reported in the trial for ublituximab, at 24 weeks, 9.6% of the patients treated with ublituximab recorded disability improvement as compared to 5.1% of the patients treated with teriflunomide (HR of 2.03). Therefore, in this scenario analysis, we added an absolute 9.6% to the probability of transitioning to the health state immediately prior to the current health state for ublituximab and added an absolute 5.1% for the patients treated with dimethyl fumarate (assuming teriflunomide and dimethyl fumarate would perform similarly). Table E33 reports the incremental cost-effectiveness ratios from this scenario analysis for ublituximab. The cost-effectiveness estimates improve, but still far exceed common thresholds.

Table E33. Incremental Cost-Effectiveness Ratios, Reduced Frequency of Administration

Treatment	Cost per Additional Year without Ambulatory Restrictions*	Cost per Additional Year without a Wheelchair†	Cost per QALY Gained	Cost per Life Year Gained	Cost per evLY Gained
Ublituximab	$327,000	$389,000	$492,000	$1,300,000	$445,000

evLY: equal-value life year, QALY: quality-adjusted life year

*As measured by time in EDSS health states less than 5.

†As measured by time in EDSS health states less than 7.

E6. Model Validation

Model validation followed standard practices in the field. We tested all mathematical functions in the model to ensure they were consistent with the report (and supplemental materials). We also conducted sensitivity analyses with null input values to ensure the model was producing findings consistent with expectations. Further, independent modelers tested the mathematical functions in the model as well as the specific inputs and corresponding outputs.

Model validation was also conducted in terms of comparisons to other model findings. We searched the literature to identify models that were similar to our analysis, with comparable populations, settings, perspective, and treatments.

Prior Economic Models

We compared our model findings to those reported previously in the 2017 relapsing-remitting MS review conducted by ICER. A number of model parameters and structural assumptions have changed since the economic model used in the prior 2017 ICER review in relapsing-remitting multiple sclerosis as the clinical landscape has changed, namely:

- The comparator of dimethyl fumarate in this review versus the comparator of best supportive care in the 2017 review
- The baseline population age was older than the baseline population age in the 2017 review
- Treatment continuation until death versus treatment stopping at an EDSS of 7 in the 2017 review
- A consistent second line treatment across all interventions and the comparator versus a differential second line treatment in the 2017 review
- An updated source for direct and indirect costs
- Higher health state utilities for EDSS 8 and 9 versus the negative health state utilities used in the 2017 review

However, to compare our model to the prior economic model, we compared the best supportive care arm in the economic model developed for this review to the best supportive care arm in the economic model developed for the 2017 review. The best supportive care arm for this review is not used as an intervention or comparator, but was developed to serve as an anchor for the intervention and comparator treatment effectiveness.

For this comparison only, we changed the baseline age, the health state costs, and the utility estimates in the model developed for this review to match those that were used in the model developed for the 2017 review. After making those updates, our model nearly replicates the findings from the 2017 review for the best supportive care arm. When comparing the life years gained for best supportive care, this model produces 21.9 discounted life years over the lifetime time horizon as compared to 21.8 discounted life years in the 2017 model. When comparing the number of relapses that occurred, this model produced 16.8 relapses over the lifetime time horizon as compared to 16.7 relapses in the 2017 model. When comparing the QALYs, this model produces 5.6 discounted QALYs over the lifetime time horizon as compared to 5.7 discounted QALYs in the 2017 model. When comparing total discounted health system costs, this model estimated a lifetime discounted total cost of $333,000 as compared to $340,000 discounted costs over the lifetime in the 2017 model.

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 of ublituximab for patients with relapsing forms of MS. Potential budget impact was defined as the total differential cost of using each 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 five-year timeframe was of primary interest, given the potential for cost offsets to accrue over time and to allow a more realistic impact on the number of patients treated with the new therapy.

ICER's methods for estimating potential budget impact are described in detail elsewhere.[134,135] 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.

Briefly, we evaluate a new drug that would take market share from one or more drugs, and calculate the blended budget impact associated with displacing use of existing therapies with the new intervention. Using this approach to estimate potential budget impact, we then compared 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, 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.