Disease-Modifying Therapies for Relapsing-Remitting and Primary-Progressive Multiple Sclerosis: Effectiveness and Value

Final Evidence Report

March 6, 2017

Prepared for

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DATE OF PUBLICATION: March 6, 2017

We would also like to thank Margaret Webb for her contributions to this report.

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In the development if this report, ICER's researchers consulted with several clinical experts, patients, manufacturers and other stakeholders. The following clinical experts provided input that helped guide the ICER team as we shaped our scope and report. None of these individuals is responsible for the final contents of this report or should be assumed to support any part of this report, which is solely the work of the ICER team and its affiliated researchers.

For a complete list of stakeholders from whom we requested input, please visit: https://icer-review.org/material/ms-stakeholder-list/

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List of Acronyms Used in this Report

AHRQ	Agency for Healthcare Research and Quality
BID	Twice daily
CDMS	Clinically definite multiple sclerosis
CI	Confidence interval
CIS	Clinically isolated syndrome
CNS	Central nervous system
CPI	Consumer price index
CrI	Credible interval
DMT	Disease-modifying therapy
DRG	Diagnosis related group
EDSS	Expanded Disability Status Scale
EQ-5D	EuroQol five dimensions questionnaire
FS	Functional score
HR	Hazard ratio
IM	Intramuscular
ITP	Immune thrombocytopenic purpura
IV	Intravenous
JC virus	John Cunningham virus
MS	Multiple sclerosis
MRI	Magnetic resonance imaging
MSFC	Multiple Sclerosis Functional Composite
MSIS-29	Multiple Sclerosis Impact Scale
NNT	Number needed to treat
OR	Odds ratio
PML	Progressive multifocal leukoencephalopathy
PPMS	Primary-progressive multiple sclerosis
QALY	Quality-adjusted life year
QD	Once daily
QOD	Once every other day
QoL	Quality of life
REMS	Risk evaluation and mitigation strategy
RRMS	Relapsing-remitting multiple sclerosis
RR	Rate ratio or risk ratio
RRR	Relative risk reduction
SC	Subcutaneous
SF-12	12-item short form health survey
SPMS	Secondary-progressive multiple sclerosis
TIW	Three times a week
USPSTF	US Preventive Services Task Force
WTP	Willingness to Pay

Executive Summary

Background

Multiple sclerosis (MS) is a chronic, immune-mediated inflammatory, neurodegenerative, and demyelinating disease of the central nervous system (CNS).[1] Approximately 400,000 Americans have MS, although this may be an underestimate. The disease affects about three times as many women as men.[2] Some patient groups, such as African Americans, experience a more rapid and severe clinical course. The annual cost of MS in the United States is estimated to be $28 billion.[3]

RRMS

The most common form of MS is relapsing-remitting MS (RRMS), which affects 85% to 90% of patients at presentation.[1] RRMS is characterized by periodic relapses with neurologic symptoms that may diminish or resolve with treatment. Over one to two decades, more than half of untreated patients with RRMS transition to a disease course of slowly accumulating neurologic deficits known as secondary progressive MS (SPMS).[4]

There are more than 10 disease-modifying therapies (DMTs) approved by the Food and Drug Administration (FDA) for the treatment of RRMS. The therapeutic goal of DMTs is to decrease the frequency of relapses and to prevent the disability that accumulates with disease progression over time. Some neurologists believe that the goal of treatment should be to eradicate all evidence of disease activity, including magnetic resonance imaging (MRI) findings. There is controversy about the relative efficacy of the drugs, and several of the newer drugs have been associated with life-threatening adverse events (e.g., CNS infections, autoimmune diseases, liver toxicity, cancers). In addition, RRMS is a heterogeneous disease, which complicates comparisons across studies of DMTs.

PPMS

Approximately 10-15% of MS patients have primary-progressive MS (PPMS), a clinical course that is characterized by steadily worsening neurologic function, largely without remissions.[5,6] The mean age of onset of PPMS is 10 years older than that of RRMS and patients with PPMS generally experience more severe disability.[5,6] While RRMS affects around three times as many women as men, PPMS affects both sexes in approximately equal numbers.[5]

On June 27, 2016, the Food and Drug Administration (FDA) announced that it had granted Priority Review Designation to ocrelizumab for use in PPMS, and plans to issue a decision on March 28, 2017.[7,8] If approved, ocrelizumab would be the first agent with a PPMS indication. Several other agents have been studied for use in PPMS, but one – rituximab – is of particular interest to

practitioners, patients, and insurers because its mechanism of action is similar to that of ocrelizumab, despite its lack of a labeled indication for MS.[9]

The Topic in Context

There is no definitive clinical guideline to help clinicians and patients with decisions about both initial therapy and choices for subsequent therapies following treatment failure. Shared decision-making plays an important role when choosing initial and subsequent therapy, as patients and providers must balance considerations around efficacy, side effects, potential harms, route and frequency of administration, cost, and personal experience. Advocacy organizations have noted that patient preference strongly influences treatment adherence and resultant clinical outcomes. In addition, the advocacy organizations emphasized that some patients have a low tolerance for risk and are less likely to choose DMTs with known, potentially severe side effects. In addition, coverage policies often require patients to attempt treatment with at least one of the interferons or glatiramer acetate (the longest-tenured DMTs on the US market) and that they experience inadequate response prior to covering the newer DMTs because of the extended clinical experience with the older agents and the perception that they are safer and less costly. These combined factors demonstrate the considerable uncertainty about the interpretation and application of the current evidence base to guide clinical practice and insurance coverage policy.

One of the dreaded risks of DMTs for MS is progressive multifocal leukoencephalopathy (PML). PML is caused by an infection by the John Cunningham (JC) virus that attacks the myelin sheaths of nerves in patients with decreased function of the immune system. When PML occurs in MS, approximately 25% of patients die within 6 months and the survivors have increased long-term disability.[10] Other rare, but life-threatening risks of DMTs include autoimmune hepatitis and autoimmune blood disorders. The DMTs that are most effective at slowing the progression of MS tend to have the highest risk for these life-threatening unintended consequences.

Disease-Modifying Therapies for MS

The DMTs for multiple sclerosis that are the focus of this review are summarized in Table 1 below. For RRMS, they are intended to decrease relapses and progressive disability, which are the hallmarks of MS. All DMTs are thought to modulate the immune system to decrease the autoimmune damage that is believed to cause the CNS changes responsible for the symptoms of MS. All the drugs in the Table have an FDA indication for RRMS with the exception of ocrelizumab, which the FDA is expected to approve in March 2017 for both RRMS and PPMS, and rituximab, which is approved for other conditions and is used off-label for RRMS and PPMS. Both ocrelizumab and rituximab are monoclonal antibodies directed against the same protein, CD20, which is expressed on B-lymphocyte.

Table ES1. DMTs of Interest for the Evidence Review

Drug (Brand name)	Abbreviation in Tables/Figures	Class	FDA-Approved Dose	Year 1 Acquisition Cost
Subcutaneous injection				
Interferon β-1a (Avonex®, Biogen)	IFN β-1a 30 mcg	Interferon	30 mcg weekly	$81,965
Interferon β-1b (Betaseron®, Bayer)	IFN β-1b 250 mcg (Betaseron)	Interferon	250 mcg every other day	$86,659
Interferon β-1b (Extavia®, Novartis)	IFN β-1b 250 mcg (Extavia)	Interferon	250 mcg every other day	$72,359
Glatiramer acetate (Copaxone®, Teva)	GA 20 mg	Mixed polymers	20 mg daily	$86,554
Glatiramer acetate (Copaxone®, Teva)	GA 40 mg	Mixed polymers	40 mg three times weekly	$76,024
Glatiramer acetate (Glatopa®, Sandoz)	GA 20 mg (Glatopa)	Mixed polymers	20 mg daily	$63,193
Interferon β-1a (Rebif®, EMD Serono)	IFN β-1a 22 mcg or 44 mcg	Interferon	22 mcg or 44 mcg three times weekly	$86,416
Peginterferon β-1a (Plegridy®, Biogen)	PEG	Interferon	125 mcg every 14 days	$81,956
Daclizumab (Zinbryta®, Biogen and AbbVie)	DAC	Anti-CD25 monoclonal antibody	150 mg once monthly	$82,000
Oral				
Fingolimod (Gilenya®, Novartis)	FIN	Sphingosine 1-phosphate receptor modulator	0.5 mg once daily	$82,043
Teriflunomide (Aubagio®, Sanofi Genzyme)	TER	Pyrimidine synthesis inhibitor	7 mg or 14 mg daily	$76,612
Dimethyl fumarate (Tecfidera®, Biogen)	DMF	Multifactorial	240 mg twice daily	$82,977
Intravenous infusion				
Natalizumab (Tysabri®, Biogen)	NAT	Anti α4β1/ α4β7 integrin monoclonal antibody	300 mg every 4 weeks	$78,214
Alemtuzumab (Lemtrada®, Sanofi Genzyme)	ALE	Anti-CD52 monoclonal antibody	12 mg per day for 5 days in the first year, 3 days in second year and every subsequent year when treatment is required	$103,749

Drug (Brand name)	Abbreviation in Tables/Figures	Class	FDA-Approved Dose	Year 1 Acquisition Cost
Ocrelizumab (Ocrevus®, Genentech)	OCR	Anti-CD20 monoclonal antibody	RRMS: 300 mg twice 14 days apart, then 600 mg once every 24 weeks* PPMS: 300 mg twice 14 days apart, cycle begins every 24 weeks*	Unknown
Rituximab (Rituxan®, Genentech)	RIT	Anti-CD20 monoclonal antibody	2000 mg every 6 months*	$33,408

WAC: wholesale acquisition cost

*Ocrelizumab and rituximab have not been approved by the FDA for use in MS, dosing data from clinical trials was used.

Insights Gained from Discussions with Patients and Patient Groups

ICER had conversations with individual patients and multiple patient advocacy organizations, including the MS Coalition (which also includes clinical societies), the National MS Society, Accelerated Cure, MS Association of America, and PatientsLikeMe. A full description of the insights gained from these conversations is presented in the full report, but several important themes are summarized below.

- A diagnosis of MS poses many burdens, including economic hardships that are underappreciated in most economic analyses of MS. These include lost wages from missed work, the need to transition from full- to part-time work, the inability to continue working, and the high cost of medications and medical equipment.
- Patients want their provider to be able to choose the medication that is best for them without restriction, but feel that their choice of therapy is driven by insurance coverage and the willingness of their provider to appeal coverage denials. The high cost of DMTs for MS can result in large out-of-pocket costs for individuals who are unaware of, or ineligible for, patient-assistance programs offered by manufacturers or non-profit organizations.
- The primary goal for patients is to remain independent, but it must be balanced with the risks for adverse events that are carried by the therapies most likely to keep them independent. These risk-benefit assessments are complicated by the lack of long-term data; many of the studies of DMTs are short term (1-3 years) whereas disability typically accumulates over a much longer time horizon of 10 to 15 years.
- The MS Coalition created an online questionnaire to assess patient perspectives on the most important issues for patients when making decisions about which therapy to take. The most important factors included how well a DMT delays the onset of disability and prevents relapses or new MRI lesions. In addition, the ability to continue working and performing

normal activities, provider recommendation of a therapy, other long-term risks, and the restrictions that their insurer places on access to therapies were also deemed very important.

- Some patients have a strong preference for oral medications over injectable ones because of their dislike of needles, injection site reactions, and the difficulty of storing medications that require refrigeration. Other patients are equally comfortable with injectable medications.[11,12]

Comparative Clinical Effectiveness

To inform our analysis of the comparative clinical effectiveness of DMTs in the treatment of RRMS and PPMS, we abstracted evidence from available clinical studies of these agents, whether in published or abstract form. There were 33 unique randomized trials with 21,768 patients for the RRMS indication and 2 randomized trials for the PPMS indication. The oldest trial[13] was published in 1987 and the most recent trial was published in 2017.[14] This evidence was sufficient to perform network meta-analyses (NMA) that combined direct (head-to-head) and indirect evidence for relapse rate and sustained disability progression. The results of the overall NMA were consistent with the findings of the head-to-head trials for these two outcomes. There was sparse evidence and no consistent outcome measure for MRI and quality of life outcomes, so NMAs were not performed for these outcomes.

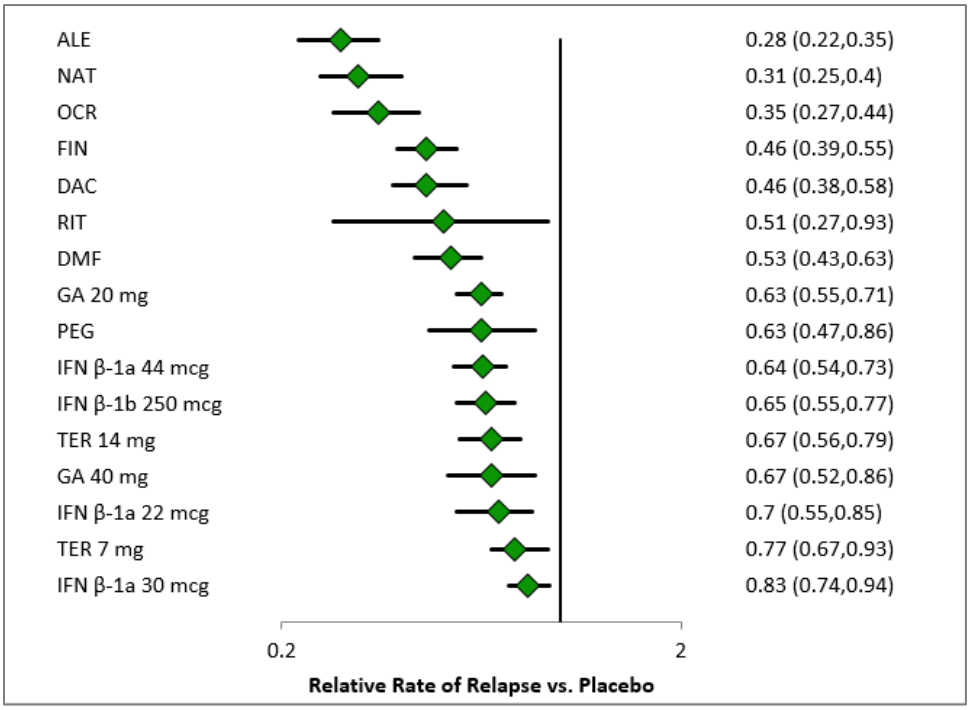
RRMS

Clinical Benefits

Relapse Rate

In our NMA, alemtuzumab, natalizumab, and ocrelizumab had the greatest reduction in ARR (approximately 70% reduction compared to placebo). Fingolimod, daclizumab, rituximab, and dimethyl fumarate were the next most effective (47% to 54% reduction). The interferons, glatiramer acetate 20 mg, and teriflunomide were less effective (17% to 37% reduction). Within these groupings, however, the 95% credible intervals (the Bayesian equivalent of confidence intervals) overlapped, suggesting no material differences within the three sets of drugs, but all of the drugs were significantly better than placebo. A forest plot summarizing the relative risks and 95% credible intervals for each drug compared to placebo is presented below (Figure ES1).

Figure ES1. Forest Plot of DMTs vs. Placebo for Annualized Relapse Rate



Legend: The diamonds represent the point estimate from the NMA for the relative risk of relapse rate for each drug compared to placebo and the horizontal bars represent the 95% credible intervals. Any numbers less than 1 indicate a reduction in the relapse rate compared to placebo.

The forest plot also graphically demonstrates the superiority of alemtuzumab, natalizumab, and ocrelizumab to the other agents. The study of rituximab was underpowered compared to the other studies (much wider credible intervals, greater uncertainty), but the point estimate was similar to that of fingolimod, daclizumab, and dimethyl fumarate. The interferons, glatiramer acetate, and teriflunomide appear to be less effective at reducing relapse rates than the other drugs. Nevertheless, interferon β-1a 30 mcg, which was the least effective drug in the NMA, is still superior to placebo. Comprehensive sensitivity analyses are described in detail in the full report; across these analyses, there were no important changes in the ordering of drugs or the estimated efficacy versus placebo. Published NMAs reported similar rankings of the DMTs for relapse rates.

Disability Progression

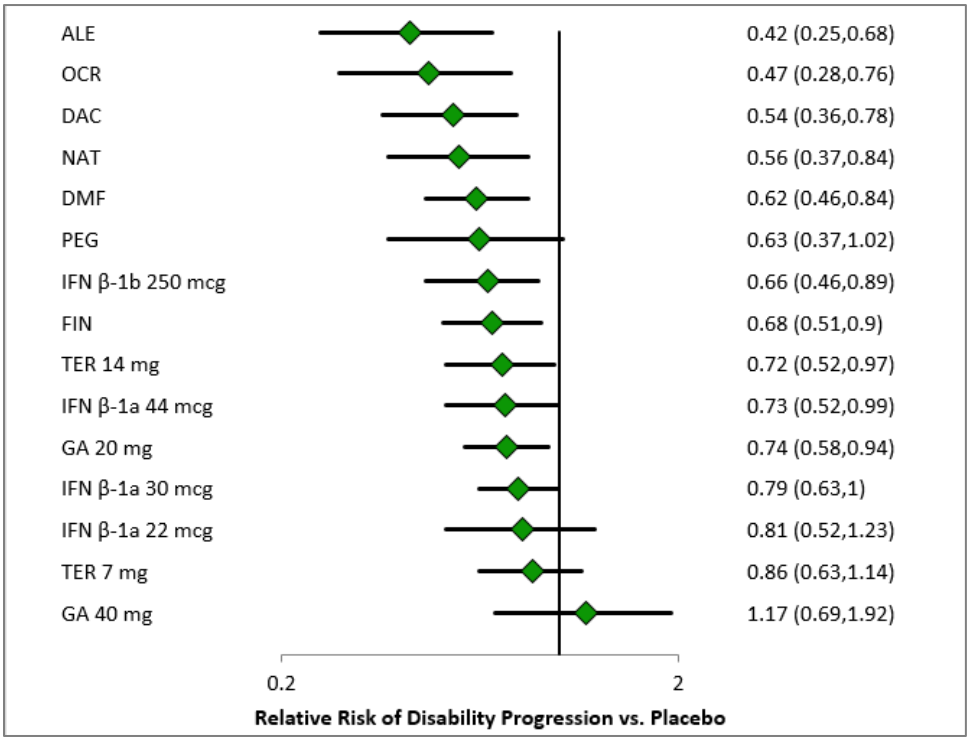
We identified 27 trials that reported dichotomous results for disability progression (measured by Expanded Disability Status Score [EDSS]), including 16 head-to-head studies (4 of which also had a placebo arm) and an additional 11 placebo-controlled studies, all of which contributed results to the NMA of disability progression. Ideally, studies would measure disability progression over at least five years.[15] Unfortunately, all but two of the studies were two years or less in duration and many

studies did not report the preferred measure: the number of patients with confirmed disability progression sustained for a minimum of 24 weeks.

In our NMA, ocrelizumab and alemtuzumab had the greatest reduction in disability progression (53% to 58% reduction compared to placebo respectively), closely followed by daclizumab (46%) and natalizumab (44%). Dimethyl fumarate, peginterferon β-1a, interferon β-1b 250 mcg, and fingolimod were next (32% to 38%). Teriflunomide, glatiramer acetate, and the remaining interferons were less effective (14% to 28%). Four of the drugs were not significantly better than placebo (interferon β-1a 30 mcg, interferon β-1a 22 mcg, teriflunomide 7 mg, and glatiramer acetate 40 mg; credible interval contains 1.0). In the only trial of glatiramer acetate 40 mg (GALA trial), there was a non-significant trend towards greater disability progression in the glatiramer acetate 40 mg group.[16] It is unlikely that glatiramer acetate 40 mg increases disability progression. Indeed, in the three-year open-label extension of the same GALA trial, there was a trend towards a reduction in disability in the glatiramer acetate 40 mg arm, although this also was not statistically significant (HR 0.76, 95% CI 0.55-1.04, p=0.09).[17]

A forest plot summarizing the relative risks and 95% credible intervals for each drug compared to placebo is below (Figure ES2). The credible intervals for most of the drugs are quite wide, highlighting the limitations of indirect evidence to distinguish one drug or set of drugs from the others. This also reflects the small number of patients with disability progression due to the relatively short follow-up and small size of most of the trials.

Figure ES2. Forest Plot of DMTs vs. Placebo for Disability Progression



Legend: The diamonds represent the point estimate from the NMA for the relative risk of disability progression for each drug compared to placebo and the horizontal bars represent the 95% credible intervals. Any numbers less than 1 indicate a reduction in disability progression compared to placebo.

Subgroup and sensitivity analyses did not identify any substantial inconsistencies in the network. The published NMAs based on a smaller set of trials and a variety of methodologic approaches came to similar conclusions.

MRI Outcomes

MRI findings are used in the diagnosis and management of MS. It is, however, difficult to compare MRI findings across trials because of variability in how MRI measures were performed and reported. We were unable to perform a network meta-analysis on MRI outcomes. MRI outcomes in the key randomized trials are described in the full report.

Quality of Life / Patient-Centered Outcomes

Quality of life is worse in patients with MS compared to age- and sex-matched individuals in the general population.[18,19] Quality of life correlates with EDSS scores: as EDSS scores increase, quality of life declines. In general, studies of DMTs for MS have focused on reducing relapses and disability progression, not quality of life. The depression, fatigue, musculoskeletal, and urinary symptoms that patients with MS experience are usually managed by other interventions. Treatments for

depression in MS include conventional antidepressant medications, cognitive behavioral therapy, and mindfulness. Treatments for fatigue include amantadine, methylphenidate, and modafinil. Physical therapy, anti-spasticity drugs, medical devices, and botulinum toxin are all employed to help address musculoskeletal and urologic needs. At high-quality MS centers, multidisciplinary teams employ multiple modalities to help improve these outcomes.

The most commonly reported measures were the EQ-5D and the SF-36. Most of the trials reporting SF-36 results found significant improvements in the Physical Component Summary Scale (PCS), but not the Mental Component Summary Scale. During relapses, quality of life decreases. The primary intermediate-term quality of life benefit from the DMTs appear to be physical and correlates with changes in level of disability. Even when statistically significant, the magnitude of benefit, when found, was small. The few trials that reported fatigue and depression measures did not find consistent improvements with DMTs compared to placebo.

Harms

The harms of the DMTs are summarized in Table ES2. In the randomized trials, specific SAEs were generally uncommon (<1% of treated patients) and not statistically different from the control group, whether active or placebo. However, a number of potentially life-threatening harms have been identified from post-marketing data leading to Black Box warnings for five of the DMTs. For non-serious AEs, flu-like symptoms were more common in patients treated with interferons, injection site reactions were more common for all of the injectable agents, and infusion reactions were more common for the infused agents. Fingolimod has first dose cardiac effects that must be monitored. However, it is the less common, more serious AEs that cause the greatest concerns for both patients and their treating providers.

Table ES2. Harms of DMTs

Drug (Brand name)	Major safety concerns	D/C rates	SAEs
Subcutaneous injections			
Interferon β-1a 30 mcg (Avonex)	Depression, suicide, psychosis, liver toxicity, seizures, allergic reactions, CHF, ↓ peripheral blood counts, thrombotic microangiopathy, flu-like symptoms are common (49%)	4%	14%
Interferon β-1b 250 mcg (Betaseron, Extavia)	Liver toxicity, allergic reactions, depression, suicide, CHF, injection site necrosis (4%), leukopenia, thrombotic microangiopathy, flu-like symptoms are common (57%)	6%	11%
Glatiramer acetate (Copaxone, Glatopa)	Post-injection reaction (16%), transient chest pain (13%), lipoatrophy, skin necrosis, injection site reactions	3%	13%
Interferon β-1a 22/44 mcg (Rebif)	Depression, suicide, livery injury, allergic reactions, ↓ peripheral blood counts, thrombotic microangiopathy, seizures, injection site reactions common (~90%), injection site necrosis (3%), flu-like symptoms are common (59%)	5%	16%

Drug (Brand name)	Major safety concerns	D/C rates	SAEs
Peginterferon β-1a (Plegridy)	Liver toxicity, depression, suicide, seizures, allergic reactions, CHF, ↓ peripheral blood counts, thrombotic microangiopathy, flu-like symptoms are common (47%)	5%	11%
Daclizumab (Zinbryta)	↑ risk of infection and skin reactions. Hypersensitivity reactions, depression, and suicide. Boxed warning: significant hepatic injury (0.7%), autoimmune hepatitis (0.3%), other immune mediated disorders. Serious immune-mediated reactions in 5% of patients. Only available through **REMS**.*	15%	22%
Oral agents			
Fingolimod (Gilenya)	1st dose bradycardia, ↑ risk of serious infection, PML, macular edema, PRES, ↓ respiratory function (↓FEV1), liver toxicity, ↑BP, basal cell carcinoma (2%). **REMS* requirement lifted in late 2016.**	12%	10%
Teriflunomide (Aubagio)	Boxed warning for hepatotoxicity (including fatal liver failure) and teratogenicity. ↓ WBC, possible infection risk, peripheral neuropathy (1.4 – 1.9%); ↑ BP (3-4%). Hair thinning.	13%	13%
Dimethyl fumarate (Tecfidera)	Anaphylaxis, angioedema, PML, ↓ WBC, liver injury, flushing (40%)	14%	18%
Intravenous infusions			
Natalizumab (Tysabri)	Boxed warning for PML. ↑ risk for herpes encephalitis and meningitis, liver toxicity, hypersensitivity (including anaphylaxis) reactions, ↑ risk of infection. Only available through **REMS.***	6%	19%
Alemtuzumab (Lemtrada)	Boxed warning for serious (sometimes fatal) autoimmune conditions such as ITP, life-threatening infusion reactions, may cause ↑ risk of malignancies. Infusion reactions (92%), rash (53%), lymphopenia (99.9%). Only available through **REMS**.*	2%	13%
Ocrelizumab (Ocrevus)	It is unknown if there will be a Boxed Warning as ocrelizumab is not yet FDA approved. Risk of infection, possible ↑ risk for PML (due to similarity in mechanism to rituximab and ofatumumab)[20]	4%	7%
Rituximab (Rituxan)	Boxed warning for fatal infusion reactions within 24 hours of infusion, severe mucocutaneous reactions (including fatalities), HBV reactivation, PML (all for non-MS indications). ↑ risk of infection, ↑ risk of cardiac arrhythmia, bowel obstruction, cytopenias	4%	13%

BP: blood pressure, CHF: congestive heart failure, D/C rates: discontinuation due to adverse events, FEV1: forced expiratory volume in 1 second, HBV: hepatitis B virus, ITP: idiopathic thrombocytopenic purpura, PRES: posterior reversible encephalopathy syndrome, PML: progressive multifocal leukoencephalopathy, WBC: white blood cell count

*REMS: Risk Evaluation and Mitigation Strategy

Because of the risk for serious adverse events, both alemtuzumab and daclizumab's FDA indications state that they "should generally be reserved for patients who have had an inadequate response to two or more drugs indicated for the treatment of MS. Similarly, the FDA indication for natalizumab originally stated "Tysabri is generally recommended for patients who have had an inadequate response to, or are unable to tolerate, an alternate MS therapy." It now reads "Tysabri increases the risk of PML. When initiating and continuing treatment with Tysabri, physicians should consider whether the expected benefit of Tysabri is sufficient to offset this risk." The incidence of PML ranges from < 0.09 per 1000 patients for John Cunningham (JC) virus antibody-negative patients to 11.1 per 1000 patients for JC virus antibody positive patients on natalizumab for 2 to 4 years with prior exposure to immunosuppressive drugs.[21] In clinical practice, this generally precludes the use of natalizumab in patients with JC virus antibodies.

Balancing the benefits and harms is challenging for both patients and their providers, as the more powerful drugs are more effective, but carry with them higher risks for life-threatening complications.

PPMS

Clinical Evidence

There is one placebo controlled trial of ocrelizumab (ORATORIO) and one of rituximab (OLYMPUS). For ocrelizumab, confirmed disability progression sustained for at least 12 weeks, the primary endpoint of the trial, was significantly lower than placebo (HR 0.76, 95% CI 0.59 - 0.98, p=0.032). Confirmed disability progression sustained for at least 24 weeks was also significantly lower (HR 0.75, 95% CI 0.58-0.98, p=0.04), and there was a significant reduction in the T2 lesion volume (p<0.001), faster performance of the 25-foot walk (p=0.04) and a significant improvement in the change in brain volume (p=0.02). There was no excess of adverse events associated with ocrelizumab.

For rituximab, the OLYMPUS trial was a good-quality trial that did not find a significant difference in the time to confirmed disease progression sustained for at least 12 weeks (HR 0.77, p=0.14). There was a significant reduction in the T2 lesion volume (p<0.001), but not in the change in brain volume (p=0.62). Preplanned subgroup analyses found that rituximab significantly delayed the time to progression for patients aged < 51 years (HR 0.52, p=0.01) and in those patients with gadolinium-enhancing lesions at baseline (HR=0.41, p=0.007). Infection-associated SAEs were more common with rituximab. In summary, the trial did not meet its primary endpoint, but suggested that rituximab shows promise for younger patients with PPMS who have gadolinium-enhancing lesions on MRI.

The potential harms of ocrelizumab and rituximab discussed in the RRMS section apply equally to the use of those therapies in patients with PPMS.

Controversies and Uncertainties

Several limitations to the evidence base reduced our ability to make confident judgments about the comparative net health benefits of DMTs for MS. First, the evolving diagnostic criteria for clinically-definite MS over the decades of clinical trials of DMTs caused important variation among the studied patient populations. Many patients enrolled in trials that used the McDonald criteria would have been diagnosed with clinically-isolated syndrome (CIS, the first episode of neurologic symptoms lasting greater than 24 hours that is compatible with MS, but does not meet diagnostic criteria) under the Poser criteria. Prior analyses have also demonstrated a decrease in ARRs and risk of disability progression in the clinical trial populations over the past 25 years.[22-26] There is not consensus about the reason or reasons for the observed change in rates. However, the relative benefits of DMTs appear similar across these different populations.

A second limitation was the short follow-up of the randomized trials. The important clinical impacts of MS must be measured over decades and European research guidelines recommend 5-year trials. However, the majority of the RCTs followed patients for 1 or 2 years before unblinding. While long-term extension trials demonstrate continued DMT efficacy over time, the true impact of individual drugs is difficult to assess because loss to follow-up introduces selection bias and unblinding introduces measurement bias and differential co-interventions. The short follow-up time in the trials most directly impacted the estimates of sustained disability progression, as demonstrated by the wide credible intervals that often included 1 in the ICER NMA.

Ideally, comparative effectiveness assessments are informed by information from large, high-quality, head-to-head trials. Although NMAs may be performed in the absence of such evidence, the assumptions that are necessary to perform indirect comparisons through common comparators introduce additional uncertainty. In general, our NMA results mirror the findings of the available head to head trials.

In the NMA and in the model below, we treated all of the DMTs equally, as if each could be used as first line therapy. In reality, most insurance plans support using one of the interferons or glatiramer acetate as first line therapy and the FDA indications for alemtuzumab, daclizumab, and natalizumab discourage their use as first line therapy.

Finally, the results of the randomized trials of ocrelizumab for patients with RRMS and PPMS are encouraging, but ocrelizumab has not yet received FDA approval. Thus, there is no real-world data to assess uncommon, serious adverse events and to corroborate the findings of the clinical trials performed for regulatory approval. In addition, the independent review of the full set of clinical trial data performed by the FDA will be invaluable in assessing the balance of risks and benefits for ocrelizumab. Furthermore, the limited numbers of patients and short follow-up among those treated with ocrelizumab add to the uncertainty about rare, but serious adverse events that may

not be fully appreciated until post-marketing data are available. It is the only DMT under consideration in this review that has no real-world data on safety.

Summary

RRMS: DMTs Compared to Best Supportive Care

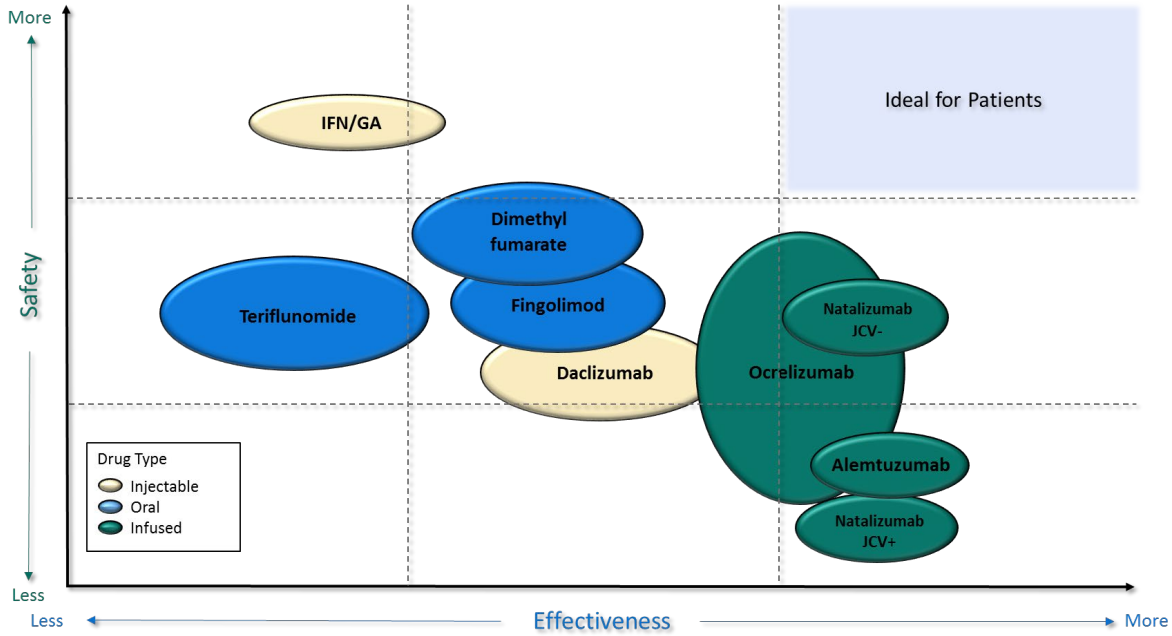
From the patient perspective, the most important outcome is the prevention of disability progression, followed by a reduction in relapses. Patient-centered outcomes such as quality of life are also of great interest to patients, though they are sparsely and inconsistently reported in the pivotal trials, and we were unable to arrive at any judgments of the comparative effectiveness of DMTs on these outcomes. The data on relapse rates and disability progression are most robust comparing DMTs to placebo. Of all the agents included in this review, alemtuzumab, natalizumab, and ocrelizumab were the most effective drugs in reducing relapses and they were significantly better than the other DMTs. They were also three of the four most effective drugs at reducing disability progression, although the separation from other DMTs was not as substantial. The differences in efficacy between the alemtuzumab, natalizumab, and ocrelizumab were relatively small and non-significant. We gave alemtuzumab and natalizumab an "A" rating - high certainty of a moderate to large net health benefit. The primary factor distinguishing the two drugs, apart from mechanism of action, is their unique risks for adverse events. Patients treated with natalizumab are at high risk for PML and must be monitored closely for its signs and symptoms of PML and other infections. Patients treated with alemtuzumab are at risk for life-threatening ITP, infusion reactions, and less severe, but common autoimmune thyroid diseases. Among JC virus antibody negative patients, who are at lower risk for PML, natalizumab is safer and equally effective. For JC virus antibody-positive patients, the risk for PML generally precludes the use of natalizumab. We gave ocrelizumab a lower B+ rating (incremental or better net health benefits when compared to placebo) because of additional uncertainty with pending FDA approval and the lack of real-world experience with the drug.

The next most effective group for relapse reduction included daclizumab, rituximab, fingolimod, and dimethyl fumarate. There is only one small trial of rituximab with no data on disability progression, but impressive MRI data, so we judge the evidence on rituximab to be promising, but inconclusive (P/I). We judge daclizumab, fingolimod, and dimethyl fumarate to produce incremental or better net health benefits ("B+"); although point estimates of their benefits may be slightly less than those of ocrelizumab, there is substantial overlap of all four agents' credible intervals compared with one another in both ARR and disability progression NMAs. Daclizumab, fingolimod, and dimethyl fumarate have some real-world experience, but substantially less than the interferons and glatiramer acetate. Of the three, dimethyl fumarate may have a lower risk for very serious adverse events because it does not carry a black box warning, nor is its use monitored under a REMS program.

Finally, our NMA suggested that the interferons, glatiramer acetate, and teriflunomide were substantially similar with respect to their effects on ARR and disability progression. Each of the four prior NMAs came to the same conclusion either about the interferons and glatiramer acetate[27], or those agents plus teriflunomide.[28-30] In addition, a 2017 systematic review of 36 observational trials with data from more than 32,000 patients concluded that the interferons show similar effectiveness in real world practice.[31] All are effective at reducing relapses and have good safety profiles with decades of treatment experience to support their safety. The higher doses of interferon β-1a and teriflunomide are consistently more effective than the lower doses. Some of the injectable DMTs can be dosed less frequently and teriflunomide is taken orally. These differences be important for patients when choosing among different options, but the clinical differences in important outcomes are small. As such, we judged with high certainty that these nine DMTs provide incremental net health benefits compared to best supportive care ("B").

Figure ES3 below qualitatively summarizes the relative safety and effectiveness of the DMTs for RRMS. Each drug or group of drugs is represented by an oval. The width of the oval reflects uncertainty about its overall effectiveness and the height of the oval represents uncertainty about the safety of the drug. The safest drugs are highest on the graph and the most effective are to the right. Thus alemtuzumab, which was consistently the most effective drug, is on the right side of the figure but relatively low. The interferon/glatiramer acetate group is on the upper left as those DMTs are among the safest, but least effective. The ideal DMT, both safe and highly effective, would be to the upper right.

Figure ES3. Safety and Effectiveness of DMTs for RRMS



Wider and taller shapes indicate greater uncertainty. Not drawn to scale.

RRMS: Newer DMTs Compared to Interferons and Glatiramer Acetate

The comparison of the newer agents to the interferons and glatiramer acetate is of greater interest to many stakeholders. Alemtuzumab significantly reduces relapses and disability progression compared to the early injectable DMTs, but carries significant risks for life-threatening complications. We judge it to incremental or better compared to the earlier DMTs (B+). Natalizumab also significantly reduces relapse rates compared to the early injectable agents, but is not significantly better than most for disability progression. The AFFIRM trial demonstrated a large decrease in disability progression compared with placebo, but there are no large randomized trials comparing natalizumab to another DMT.[32] Given the lack of direct comparative trial results, the availability of data from only a single trial, and the additional harms associated with natalizumab, we judge it to be incremental or better when compared to the injectable DMTs (B+). Daclizumab, fingolimod, and dimethyl fumarate significantly reduced relapses compared to the early injectable DMTs, but are not significantly better at reducing disability progression. They all have greater risks for life-threatening adverse events than the earlier DMTs. Thus, we judge them to be comparable or better when compared to the injectable DMTs (C+).

As noted above, there is only one small trial of rituximab compared to placebo with no data on disability progression, but impressive MRI data. We judge the evidence on rituximab to be promising, but inconclusive (P/I). Ocrelizumab significantly reduces relapses and disability progression compared to the interferons and glatiramer acetate. To date, it has few known severe adverse events. However, there is no real-world evidence supporting its efficacy. Thus, we judge it to produce incremental or better net health benefits when compared to the earlier agents, a "B+" rating. The ARR and disability progression for teriflunomide were not significantly different compared with the interferons and glatiramer acetate. It has the advantage of being an oral agent, but has a boxed warning for hepatotoxicity and has other important side effects. Overall, we judge that teriflunomide has comparable net health benefits (C) to the interferons and glatiramer acetate.

Interferon β-1a 44 mcg SC TIW (Rebif) and Interferon β-1a 30 mcg IM Once Weekly (Avonex)

We were aware of specific interest in the comparative effectiveness of interferon β-1a 44 mcg SC three times weekly (Rebif) to interferon β-1a 30 mcg IM once weekly (Avonex) because of differing judgments about the head-to-head EVIDENCE trial. In the NMA, Rebif had a significantly lower relapse rate than Avonex (RR 0.77, 95% CrI 0.65-0.88) and a non-significantly lower disability progression (RR 0.92, 95% CrI 0.65-1.27). In the EVIDENCE trial, which compared these two different formulations head to head, there were non-significant trends towards lower relapse rates (RR 0.84, 95% CI not reported, p=0.093) and disability progression (RR 0.70, 95% CI 0.39-1.25) that were similar to the findings of the NMA. The primary endpoint in the EVIDENCE trial, the proportion of patients remaining free from relapse, was lower with Rebif (HR 0.70, 95% CI 0.55-0.88, p=0.003). In addition, the MRI outcomes (number of combined unique active lesions, T1

gadolinium-enhancing lesions, and active T2 lesions) were significantly better in the patients treated with Rebif (P<0.001 for all 3 comparisons). Overall the differences in harms were small. Based on these data we judge there to be moderate certainty of a small-to-substantial net health benefit for Rebif compared to Avonex, with high certainty of at least a small net health benefit (B+).

PPMS

For ocrelizumab, we judge there to be moderate certainty of small to substantial net benefit, tempered primarily by the lack of real-world experience with the drug (ICER rating B+). We judge the evidence for the effectiveness of rituximab in PPMS to be promising, but inconclusive (P/I) because the findings in the only trial were not statistically significant, but the subgroup analyses suggested that there was a clinically and statistically significant benefit in younger patients with PPMS who have gadolinium enhancing lesions on MRI.

Other Benefits or Disadvantages

The route of administration is important for patients.[33,34] Many patients would prefer to take one to two pills each day rather than inject themselves with medication or be required to visit the doctor for a drug infusion, particularly when starting therapy. However, many patients who have been stable on daily injectable therapy for years choose to continue daily injections rather than switch to another agent with less frequent injections or oral administration, suggesting that once patients are comfortable with an effective drug for them, the route of administration may be less important.

Similarly, the travel and time commitment posed by an office visit to receive an IV infusion may discourage some patients from treatment with the infused agents. Conversely, avoiding regular injections or daily pills may appeal to some patients. In addition, the required contact with neurology professionals on a regular basis may enhance the overall care of their MS.

It is also important to recognize the value of having drugs with multiple mechanisms of action. The availability of more potent drugs for those who appear to have aggressive disease is reassuring. Similarly, patients value the ability to switch to a drug with a different mechanism of action when their current therapy is not working. Currently there is no way to match an individual patient to the drug with the most appropriate mechanism of action for their individual form of MS, but future research into the underlying mechanisms of MS may allow physicians to personize therapy in the future.

A reduction in relapse rates and disability progression also has non-medical benefits for patients, their caregivers, and society. Patients with MS are commonly in their most productive years at home, work and volunteering in the community. Relapses cause absence from work and other important life tasks. Progressive disability leads to early retirement with associated loss of income,

both for the patient and for caregivers who devote time to caring for the affected individual. Improved outcomes lead to increased productivity in each of these areas. Clinical trial results do not capture these benefits of therapy.

The stress that caregivers experience in supporting patients with MS is not captured in any of the clinical trial results and is an important benefit of improvement in therapy. Relapses and progressive disability have important effects on the quality of life of the caregivers in addition to that experienced by the patient.

Ocrelizumab will likely be the first drug to receive FDA approval for the treatment of PPMS, which is an important benefit.

Comparative Value

We developed a simulation model to estimate the lifetime cost-effectiveness of various DMTs for patients initiating treatment for 1) RRMS and 2) PPMS. The results of our NMA and other estimates from the published literature served as model inputs. Upon discontinuing treatment, RRMS patients continued to an aggregate second-line therapy (modelled as the average of natalizumab, fingolimod, alemtuzumab, daclizumab, and dimethyl fumarate) then to supportive care, and PPMS patients moved directly to supportive care. Each DMT was associated with an annual cost based on the wholesale acquisition cost (WAC), dosing, administration, and monitoring. Average discounts applied to each drug were derived using data from SSR Health that combined data on net US dollar sales with information on unit sales to derive net pricing at the unit level across all payer types. For best supportive care, we used data on the natural history progression, regression, relapse rates, and mortality from publicly available sources. Costs for best supportive care were based a previous analysis that modeled costs by EDSS state and included inpatient and outpatient admissions, office visits to physicians and other health professionals, examinations, medical devices, non-DMT drugs, and over the counter medicines.

The model estimated the average amount of time that patients spent in each health state, defined by EDSS category. Model outputs included total costs, relapses (RRMS only), life-years, quality-adjusted life years (QALYs), and incremental costs per additional life year, QALY, and prevented relapse (RRMS only) over a lifetime time horizon. Cost effectiveness ratios for the RRMS model were calculated versus no DMT (i.e., best supportive care) and versus generic glatiramer acetate 20 mg (Glatopa); cost-effectiveness ratios for the PPMS model were calculated versus best supportive care. Further details on the model structure and assumptions are provided in Section 6 of the full report.

Base Case Results

Total discounted costs, relapses, life-years, and QALYs over the lifetime time horizon are shown in Table ES3, with results arranged in order of increasing QALYs. Among patients with RRMS, discounted costs for DMT therapy, SAEs, and MS-related healthcare over the projected lifetime were approximately $341,100 for supportive care, and ranged from approximately $601,100 for alemtuzumab to $1.3 million for natalizumab. The projected number of relapses was 16.72 for supportive care, and ranged from 11.40 for alemtuzumab to 15.94 for interferon β-1a 30 mcg. Discounted life expectancy from age of DMT initiation (age 29 years for RRMS) was 21.82 years for supportive care, and ranged narrowly from 22.25 years for teriflunomide 7 mg to 23.38 years for alemtuzumab. Finally, projected discounted QALYs were 5.67 for supportive care, and ranged from 7.76 for teriflunomide 7 mg to 12.46 for alemtuzumab.

Among patients with PPMS, projected discounted costs, life-years, and QALYs for supportive care were approximately $264,800, 15.61 years, and 2.75 QALYs, respectively, compared to approximately 16.11 years and 3.33 QALYs for ocrelizumab.

Table ES3. Results for Base-case Analysis

Drug	Cost	Relapses	Life-Years	QALYs
RRMS				
Supportive Care	$341,120	16.72	21.82	5.67
Teriflunomide 7 mg	$986,499	15.21	22.25	7.76
Interferon β-1a 22 mcg (Rebif)	$1,125,894	14.94	22.28	7.88
Interferon β-1a 30 mcg (Avonex)	$1,078,976	15.94	22.32	7.92
Teriflunomide 14 mg	$1,005,404	15.11	22.39	8.41
Interferon β-1a 44 mcg (Rebif)	$1,088,038	14.88	22.40	8.43
Glatiramer acetate 20 mg (Copaxone)	$1,169,725	14.68	22.41	8.43
Glatiramer acetate 20 mg (Glatopa)	$871,708	14.68	22.41	8.43
Fingolimod	$1,104,382	13.96	22.49	8.94
Dimethyl fumarate	$1,033,081	14.63	22.50	8.97
Interferon β-1b 250 mcg (Betaseron)	$1,061,275	15.16	22.58	9.07
Interferon β-1b 250 mcg (Extavia)	$965,217	15.16	22.58	9.07
Peginterferon β-1a	$1,230,613	15.12	22.63	9.30
Daclizumab	$1,148,145	14.32	22.66	9.64
Natalizumab	$1,273,664	12.62	22.78	10.17
Ocrelizumab	-	13.19	22.98	10.94
Alemtuzumab	$601,053	11.40	23.38	12.46
PPMS				
Supportive Care	$264,760	N/A	15.61	2.75
Ocrelizumab	-	N/A	16.11	3.33

***Ocrelizumab has yet to be approved by the FDA, so no total costs could be calculated**

We also calculated the cost per additional QALY, cost per additional life-year, and cost per relapse avoided for each DMT compared to supportive care (Table ES4) and compared to generic glatiramer acetate 20 mg (see full report for details). When compared to supportive care for RRMS, costs per additional QALY ranged from approximately $38,300 per QALY for alemtuzumab to $355,100 for interferon β-1a 22 mcg; costs per additional life-year ranged from approximately $166,100 per year for alemtuzumab to $1.7 million for interferon β-1a 22 mcg; and costs per relapse avoided ranged from approximately $48,800 for alemtuzumab to $942,000 for interferon β-1a 30 mcg.

Table ES4. Pairwise Results for DMTs Compared to Supportive Care for RRMS

Drug	Cost per Additional QALY	Cost per Additional Life-Year	Cost per Relapse Avoided
Teriflunomide 7 mg	$309,236	$1,511,475	$425,498
Interferon β-1a 22 mcg (Rebif)	$355,115	$1,684,239	$439,473
Interferon β-1a 30 mcg (Avonex)	$327,639	$1,479,572	$942,036
Teriflunomide 14 mg	$242,043	$1,162,876	$411,786
Interferon β-1a 44 mcg (Rebif)	$270,883	$1,285,688	$405,626
Glatiramer acetate 20 mg (Copaxone)	$300,171	$1,411,303	$405,493
Glatiramer acetate 20 mg (Glatopa)	$192,211	$903,711	$259,652
Fingolimod	$232,983	$1,128,922	$276,208
Dimethyl fumarate	$209,327	$1,010,592	$330,591
Interferon β-1b 250 mcg (Betaseron)	$211,444	$951,083	$459,962
Interferon β-1b 250 mcg (Extavia)	$183,240	$824,222	$398,609
Peginterferon β-1a	$244,802	$1,101,324	$555,894
Daclizumab	$203,375	$959,547	$335,738
Natalizumab	$206,934	$972,577	$227,149
Alemtuzumab	$38,277	$166,077	$48,787

When compared to generic glatiramer acetate 20 mg, five DMTs were less effective and more costly (interferon β-1a 22, 44, and 30 mcg, teriflunomide 7 and 14 mg) for cost per additional QALY and cost per additional life-year, and eight were less effective and more costly for cost per relapse avoided (interferon β-1a 22, 44, and 30 mcg; teriflunomide 7 and 14 mg; interferon β-1b 250 mcg [Betaseron and Extavia]; peginterferon β-1a). As branded and generic glatiramer acetate 20 mg were assumed to have equivalent effectiveness, the more expensive branded product would be considered cost-increasing in a cost-minimization analysis. Among those DMTs with better health outcomes compared to generic glatiramer acetate 20 mg, costs per additional QALY ranged from approximately approximately $144,900 per QALY for interferon β-1b 250 mcg (Extavia) to approximately $451,300 per QALY for fingolimod; costs per additional life-year ranged from approximately $549,800 per year for interferon β-1b 250 mcg (Extavia) to $2.6 million per life-year for fingolimod; and costs per relapse avoided ranged from approximately $195,000 for natalizumab to $3.3 million for dimethyl fumarate. The incremental results for interferon β-1a 44 mcg are particularly high because the health outcomes are very close to those for generic glatiramer acetate 20 mg, while the costs are higher. Alemtuzumab was more effective and less costly for cost per additional QALY, cost per additional life-year, and cost per relapse avoided, meaning that projected costs were lower, projected QALYs and life-years were higher, and projected relapses were lower than glatiramer acetate.

Sensitivity Analysis Results

To demonstrate effects of uncertainty on both costs and health outcomes, we varied input parameters across plausible ranges to evaluate changes in the cost per additional QALY for each DMT compared to generic glatiramer acetate 20 mg. Uncertainty in the costs of DMTs and relative risks for progression had the largest impact on model results.

The results of our probabilistic sensitivity analysis can be found in Appendix Tables E12-E16. Wide variability in the incremental cost-effectiveness ratios was observed, especially when agents were compared to generic glatiramer acetate 20 mg rather than to supportive care. For example, the cost per additional QALY for daclizumab ranged from approximately $143,500 to $281,100 when compared to supportive care and from $85,500 to less effective and more costly when compared to generic glatiramer acetate 20 mg. Only alemtuzumab had greater than a 50% chance of meeting the $150,000 per QALY threshold compared to supportive care; and interferon β-1b 250 mcg (Extavia) and alemtuzumab had greater than a 50% chance of meeting the $150,000 per QALY willingness-to-pay level when compared to generic glatiramer acetate.

Threshold Analysis Results

Prices for each drug that would achieve cost-effectiveness thresholds ranging from $50,000 to $150,000 per QALY gained are presented in Table ES5. It was not possible to calculate a threshold price for all DMTs at the lower thresholds. This was because even if the price of the DMT were $0, the patient still accrued costs from second-line drugs and other care. As those other costs are particularly high relative to supportive care, it was not possible to decrease the WAC enough to reach the threshold. Note that the price of alemtuzumab would increase to reach these cost-effectiveness thresholds, as its cost-effectiveness at WAC is below $50,000/QALY. The net price with SSR discount was higher than the $150,000 threshold prices for all DMTs except alemtuzumab (net price $19,712).

Table ES5. Resulting Package Prices for Each DMT to Reach Cost per QALY Thresholds

DMT	WAC (per package)	$50,000	$100,000	$150,000
Interferon β-1a 30 mcg (Avonex)	$6,287	N/C; at $0 WAC, ICER is $70,003	$586	$1,562
Interferon β-1b 250 mcg (Betaseron)	$6,648	$239	$1,504	$2,768
Interferon β-1b 250 mcg (Extavia)	$5,947	$256	$1,611	$2,965
Glatiramer Acetate 20 mg (Copaxone)	$7,114	N/C; at $0 WAC, ICER is $55,746	$1,095	$2,332
Glatiramer Acetate 20 mg (Glatopa)	$5,194	N/C; at $0 WAC, ICER is $55,746	$1,095	$2,332
Interferon β-1a 22 mcg (Rebif)	$6,629	N/C; at $0 WAC, ICER is $72,919	$541	$1,539
Interferon β-1a 44 mcg (Rebif)	$6,629	N/C; at $0 WAC, ICER is $78,710	$624	$2,090
Peginterferon β-1a	$6,287	$230	$1,623	$3,017
Daclizumab	$6,833	N/C; at $0 WAC, ICER is $54,813	$1,975	$4,159
Fingolimod	$6,743	N/C; at $0 WAC, ICER is $63,186	$1,316	$3,103
Teriflunomide 14 mg	$5,877	N/C; at $0 WAC, ICER is $96,456	$129	$1,945
Teriflunomide 7 mg	$5,877	N/C; at $0 WAC, ICER is $121,549		$802
Dimethyl Fumarate	$6,820	N/C; at $0 WAC, ICER is $79,176	$982	$3,340
Natalizumab	$6,000	$485	$2,147	$3,808
Alemtuzumab	$20,750	$28,322	$65,047	$101,771
Ocrelizumab (RRMS)*	--	$9,861	$34,235	$58,608
Ocrelizumab (PPMS)*	--	$4,208	$9,288	$14,367

*Annual prices are presented for ocrelizumab because package prices are not currently available.
N/C: Not calculable; there is no price that can achieve a given cost-effectiveness threshold, even at $0

Potential Budget Impact

We used results from the same model employed for the cost-effectiveness analyses to estimate total potential budget impact, calculating incremental health care costs (including drug costs) minus any offsets in these costs from averted health care events. We estimated the potential budget impact of two new treatments in the RRMS patient population: daclizumab, which received FDA approval in 2016, and ocrelizumab, for which FDA approval is pending. As the price of ocrelizumab is currently unknown, we used prices required to achieve WTP thresholds of $150,000, $100,000

and $50,000 per QALY in our estimates of budget impact. We also assessed the potential budget impact of ocrelizumab as the first agent likely to secure FDA approval in PPMS, using the threshold prices listed above. We did not include other therapies modeled above in this potential budget impact analysis, given their established presence in the market.

In the RRMS cohort, potential budget impact was defined as the total incremental net cost of using daclizumab versus natalizumab for the treated population, as clinical input suggested that natalizumab was the most likely competitor for daclizumab market share in the near term. For RRMS patients, we assumed that the share of patients using ocrelizumab would be drawn equally from three existing competitors: natalizumab, fingolimod, and dimethyl fumarate. For the PPMS population, we analyzed the potential budget impact of using ocrelizumab rather than best supportive care, as there is no DMT currently approved for these patients.

The potential budget impact analysis included the entire candidate population for treatment, which consisted of adults with RRMS, whether DMT treatment-naïve or -experienced. Because no DMT has been approved for use in PPMS patients, we assumed all patients in this cohort to be DMT treatment-naïve. The estimated prevalence of MS in the US has been reported as 142.9 cases per 100,000 persons.[35] We estimated the proportion of MS patients following the RRMS disease course to be 85%, with the remaining 15% following the PPMS disease course.[1] Applying these proportions to the projected 2016 US population resulted in an estimate of 410,900 RRMS patients and 72,500 PPMS patients in the US over a five-year period. We recognize that both new treatments and the drugs they are displacing will have only a share of the potential market; in the absence of any rigorous projection on what changes in market share would look like, we felt it best to document the percentage of all possible patients who would have access to new medications without crossing the budget impact threshold in order to compare new interventions on a consistent scale.

When treating the eligible RRMS cohort with daclizumab at discounted WAC price, the potential budget impact was estimated to be approximately $2,200 per patient over 5 years. Using threshold prices, the potential budget impact was estimated to be cost-saving over 5 years, ranging from approximately $71,400 per patient when using the price ($4,159) to reach the $150,000/QALY WTP threshold, to approximately $140,500 per patient when using the price to reach the $100,000/QALY WTP threshold ($1,975). At both the WTP threshold prices as well as discounted WAC, 100% of patients could be treated without crossing the ICER budget impact threshold, while 76% of the population could be treated without crossing the threshold at the full WAC. Although the difference between WAC and discounted WAC per dose is only approximately $350, this rather minimal difference leads to a large difference in budget impact owing to the total population size and 5-year time horizon.

Table ES6 below illustrates the per-patient budget impact calculations for ocrelizumab in more detail, based on the price ($58,608) to achieve a WTP threshold of $150,000/QALY for ocrelizumab

and the DMTs it would displace. At that price, ocrelizumab would result in cost savings relative to the DMTs it would displace; cost savings would increase at threshold prices to achieve $50,000 and $100,000 per QALY gained. Note that we have not assumed a WAC or discounted WAC for ocrelizumab as a price will not be available until after FDA approval.

Table ES6. Per-Patient Potential Budget Impact of Ocrelizumab in RRMS Population, Using Price to Reach WTP Threshold of $150,000/QALY Gained

	Avg. Annual Per-Patient Budget Impact (Over 5-year Time Horizon)	Weighted† Avg. Annual Per-Patient Budget Impact (over 5-year Horizon)
Ocrelizumab	$66,985	$200,371
Natalizumab+Fingolimod+Dimethyl fumarate*	$81,600	$242,605
Net	-$14,615†	-$42,234‡

*Weighted equally among all three drugs

†For five-year horizon, drug costs and cost offsets apportioned assuming 20% of patients in uptake target initiate therapy each year. Those initiating in year 1 receive full drug costs and cost offsets, those initiating in year 2 receive 80% of drug costs and cost offsets, etc.

‡Indicates cost-saving

Finally, when treating the eligible PPMS cohort with ocrelizumab, the annual average potential weighted budgetary impact per patient over 5 years ranged from approximately $18,300 using the price ($4,208) to achieve a WTP threshold of $50,000/QALY to approximately $44,200 using the price ($14,367) to achieve a WTP threshold of $150,000/QALY. The annual budget impact of treating the entire PPMS cohort across all WTP threshold prices did not exceed the $915 million threshold due to the relatively small number of PPMS patients and the assumed prices for ocrelizumab.

Value-based Benchmark Prices

Our value-based benchmark prices for each MS treatment are provided in Table ES7. As noted in ICER methods document, the value-based benchmark price for a drug is defined as the price range that would achieve cost-effectiveness ratios between $100,000 and $150,000 per QALY gained.

With the exception of alemtuzumab, all drugs would require discounts from current WAC prices to fall within ICER's threshold value range of $100,000 to $150,000/QALY, and the discounts required to achieve both WTP threshold prices are greater than the current discounted WAC. There was no price for which teriflunomide 7mg dose would achieve a $100,000/QALY threshold. Costs of alemtuzumab were much lower than other DMTs, largely due to not requiring continuous dosing over time, contributing to the estimated cost-effectiveness of alemtuzumab being well below

$100,000/QALY in our base case. Therefore, its price could be increased substantially before reaching $100,000/QALY or $150,000/QALY thresholds.

Table ES7. Value-based Price Benchmarks for MS Disease-Modifying Therapies

DMT	WAC (per package)	Cost to achieve $100,000/QALY	Cost to achieve $150,000/QALY	Discount from WAC to reach WTP threshold
Interferon β-1a 30 mcg (Avonex)	$6,287	$586	$1,562	75% to 91%
Interferon β-1b 250 mcg (Betaseron)	$6,648	$1,504	$2,768	58% to 77%
Interferon β-1b 250 mcg (Extavia)	$5,947	$1,611	$2,965	50% to 73%
Glatiramer Acetate 20 mg (Copaxone)	$7,114	$1,095	$2,332	67% to 85%
Glatiramer Acetate 20 mg (Glatopa)	$5,194	$1,095	$2,332	55% to 79%
Interferon β-1a 22 mcg (Rebif)	$6,629	$541	$1,539	77% to 92%
Interferon β-1a 44 mcg (Rebif)	$6,629	$624	$2,090	68% to 91%
Peginterferon β-1a	$6,287	$1,623	$3,017	52% to 74%
Daclizumab	$6,833	$1,975	$4,159	39% to 71%
Fingolimod	$6,743	$1,316	$3,103	54% to 81%
Teriflunomide 14 mg	$5,877	$129	$1,945	67% to 98%
Teriflunomide 7 mg	$5,877	N/C	$802	86%
Dimethyl Fumarate	$6,820	$982	$3,340	51% to 86%
Natalizumab	$6,000	$2,147	$3,808	37% to 64%
Alemtuzumab	$20,750	$65,047	$101,771	213% to 390% increase
Ocrelizumab (RRMS)*	--	$34,235	$58,608	--
Ocrelizumab (PPMS)*	--	$9,288	$14,367	--

*Annual prices are presented for ocrelizumab because package prices are not currently available.
N/C: Not calculable; there is no price that can achieve a given cost-effectiveness threshold, even at $0

Summary and Comment

Compared to supportive care for RRMS, costs per additional QALY were estimated to total approximately $38,300 for alemtuzumab, but exceeded the commonly-cited threshold of $150,000 per QALY for all other DMTs (range: $183,300 to $355,300). Alemtuzumab provided the highest number of QALYs gained while costing less than all other treatments except supportive care. The newest approved agent, daclizumab, produced an estimate of approximately $219,100 per QALY gained. Among patients with PPMS, ocrelizumab was estimated to produce an additional 0.58 QALY or an additional 0.50 life year compared to supportive care, based on relatively modest clinical benefits in this more difficult-to-treat population; the cost per QALY was not estimated as there is no listed price for the drug.

When compared to generic glatiramer acetate 20 mg, alemtuzumab was more effective and less costly, meaning that projected costs were lower and projected QALYs and life-years were higher. The other DMTs were either less effective and more costly or not cost effective by standard metrics (from approximately $150,000 to $10 million per QALY). The cost-effectiveness of daclizumab was estimated to be approximately $250,400 per QALY gained.

There are a number of limitations to the model due to inadequate or older sources for data (see full report for details), but no better sources were identified by those who provided comments on our draft model and preliminary report. There is also uncertainty in the estimates used for the benefits and harms of the data, but the overall findings were robust in our sensitivity analyses.

Our budget impact estimates for daclizumab suggest that its use in RRMS will not increase costs to a level that raises concerns regarding short-term affordability for the health-care system. Our potential budget impact estimates indicate that all eligible RRMS and PPMS patients could be treated with ocrelizumab at its $150,000 per QALY gained price without exceeding the budget impact threshold.

Conclusions

In summary, our analyses indicate that the DMTs of interest in this evaluation uniformly and substantially improved health outcomes compared to best supportive care, but demonstrated mixed results compared to generic glatiramer acetate. These outcomes come at a high relative cost. In almost all cases, pairwise results were well above commonly cited thresholds for cost-effectiveness. The notable exception to this finding was alemtuzumab, which consistently demonstrated improved health outcomes and good value compared to both supportive care and generic glatiramer acetate 20 mg. The costs of alemtuzumab were much lower than other DMTs, as it does not require continuous dosing over time and the manufacturer covers the costs of laboratory monitoring, which led to lower incremental cost-effectiveness ratios. Caution in considering the cost-effectiveness findings for alemtuzumab is required, however, given the safety concerns relevant to this DMT described in Section 4 of this report and elsewhere.

California Technology Assessment Forum Votes

The California Technology Assessment Forum (CTAF) deliberated on key questions raised by ICER's report at a public meeting on February 16, 2017 in Oakland, California. The results of these votes are presented below, and additional information on the deliberation surrounding the votes can be found in the full report.

1) For patients with RRMS, is the evidence adequate to demonstrate that the net health benefit of dimethyl fumarate (Tecfidera®, Biogen Inc.) is greater than that of teriflunomide 14 mg (Aubagio®, Sanofi-Genzyme, Inc.)?

Yes: 2 votes	***No: 12 votes***

2) For patients with RRMS, is the evidence adequate to demonstrate that the net health benefit of fingolimod (Gilenya®, Novartis, Inc.) is greater than that of teriflunomide 14 mg?

Yes: 7 votes	No: 7 votes

3) For patients with RRMS, is the evidence adequate to distinguish the net health benefit between dimethyl fumarate and fingolimod?

Yes: 2 votes	***No: 12 votes***

4) For patients with RRMS, is the evidence adequate to demonstrate that the net health benefit of daclizumab (Zinbryta®, Biogen Inc. and AbbVie Inc.) is greater than that of dimethyl fumarate or fingolimod?

Yes: 0 votes	***No: 14 votes***

5) For patients with RRMS, is the evidence adequate to demonstrate that the net health benefit of daclizumab is greater than that of generic glatiramer acetate 20 mg (Glatopa®, Sandoz, Inc.)?

Yes: 7 votes	No: 7 votes

6) For patients with RRMS, is the evidence adequate to demonstrate that the net health benefit of ocrelizumab (Ocrevus®, Roche Genentech Inc.) is greater than that of generic glatiramer acetate 20 mg?

Yes: 12 votes	No: 2 votes

7) Given the available evidence for patients with RRMS, what is the long-term value for money of treatment with daclizumab versus treatment with generic glatiramer acetate 20 mg?

Low: 12 votes	Intermediate: 2 votes	High: 0 votes

8) For patients with primary-progressive multiple sclerosis (PPMS), is the evidence adequate to demonstrate that the net health benefit of treatment with ocrelizumab is greater than that of best supportive care?

Yes: 11 votes	No: 3 votes

Key Policy Implications

Following its deliberation on the evidence, the CTAF Panel engaged in a moderated discussion with a policy roundtable about how best to apply the evidence on disease-modifying therapies for MS to policy and practice. The policy roundtable members included two patient advocates, two clinical experts, two private payers, and a representative from a pharmaceutical manufacturer. The discussion reflected multiple perspectives and opinions, and therefore, none of the statements below should be taken as a consensus view held by all participants. The top-line policy implications are presented below, and additional information can be found in the full report.

Manufacturers

- Link launch prices of new disease modifying therapies (DMTs) to the added value they bring to patients compared to existing clinical options. Cease annual price increases that exceed medical inflation without new evidence of improved outcomes.
- Leverage clinical trial data to identify characteristics that determine which patients are likely to respond best to specific drugs.
- Prioritize the development of drugs that have a finite treatment duration.

Payers

- In line with recommendations from key patient groups, implement policies to allow patients to remain on a treatment that works regardless of coverage or formulary changes, and without onerous prior authorization documentation required of providers each year.
- If drug prices come into alignment with the value they bring to patients, reduce step therapy barriers to these therapies.
- Develop policies to allow clinicians to prescribe rituximab for appropriate patients with MS.

Patient Advocacy Organizations

- Engage with manufacturers in the design and conduct of pre- and post-approval studies of MS therapies.
- Advocate for value-based pricing of MS therapies.

Specialty Societies

- Develop guidelines that include treatment sequencing and a definition of patients at high risk for more aggressive disease. Consider including assessments of value as part of the guideline development process.

Clinicians

- Discuss potential cost burdens with patients as part of the shared decision-making process.

Regulators

- Require that pivotal trials of MS agents be conducted against an active comparator.

Researchers

- Work with patients to standardize the patient-centered outcomes that are included in trials of MS drugs.
- Conduct studies of new drugs for MS that include long-term data on disability progression.

1. Background

1.1 Introduction

Background

Multiple sclerosis (MS) is a chronic, immune-mediated inflammatory, neurodegenerative, and demyelinating disease of the central nervous system (CNS).[1] Approximately 400,000 Americans have MS, although this may be an underestimate. The disease affects about three times as many women as men.[2] Some patient groups, such as African Americans, experience a more rapid and severe clinical course. The annual cost of MS in the United States is estimated to be $28 billion.[3]

RRMS

The most common form of MS is relapsing-remitting MS (RRMS), which affects 85% to 90% of patients at presentation.[1] RRMS is characterized by periodic relapses with neurologic symptoms that may diminish or resolve with treatment. Over one to two decades, more than half of untreated patients with RRMS transition to a disease course of slowly accumulating neurologic deficits known as secondary progressive MS (SPMS).[4]

There are more than 10 disease-modifying therapies (DMTs) approved by the Food and Drug Administration (FDA) for the treatment of RRMS. The therapeutic goal of DMTs is to decrease the frequency of relapses and to prevent the disability that accumulates with disease progression over time. Some neurologists believe that the goal of treatment should be to eradicate all evidence of disease activity, including magnetic resonance imaging (MRI) findings. There is controversy about the relative efficacy of the drugs, and several of the newer drugs have been associated with life-threatening adverse events (e.g., CNS infections, autoimmune diseases, liver toxicity, cancers). In addition, RRMS is a heterogeneous disease, which complicates comparisons across studies of DMTs.

PPMS

Approximately 10-15% of MS patients have primary-progressive MS (PPMS), a clinical course that is characterized by steadily worsening neurologic function, largely without remissions.[5,6] The mean age of onset of PPMS is 10 years older than that of RRMS and patients with PPMS generally experience more severe disability.[5,6] While RRMS affects around three times as many women as men, PPMS affects both sexes in approximately equal numbers.[5]

On June 27, 2016, the Food and Drug Administration (FDA) announced that it had granted Priority Review Designation to ocrelizumab for use in PPMS, with an initial decision date of December 28, 2016.[7] The FDA later extended the review timeline for ocrelizumab to March 28, 2017 to review

additional data about the manufacturing process for the agent.[8] If approved, ocrelizumab would be the first agent with a PPMS indication. Several other agents have been studied for use in PPMS, but one – rituximab – is of particular interest to practitioners, patients, and insurers because its mechanism of action is similar to that of ocrelizumab, despite its lack of a labeled indication for MS.[9]

Scope of the Assessment

The scope for this assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence was summarized from randomized controlled trials as well as high-quality systematic reviews; high-quality comparative cohort studies were considered, particularly for long-term outcomes and uncommon adverse events. We included input from key informant interviews with patient advocacy organizations, a survey developed in collaboration with the advocacy community for this assessment, data from regulatory documents, information submitted by manufacturers, and other grey literature when the evidence met ICER standards (for more information, see https://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/).

Wherever possible, we used head-to-head studies of these interventions. In addition, due to the absence of direct comparisons for many of the agents, we compared agents indirectly through network meta-analysis.

Analytic Framework

The analytic framework for this assessment is depicted in Figure 1. The same framework was used for both RRMS and PPMS with the exception that relapses and progression to secondary-progressive MS (SPMS) were not included for the PPMS analysis.

Populations

The population for the review was adults ages 18 and older with RRMS or PPMS. The diagnostic criteria for MS have changed over time, beginning with the Shumacher Criteria, the Poser Criteria and continuing through the evolution of the McDonald Criteria (2001, 2005, 2010). Each change allowed for earlier diagnosis of MS, which makes trial populations somewhat different over time. We evaluated the impact of these changes and other sources of heterogeneity in a subgroup analysis of the comparative efficacy of DMTs. We did not include studies focused on clinically isolated syndrome (CIS).

Interventions

The list of interventions was developed with extensive input from patient organizations, which counseled ICER to include nearly all DMTs with current or projected FDA-labeled indications for

RRMS. Practicing clinicians, specialty societies, manufacturers, and payers also provided essential input. Mitoxantrone was excluded from the review and rituximab added based on feedback from the previously mentioned groups. The full set of interventions for the RRMS review is listed below, grouped by route of administration:

- Injectable agents (daclizumab, glatiramer acetate, interferon β-1a, peginterferon β-1a, interferon β-1b)
- Oral agents (dimethyl fumarate, fingolimod, teriflunomide)
- Infused agents (alemtuzumab, natalizumab, ocrelizumab, rituximab)

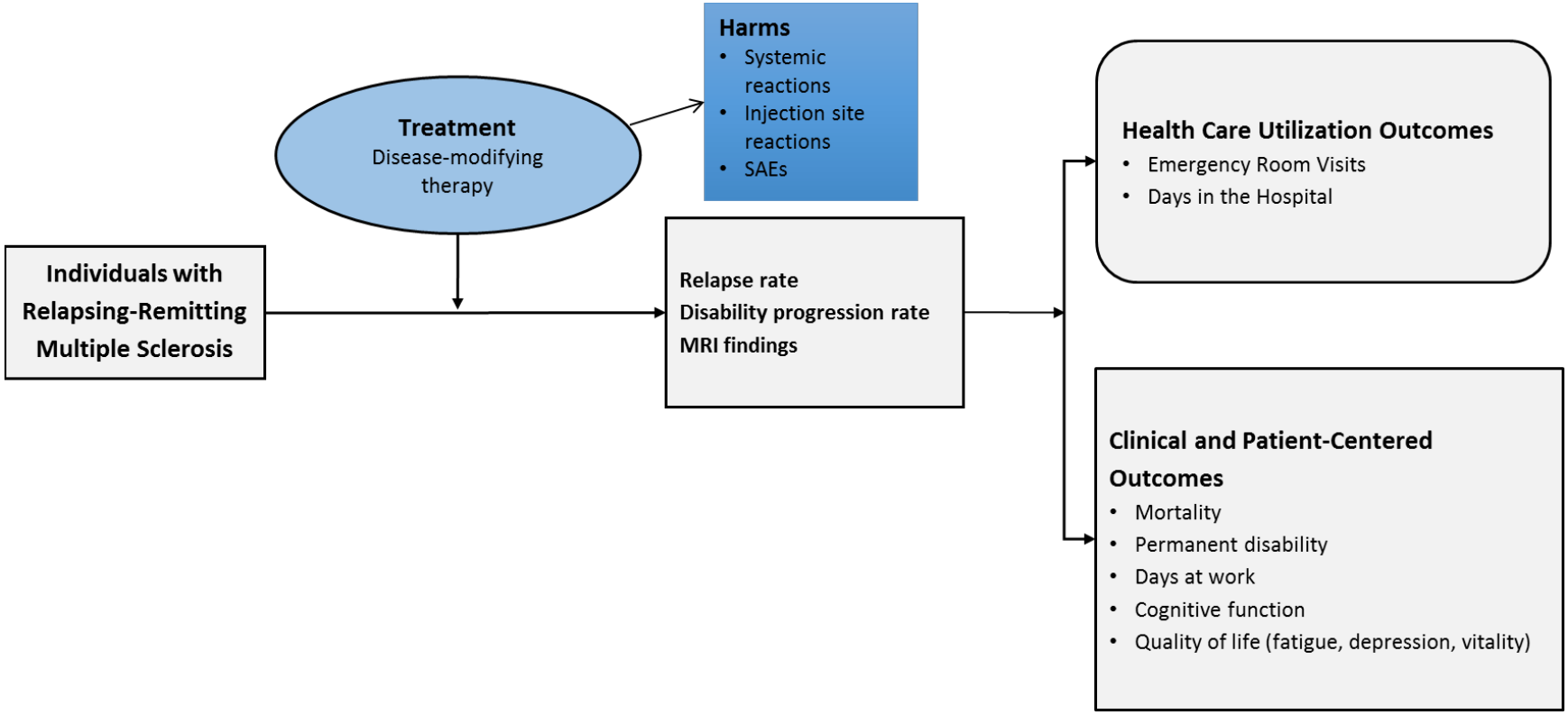
For PPMS, the included interventions were ocrelizumab and rituximab.

Comparators

We compared all of the agents within and across routes of administration as described above using head-to-head and placebo-controlled trials. We also compared all of the agents to placebo and to one another though network meta-analysis. In addition, we specifically compared Avonex® (Biogen, Inc.) and Rebif® (EMD Serono, Inc.), two distinct formulations of interferon β-1a, as multiple stakeholders indicated an interest in a detailed comparative analysis of these agents.

The primary comparator for the use of ocrelizumab and rituximab in patients with PPMS was best supportive care, as there is currently no drug with FDA approval for the treatment of PPMS.

Figure 1. Analytic Framework



Outcomes

Patient organizations advised us that the primary goal for patients is to remain independent. They also recommended the inclusion of fatigue, depression, and cognitive function among other symptoms, as these are common issues that affect their quality of life, but have not been widely reported in the seminal clinical trials. This review examined both clinical and health care utilization outcomes of DMTs. To be included, studies were required to report the impact of the intervention on either annual relapse rate or progression of disability assessed by the Expanded Disability Status Scale (EDSS). Many of these outcomes listed below were evaluated descriptively because they have not been consistently evaluated in the randomized trials, and thus cannot be included in a network meta-analysis. Additional outcomes of interest included:

- Disability
- Skilled nursing facility placement
- Need for caretaker/health aide
- Cognitive function
- Fatigue
- Depression
- Timed 25-foot walk
- Manual dexterity
- Visual acuity
- Multiple Sclerosis Functional Composite Measure (MSFC)
- Acceptability of route of administration
- Other measures of functional status, and/or health-related quality of life
- Magnetic resonance imaging (MRI) outcomes (T2, T1, brain volume changes)
- No evidence of disease activity (NEDA 3 and/or 4)
- Adherence
- Treatment-related adverse events including:
    - Serious adverse events (SAEs)
    - Adverse events (AEs) leading to discontinuation of therapy
    - Adverse events unique to specific drugs
- Time to secondary progressive MS
- Time to death
- Costs and cost-effectiveness of DMTs

Where possible we reported the absolute risk reduction in addition to the relative risk reduction for the treatment comparisons.

For PPMS, we assessed the same outcomes listed above with the exception of advancement to secondary-progressive MS and relapse rates. Though relapses may occur in PPMS, they are relatively infrequent and thus were not included as outcomes in studies of the disease course.

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 United States (US) given the prolonged natural history of RRMS and PPMS.

2. The Topic in Context

There is no definitive clinical guideline to help clinicians and patients with decisions about both initial therapy and choices for subsequent therapies following treatment failure. Shared decision-making plays an important role when choosing initial and subsequent therapy, as patients and providers must balance considerations around efficacy, side effects, potential harms, route and frequency of administration, cost, and personal experience. Advocacy organizations have noted that patient preference strongly influences treatment adherence and resultant clinical outcomes. Specifically, ICER received input from advocacy organizations that some patients have a strong preference for oral medications over injectable ones because of their dislike of needles, injection site reactions, and the difficulty of storing medications that require refrigeration. Other patients are equally comfortable with injectable medications.[11,12] In addition, the advocacy organizations emphasized that some patients have a low tolerance for risk and are less likely to choose DMTs with known, potentially severe side effects. In addition, coverage policies often require patients to attempt treatment with at least one of the interferons or glatiramer acetate and that they experience inadequate response prior to covering the newer DMTs because of the extended clinical experience with the older agents and the perception that they are safer and less costly. These combined factors demonstrate the considerable uncertainty about the interpretation and application of the current evidence base to guide clinical practice and insurance coverage policy.

Some clinicians advocate the first-line use of drugs that are perceived as more efficacious in a subgroup of patients that they identify as being at high risk for rapid progression of their disease. However, there is no accepted scale for separating patients into "high-risk" and "low-risk" groups. Investigators have identified many risk factors for rapid progression of MS, but most are not reliable and there is no consensus definition for high-risk patients. Some of the characteristics that are commonly cited include the frequency of relapses in the first five years of disease, two or more gadolinium enhancing lesions on MRI, new T2 lesions, the volume and number of T2 lesions on MRI, early brainstem or spinal cord lesions, rapid disability progression, African ancestry, and presenting with bowel or bladder symptoms.[36-41]

Thus, our analysis compares each of the DMTs to the others. Head-to-head trials are not available for each pair of drugs, but all of the DMTs have been compared in randomized trials to placebo or to the first drugs approved for the treatment of MS: the interferons and glatiramer acetate. As such, indirect comparisons can be made to assess for differences in treatment effects between all of the agents that have not been directly compared. Where head-to-head data are available for two drugs, we augmented those data with indirect information to comprehensively evaluate the evidence base comparing the benefits and harms of the drugs.

Treatment of MS can be a double-edged sword; MS is believed to be an immune-mediated illness and therapies directed at the disease modulate the immune system to improve outcomes, but can have unintended consequences such as an increased risk for infections or an increase in autoimmune disease. One of the dreaded risks of DMTs for MS is progressive multifocal leukoencephalopathy (PML). PML is caused by an infection by the John Cunningham (JC) virus that attacks the myelin sheaths of nerves in patients with decreased function of the immune system. When PML occurs in MS, approximately 25% of patients die within 6 months and the survivors have increased long-term disability.[10] Other rare, but life-threatening risks of DMTs include autoimmune hepatitis and autoimmune blood disorders. The DMTs that are most effective at slowing the progression of MS tend to have the highest risk for these life-threatening unintended consequences.

We did not review studies in patients with clinically isolated syndrome (CIS). Some of the early trials in CIS provide provocative data suggesting value to early treatment of MS.[42] However, many patients with CIS never go on to MS, so the results are not directly applicable to the role of DMTs in RRMS.

We did not review combination therapy; unlike the experience in other chronic diseases (e.g., cancer, HIV, diabetes, hypertension), the few trials of combination therapy in MS have shown little added benefit.[43-47] Given the novel mechanisms of the newest DMTs, many combinations have not yet been evaluated and some may prove useful.

Disease-Modifying Therapies for MS

The DMTs for multiple sclerosis that are the focus of this review are summarized in Table 1 below. For RRMS, they are intended to decrease relapses and progressive disability, which are the hallmarks of MS. All DMTs are thought to modulate the immune system to decrease the autoimmune damage that is believed to cause the CNS changes responsible for the symptoms of MS. All the drugs in the Table have an FDA indication for RRMS with the exception of ocrelizumab, which the FDA is expected to approve in March 2017 for both RRMS and PPMS, and rituximab, which is approved for other conditions and is used off-label for RRMS and PPMS. Both ocrelizumab and rituximab are monoclonal antibodies directed against the same protein, CD20, which is expressed on B-lymphocytes.

Table 1. DMTs of Interest for the Evidence Review

Drug (Brand name)	Abbreviation in Tables/Figures	Class	FDA-Approved Dose	Year 1 WAC
Subcutaneous injection				
Interferon β-1a (Avonex®, Biogen)	IFN β-1a 30 mcg	Interferon	30 mcg weekly	$81,965
Interferon β-1b (Betaseron®, Bayer)	IFN β-1b 250 mcg (Betaseron)	Interferon	250 mcg every other day	$86,659
Interferon β-1b (Extavia®, Novartis)	IFN β-1b 250 mcg (Extavia)	Interferon	250 mcg every other day	$72,359
Glatiramer acetate (Copaxone®, Teva)	GA 20 mg	Mixed polymers	20 mg daily	$86,554
Glatiramer acetate (Copaxone®, Teva)	GA 40 mg	Mixed polymers	40 mg three times weekly	$76,024
Glatiramer acetate (Glatopa®, Sandoz)	GA 20 mg (Glatopa)	Mixed polymers	20 mg daily	$63,193
Interferon β-1a (Rebif®, EMD Serono)	IFN β-1a 22 mcg or 44 mcg	Interferon	22 mcg or 44 mcg three times weekly	$86,416
Peginterferon β-1a (Plegridy®, Biogen)	PEG	Interferon	125 mcg every 14 days	$81,956
Daclizumab (Zinbryta®, Biogen and AbbVie)	DAC	Anti-CD25 monoclonal antibody	150 mg once monthly	$82,000
Oral				
Fingolimod (Gilenya®, Novartis)	FIN	Sphingosine 1-phosphate receptor modulator	0.5 mg once daily	$82,043
Teriflunomide (Aubagio®, Sanofi Genzyme)	TER	Pyrimidine synthesis inhibitor	7 mg or 14 mg daily	$76,612
Dimethyl fumarate (Tecfidera®, Biogen)	DMF	Multifactorial	240 mg twice daily	$82,977
Intravenous infusion				
Natalizumab (Tysabri®, Biogen)	NAT	Anti α4β1/ α4β7 integrin monoclonal antibody	300 mg every 4 weeks	$78,214
Alemtuzumab (Lemtrada®, Sanofi Genzyme)	ALE	Anti-CD52 monoclonal antibody	12 mg per day for 5 days in the first year, 3 days in second year and every subsequent year when treatment is required	$103,749

Drug (Brand name)	Abbreviation in Tables/Figures	Class	FDA-Approved Dose	Year 1 WAC
Ocrelizumab (Ocrevus®, Genentech)	OCR	Anti-CD20 monoclonal antibody	RRMS: 300 mg twice 14 days apart, then 600 mg once every 24 weeks* PPMS: 300 mg twice 14 days apart, cycle begins every 24 weeks*	Unknown
Rituximab (Rituxan®, Genentech)	RIT	Anti-CD20 monoclonal antibody	2000 mg every 6 months*	$33,408

WAC: wholesale acquisition cost

*Ocrelizumab and rituximab have not been approved by the FDA for use in MS, dosing data from clinical trials was used.

Definitions

Commonly-used Clinical Distinctions in MS

Clinically Isolated Syndrome: The first episode of neurologic symptoms lasting greater than 24 hours that is compatible with MS (i.e., demyelination involving optic nerve, brainstem, spinal cord), but does not meet diagnostic criteria for MS.

Relapsing-Remitting MS: 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 Multiple Sclerosis: Initial RRMS for several years that is followed by gradual disease progression with or without further relapses.

Primary-Progressive Multiple Sclerosis: Progressive accumulation of disability from disease onset; usually without relapses, 10-15% of MS at onset.

Evolving Criteria for Diagnosing MS

Poser Criteria (1983): A diagnosis of clinically-definite MS requires a first clinical demyelinating event followed at least a month later by a second event that involves a different area of the CNS (i.e., dissemination of disease activity in both time and space). MRI findings are not used in the Poser Criteria. Many patients diagnosed with CIS in the era of the Poser criteria would now be diagnosed with clinically-definite MS.

McDonald Criteria (2001): The first McDonald criteria incorporated the use of MRI findings (see MRI outcomes section below) to document dissemination of disease activity in time and space at first clinical presentation.

McDonald Criteria (2005 Revision): Refinement of the 2001 criteria that allows the appearance of a new T2 lesion on MRI at least 30 days following an earlier baseline or reference scan for dissemination in time.

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.

Outcomes in MS Research

Annualized Relapse Rate: 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.[45]

Expanded Disability Status Scale: 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 2). Kurtzke first published the scale in 1983.[48] A clinician assigns a functional score (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.

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 disabilities.

Sustained Disability Progression: The irreversible worsening of neurologic findings, usually defined as an increase on the EDSS scale of 1 point for those with a baseline EDSS ≤ 5 or of 0.5 points for those with a baseline EDSS ≥ 5.5. The preferred definition of sustained disability progression is an increase in disability on the EDSS that is present for at least 24 weeks (or 6 months). Trials may also report an increase in disability on the EDSS that is present for at least 12 weeks (or 3 months), but some patients will have resolution of their symptoms between 12 and 24 weeks of follow-up.

Table 2. 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

Multiple Sclerosis 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 Magnetic Resonance Imaging (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 CNS 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.

Insights Gained from Discussions with Patients and Patient Groups

ICER had conversations with individual patients and multiple patient advocacy organizations, including the MS Coalition (which also includes clinical societies), the National MS Society, Accelerated Cure, MS Association of America, and PatientsLikeMe. Several consistent themes emerged from these discussions, including the substantial burdens posed by an MS diagnosis, the factors that patients consider to be the most important when selecting a treatment, disappointment in the absence of data on patient-centered outcomes in the clinical literature, and pervasive access and affordability issues faced by many patients.

Patients highlighted the many burdens that come with an MS diagnosis, including economic hardships that are underappreciated in most economic analyses of MS. These include lost wages from missed work, the need to transition to part-time work or the inability to continue working, the high cost of medications, the costs of supportive medical equipment, modifications of the home to accommodate disability, and home care support. Care partners experience substantial burdens as well, as they may need to take time off from work to support their friend or relative with MS. Finally, the majority of patients are young women, so the impact of the illness on children needs to be considered.

Patients want their providers to be able to choose the medication that is best for them without restriction, but feel that the choice of DMT is driven by their insurance coverage and the willingness of their providers to appeal coverage denials. The high cost of DMTs for MS can result in large out-of-pocket costs for individuals who are unaware of, or ineligible for, patient-assistance programs offered by manufacturers or non-profit organizations. For instance, Medicare patients pay an average of more than $6000 in out of pocket costs per year for Avonex, Tecfidera, or Copaxone.[49]

The primary goal for patients is to remain independent, but it must be balanced with the risks for adverse events that are carried by the therapies most likely to keep them independent. These risk-benefit assessments are complicated by the lack of long-term data; many of the studies of DMTs are short term (1-3 years) whereas disability typically accumulates over a much longer time horizon of 10 to 15 years. Advocacy organizations noted that many studies are open-label or poorly controlled, which creates uncertainty about the validity of the results.

Patients expressed frustration that patient-reported outcomes are not routinely collected and reported in the pivotal trials. They would like more data regarding the effect of DMTs on fatigue, cognitive function, visual acuity, mood, and quality of life. They want to know about the relative benefits of all available drugs and strongly encouraged ICER to include new and off-label agents, including ocrelizumab and rituximab, in our review.

The MS Coalition generously assisted ICER by creating an online questionnaire (Appendix F) to assess patient perspectives on the most important issues for patients when making decisions about disease modifying therapies. Almost 16,000 patients in the United States responded. Their average age was 51 years and 79% were women. The participants were predominantly white (88%), but 8% were black, and 4.5% were Hispanic. Respondents were taking a wide range of medications including glatiramer acetate (24%), dimethyl fumarate (19%), natalizumab (13%) and fingolimod (11%). Interestingly, 3% were taking rituximab despite the absence of an FDA indication for this therapy. We asked those currently taking an MS medication to rate the importance of a series of factors in selecting the drug that they were currently taking. Those who responded (n=2,511) rated each factor on a five-point scale from not important to very important. The percentages responding either important or very important are summarized in Table 3.

Table 3. The Patient Perspective on Important Factors when Choosing a DMT

Decision-making factor	Important / Very Important
Delay disability	94%
Prevent relapse / new MRI lesions	94%
Continue working / normal activities	90%
Provider recommends therapy	86%
Other long term risks	71%
Health plan restrictions	69%
Risk of PML	68%
Out-of-pocket costs	66%
Route of administration	61%
Dosing frequency	58%
Risk of side effects	55%
Monitoring / blood tests	44%

These results echo what we heard when speaking with individual patients and their advocacy organizations: what patients primarily care about is maintaining independence and avoiding disability. The long-term risks of the drugs also weigh heavily in decision-making, as well as the risks of rare but important side effects such as PML, an often-fatal demyelinating disease that has been associated with immunosuppressive therapies in MS and other diseases. Dosing, monitoring, side effects, and costs are all important, but much less important than maintaining function. Patients trust their care providers to recommend the therapy that is best for them.

3. Summary of Coverage Policies and Clinical Guidelines

3.1 Coverage Policies

To understand the insurance landscape for DMTs for MS, we reviewed publicly available coverage policies from Centers for Medicare and Medicaid Services (CMS), California Department of Health Care Services (DCHS), all major national private insurers (Aetna, Anthem, Cigna, Humana, United Healthcare [UHC]), and the two major private insurers in California (Health Net, Blue Shield of California [BSCA]).

We were unable to identify any CMS National Coverage Determinations (NCDs) or Local Coverage Determinations (LCDs) related to the use of DMTs for MS. We were unable to locate any policies pertaining to the injectable or oral DMTs from California DHCS, but both alemtuzumab and natalizumab are listed in the contract drug list for injectable therapies.[50,51] Most national and regional private insurers placed all DMTs on high/specialty formulary tiers, and three (Anthem, Humana, and Health Net) listed every available agent either on the highest tier or as a specialty medication. Only one payer, Cigna, included any agents at the lowest formulary tier.

All payers made use of step therapy and prior authorization policies to manage therapies for MS (Table 4). Typical step therapy policies required a contraindication, intolerance, or inadequate response demonstrated by breakthrough disease (relapses, MRI findings, or EDSS progression while receiving therapy) to one or more preferred injectable therapies (not including daclizumab) or an oral agent. For example, patients with an Aetna plan must attempt treatment with three agents (generic glatiramer acetate 20 mg, glatiramer acetate 40 mg, interferon β-1a 22/44 mcg, or fingolimod) before being authorized for treatment with dimethyl fumarate. Across nearly every payer, similar policies were applied to oral agents, infusions, and non-preferred injectable therapies.

Aetna was the only private payer with a publicly available policy authorizing the off-label use of rituximab, though patients are required to demonstrate inadequate response to six or more DMTs including an interferon β, glatiramer acetate, teriflunomide, dimethyl fumarate, fingolimod, alemtuzumab, natalizumab, or daclizumab.[52] All other payers either considered rituximab to be investigational for use in MS, or did not list the agent in their formularies or utilization management documents.

Table 4. Representative Private Payer Policies for MS DMTs

	Aetna[53]	Anthem[54]	Cigna[55]	Humana[56]	UHC[57]	Health Net[58]	BSCA[59,60]
Interferon β-1a 30 mcg (Avonex)							
Tier	5	4	2	N/C	2	SP	SP
ST	Yes	No	No	No	No	No	No
PA	Yes	Yes	Yes	Yes	Yes	Yes	No
Preferred Agent	No		Yes	No			
Interferon β-1b 250 mcg (Betaseron)							
Tier	5	4	2	5	2	SP	SP
ST	Yes	No	No	No	No	No	Yes
PA	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Preferred Agent	No		Yes	No			
Interferon β-1b 250 mcg (Extavia)							
Tier	5	5	2	N/C	3	SP	SP
ST	Yes	No	No	No	Yes	No	Yes
PA	Yes	Yes	Yes	No	Yes	Yes	Yes
Preferred Agent	No		Yes	No			
Glatiramer Acetate 20 mg (Copaxone)							
Tier	5	5	2	5	2	NL	4
ST	Yes	No	No	No	No		No
PA	Yes	Yes	Yes	Yes	Yes		No
Preferred Agent	No		Yes	No			
Glatiramer Acetate 20 mg (Glatopa)							
Tier	4 (preferred)	4	1	N/C	3	2	SP
ST	No*[52]	No	No	Yes*[61]	No	No	No
PA	Yes	Yes	Yes	Yes[61]	Yes	Yes	No
Preferred Agent	No		Yes	No			

	Aetna[53]	Anthem[54]	Cigna[55]	Humana[56]	UHC[57]	Health Net[58]	BSCA[59,60]
Glatiramer Acetate 40 mg (Copaxone)							
Tier	4 (preferred)	4	2	5	2	SP	4
ST	No	No	No	No	No	No	No
PA	Yes	Yes	Yes	Yes	Yes	Yes	No
Preferred Agent	Yes		Yes	No			
Interferon β-1a 22/44 mcg (Rebif)							
Tier	4 (preferred)	5	2	5	3	SP	SP
ST	No	No	No	No	Yes	No	No
PA	Yes	Yes	Yes	Yes	Yes	Yes	No
Preferred Agent	Yes		Yes	No			
Peginterferon β-1a (Plegridy)							
Tier	5	4	2	N/C	3	SP	SP
ST	Yes	No	No		No	No	Yes
PA	Yes	Yes	Yes		Yes	Yes	Yes
Preferred Agent	No		Yes				
Daclizumab (Zinbryta)							
Tier	5	5	3	N/C	NL	SP	SP
ST	Yes	Yes*[62]	No	Yes*[63]		No	Yes
PA	Yes	Yes	Yes			Yes	Yes
Preferred Agent	No		No				
Fingolimod (Gilenya)							
Tier	4 (preferred)	4	2	5	3	SP	4
ST	No	No	No	No	No	No	No
PA	Yes	Yes	Yes	Yes	Yes	Yes	No
Preferred Agent	Yes		Yes	No			

	Aetna[53]	Anthem[54]	Cigna[55]	Humana[56]	UHC[57]	Health Net[58]	BSCA[59,60]
Teriflunomide 7/14 mg (Aubagio)							
Tier	5	4	2	N/C	3	SP	SP
ST	Yes	No	No	No	No	No	Yes
PA	Yes	Yes	Yes	No	Yes	Yes	Yes
Preferred Agent	No		Yes	No			
Dimethyl Fumarate (Tecfidera)							
Tier	5	4	2	N/C	2	SP	SP
ST	Yes	No	No	No	No	No	No
PA	Yes	Yes	Yes	Yes	Yes	Yes	No
Preferred Agent	No		Yes	No			
Natalizumab (Tysabri)							
Tier	5	4	N/C	5	NL	NL	NL
ST	Yes*	Yes*[64]	Yes*[65]	No		Yes*[66]	
PA	Yes	Yes		Yes			
Preferred Agent	No			No			
Alemtuzumab (Lemtrada)							
Tier	5	4	N/C	N/C	NL	NL	NL
ST	Yes	Yes*[62]	Yes*[65]	Yes*[67]	Yes*[68]		
PA	Yes	Yes		Yes	Yes*[68]		
Preferred Agent	No						
Rituximab (Rituxan)							
Tier	N/A	N/C[69]	N/C[65]	N/C[70]	N/C[71]		
ST	Yes*[52]						
PA	Yes						
Preferred Agent	No						

N/C: not covered, NL: not listed, PA: prior authorization, SP: specialty, ST: step therapy

*Information available in written utilization management policies conflict with the posted drug formulary; values in these cells reflect the utilization management policy. More detailed information can be found in the citation following the asterisk.

3.2 Clinical Guidelines

American Academy of Neurology (AAN), 2016[72]

The AAN draft guidelines for the use of DMTs in MS are summarized below; they are, however, subject to change based on a public comment period, and should not be interpreted as final. The guidelines do not contain treatment sequencing recommendations, but rather recommend that choice of DMT be guided by shared decision-making between the patient and physician. Together, the patient and physician must consider safety, efficacy, tolerability, method of administration, compatibility with patient lifestyle, and cost when selecting a therapy. Physicians may begin DMT treatment after one demyelinating event or if two or more brain or spinal cord lesions consistent with MS are detected by imaging. Patients with CIS or RRMS who have not had a relapse in the previous 2 years or recent MRI activity may be monitored closely or treated with a DMT. Clinicians may consider switching therapies when a patient experiences at least one relapse, two or more new MRI lesions, or increased disability over a one-year period while on their current DMT.

The guidelines recommend that mitoxantrone, an agent that was excluded from our report, not be used in MS. Individuals with highly-active disease should be treated with alemtuzumab, fingolimod, or natalizumab, though the guidelines note that definitions of highly-active disease vary. Clinicians should advise patients about the risk for PML associated with natalizumab, fingolimod, and dimethyl fumarate, and should discuss switching from natalizumab to an agent with lower PML risk for patients who are JC virus positive. Patients who discontinue treatment with natalizumab are at increased risk for rebound disease activity (i.e., relapses and MRI activity), and if the subsequent DMT is fingolimod, treatment should begin within eight weeks to reduce said risk. Given substantial uncertainty regarding the risks of treatment cessation, physicians should advise patients that close follow-up is needed after discontinuation of DMT treatment. Clinicians should recommend that patients who achieve disease stability be allowed to continue therapy with their current agent.

The guidelines do not recommend therapy with any currently-approved DMTs for individuals with PPMS, though it should be noted that at the time the draft guidelines were published, the FDA had not issued a decision on ocrelizumab.

Canadian Agency for Drugs and Technology in Health (CADTH), 2013[73]

CADTH's 2013 guidelines for the treatment of RRMS recommend glatiramer acetate or interferon β-1b as initial therapies, noting that both agents contribute to meaningful reductions in ARR relative to placebo and are similarly cost-effective. At first-line, individuals with a contraindication to glatiramer acetate should be treated with interferon β-1b, with the opposite recommended for those with a contraindication to interferon β-1b. Unless an individual patient has a contraindication to both first-line options, dimethyl fumarate is not recommended as a first-line treatment for

RRMS. Dimethyl fumarate, fingolimod, and natalizumab are recommended for patients who do not respond to first-line treatment options. Combination therapy is not recommended for RRMS.

MS Coalition, 2016[74]

The MS Coalition consensus guidelines recommend that DMT treatment be started as soon as possible after an RRMS diagnosis, for individuals who experience a demyelinating event and MRI findings consistent with MS, and for individuals with progressive forms of MS who experience relapses and/or inflammatory activity. Treatment should be continued indefinitely unless response to therapy is inadequate, side-effects become intolerable, patients are unable to adhere to the treatment regimen, or a more appropriate therapy becomes available. Any decision to switch therapies should be driven by shared decision-making between the clinician and patient, and should only be considered for medically-appropriate reasons. Clinicians should consider treatment switches when a patient experience sub-optimal treatment response to their current agent (i.e., relapse, MRI activity, or other clinical activity). Clinicians should consider alternative regimens using a different mechanism of action when changing therapy.

The MS Coalition recommends that clinicians have access to the full armamentarium of MS treatment options given wide variation in mechanism of action, possible contraindications to one or more agents, differing DMT safety profiles, and individual patient preference. Access to treatment should not be dictated by relapse frequency, extent of disability, or patient demographic characteristics. The absence of relapse activity should not be used as justification for treatment cessation.

National Institute for Health and Care Excellence (NICE), 2002-2014[75]

The NICE Pathway recommends against the use of glatiramer acetate or an interferon β in the management of MS, except in individuals whose disease was well-managed by an agent in either class when the guidelines were released. Dimethyl fumarate and teriflunomide are recommended for individuals with RRMS, defined as having two clinically-significant relapses in the previous two years, provided the patient's disease is not highly active or rapidly progressing. Alemtuzumab is recommended without qualifying statements for the treatment of RRMS. Fingolimod should be used in individuals with highly-active MS whose relapses worsened or were ineffectively controlled over the prior year despite treatment with an interferon β. Natalizumab is recommended for use in patients with severe, rapidly-evolving RRMS, defined as at least two disabling relapses within one year, at least one gadolinium-enhancing lesion, or a significant increase in T2 lesion load in comparison with a previous MRI.

4. Comparative Clinical Effectiveness

4.1 Overview

To inform our analysis of the comparative clinical effectiveness of DMTs in the treatment of RRMS and PPMS, we abstracted evidence from available clinical studies of these agents, whether in published or abstract form.

The therapies of interest for RRMS are:

- Daclizumab
- Glatiramer acetate
- Interferon β-1a
- Peginterferon β-1a
- Interferon β-1b
- Dimethyl fumarate
- Fingolimod
- Teriflunomide
- Alemtuzumab
- Natalizumab
- Ocrelizumab
- Rituximab

The therapies of interest for PPMS are:

- Ocrelizumab
- Rituximab

As described previously in the Background section, comparators of interest include best supportive care as well as each of the individual agents compared to the others. We specifically addressed areas of interest to stakeholders that were identified during the scoping process for this review including the newer agents (daclizumab, ocrelizumab) and two specific direct comparisons (interferon β-1a 30 mcg intramuscular [IM] injection weekly compared to interferon β-1a 44 mcg subcutaneous [SC] injection three times weekly; ocrelizumab compared to rituximab).

We focused primarily on clinical benefits that matter to patients (relapse rates, disability progression) and potential harms (drug-related adverse events). Patient-reported outcomes (quality of life, fatigue, mood, cognitive function, etc.) are presented when reported in individual trials, but there was not consistent reporting across trials, so it is difficult to make broader

conclusions about them. Similarly, MRI outcomes are reported for individual trials, but many different MRI outcomes have been reported over time and MRI technology has improved markedly over the decades during which the clinical trials were performed, so it is impossible to compare across studies.

4.2 Methods

Data Sources and Searches

Procedures for the systematic literature review assessing the evidence on disease modifying therapy for RRMS and PPMS followed established best methods.[76] We conducted the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[77] The PRISMA guidelines include a list of 27 checklist items, which are described further in Appendix Table A1.

We searched MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials for relevant studies 9/15/16 without restrictions on study date. 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. The search strategies included a combination of indexing terms (MeSH terms in MEDLINE and EMTREE terms in EMBASE), as well as free-text terms, and is described in Appendix Table A2. We included abstracts from conference proceedings in the literature search. In order to supplement the above searches and ensure optimal and complete literature retrieval, we performed a manual check of the references of recent relevant reviews and meta-analyses and contacted the manufacturers of agents included in this review. Trials that were initially available in abstract form were updated when published in peer reviewed journals.

Study Selection

For the inputs to the network meta-analysis, we included evidence from phase II or III randomized controlled trials (RCTs) that directly compared the DMTs of interest to one another or to placebo and reported either relapse rates or sustained disability progression over a minimum of 48 weeks follow-up. We limited the review to the doses that match the FDA-approved indication except for drugs that do not have a current FDA indication for MS. For those drugs, we used the dose reported in the randomized trials. We supplemented our review of published studies with data from conference proceedings, regulatory documents, and information from manufacturers. Studies that did not compare at least two relevant treatment arms or one relevant treatment arm to placebo were excluded.

Data Extraction and Quality Assessment

We abstracted trial characteristics, patient characteristics and study quality measures in data tables (Appendix Tables C1-C3). We also abstracted key outcomes including annualized relapse rates (ARRs) and confirmed disability progression sustained for a minimum of 12 and 24 weeks (Appendix Tables C4-C6). The primary reviewer abstracted data from all trials and a second reviewer confirmed the results. Differences were resolved by consensus.

We use the criteria published by the US Preventive Services Task Force (USPSTF) to assess the quality of clinical trials and cohort studies, using the categories "good," "fair," or "poor."[78]

Good: *Meets all criteria: Comparable groups are assembled initially and maintained throughout the study; reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention paid to confounders in analysis. In addition, intention to treat analysis is used for RCTs.*

Fair: *Any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are addressed. Intention to treat analysis is done for RCTs.*

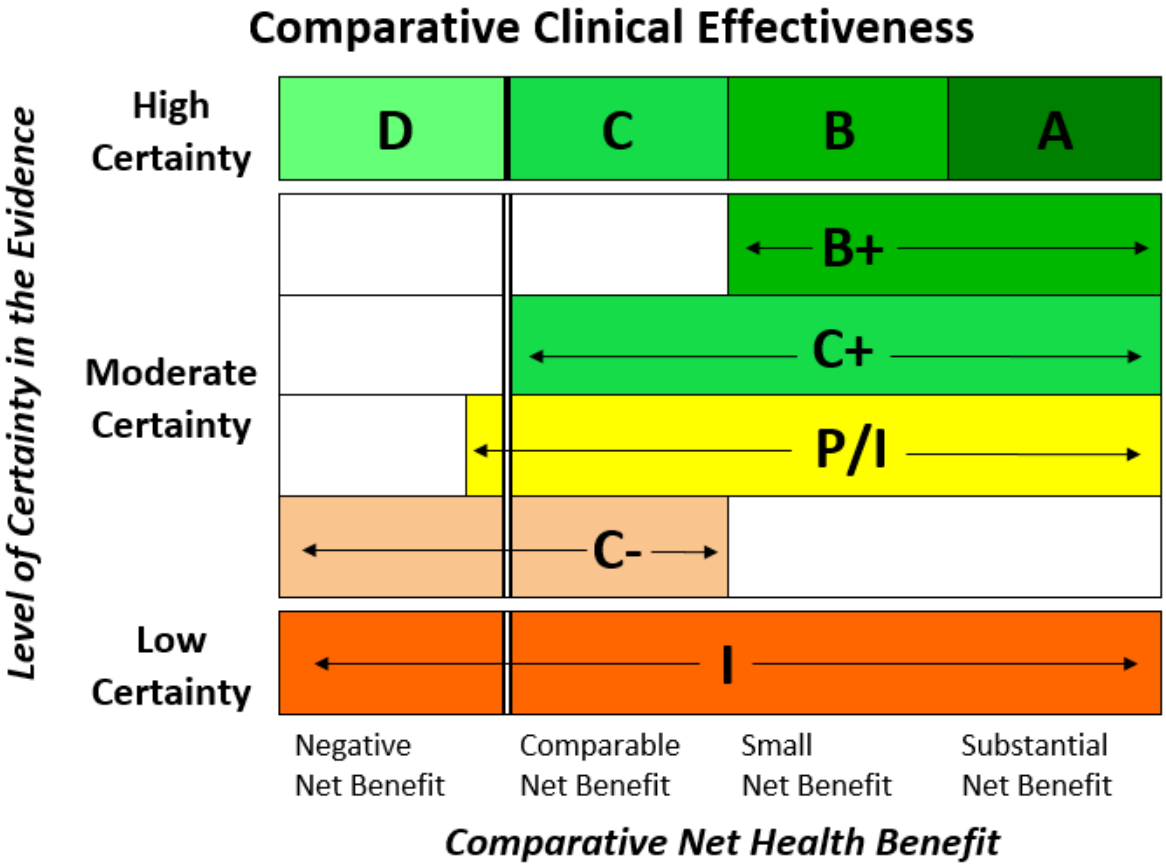
Poor: *Any of the following fatal flaws exists: groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For RCTs, intention to treat or modified intention to treat (e.g., randomized and received at least one dose of study drug) analysis is lacking.*

Assessment of Level of Certainty in Evidence

We used the ICER Evidence Rating Matrix (see Figure 2) to evaluate the evidence for a variety of outcomes. The evidence rating reflects a joint judgment of two critical components:

a) The **magnitude** of the difference between a therapeutic agent and its comparator in "net health benefit" – the balance between clinical benefits and risks and/or adverse effects AND
b) The level of **certainty** in the best point estimate of net health benefit.[79]

Figure 2. 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 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 comparable, small, or substantial net health benefit, and a small (but nonzero) likelihood of a negative net health benefit*
*C- = **"Comparable or Inferior"** - Moderate certainty that the point estimate for comparative net health benefit is either comparable or inferior*
*I = **"Insufficient"** - Any situation in which the level of certainty in the evidence is low*

Data Synthesis and Statistical Analyses

There was sufficient evidence to perform network meta-analyses (NMA) for sustained disability progression and ARRs. There was sparse evidence and no consistent outcome measure for MRI and quality of life outcomes, so NMAs were not performed. Detailed descriptions of the NMA methods and sensitivity analyses are in Appendix D.

4.3 Results

The results first consider drugs for RRMS and then drugs for PPMS. The RRMS results are grouped by relative efficacy for the primary outcomes: ARR and sustained disability progression.

Study Selection

The literature search identified 1,834 citations (Appendix Figure A1). After reviewing the titles and abstracts, 113 full text articles were evaluated. There were 33 unique randomized trials for the RRMS indication and 2 randomized trials for the PPMS indication.

RRMS

Appendix Tables C1-C3 summarizes the characteristics of the included studies. The 33 studies randomized 21,768 participants to one or more of the DMTs considered in this review or to placebo. The oldest trial[13] was published in 1987 and the most recent trial was published in 2017.[14] Eight of the trials used the Poser definition of clinically-definite MS to define their patient population and the remaining 25 trials used the McDonald criteria to define their eligible population. Eleven of the trials included only treatment-naïve patients, one trial included only treatment-experienced patients, and the remaining trials included a mix of both or did not report prior treatment status.

The average age of the study participants was about 36 years across the trials and approximately 70% were women (Appendix Table C2). The participants were predominantly white (~90%). The average duration of MS ranged from 1.1 to 10.5 years across the trials, but most averaged 5-6 years. Their EDSS grade at baseline ranged from 2.0 to 3.0 and the number of relapses in the prior year ranged from 1.0 to 2.2. Finally, the average number of gadolinium-enhancing lesions on MRI, which was not reported in 14 of the trials, ranged between 1.3 and 4.3.

PPMS

There are only two studies of DMTs for PPMS. Both are described in detail in the "Key Studies" section below.

Quality of Individual Studies

Using criteria from the USPSTF, we rated five of the trials included in our NMA to be of good quality (Appendix Table C3).[14,32,80,81] We judged these studies to be of good quality because appropriate randomization was performed, the study arms were comparable at baseline, key outcomes were measured in the same way for all study arms, and no differential or significant loss to follow-up was observed. The primary reasons that other trials were downgraded were lack of blinding of the study participants and staff, significant loss to follow-up, and lack of measurement of one of the key

outcomes: disability progression sustained for 24 weeks. We rated 17 publications to be of fair quality. We rated the remaining 11 studies as poor quality, primarily because of greater than 20% loss to follow-up.

Key Studies

The key studies described below include the pivotal trials for the newest agents (daclizumab, rituximab, and ocrelizumab), studies of interest for this review based on specific questions raised by patients, providers, and insurers during our scoping process, (direct comparison of Avonex and Rebif, two different formulations of interferon β-1a), and a brief summary of any additional trials directly comparing any of the DMTs. We also summarized prior NMAs on DMTs for RRMS.

RRMS

Daclizumab (Zinbryta)

The SELECT trial randomized 621 patients to one of two doses of daclizumab high yield process or placebo and followed them for 52 weeks.[82] For this review, we focused on the FDA approved dose of daclizumab (150 mg SC every 4 weeks, n=201) and the placebo group (n=196). We judged the study to be of fair quality, primarily because disability progression sustained for 24 weeks was not reported as well as the short follow-up (one year) and relatively large loss to follow-up (9%) for a one-year study. The primary outcome compared the relapse rate for each arm using negative binomial regression adjusted for the number of relapses in the year prior to study entry as well as baseline EDSS score and age. The rate ratio (RR) for ARR was 0.46 (95% confidence interval [CI] 0.32-0.67, p<0.0001) for daclizumab compared to placebo. The hazard ratio (HR) for confirmed disability progression sustained for at least 12 weeks was 0.43 (0.21-0.88, p=0.021). There were also significant reductions in the following MRI outcomes: new gadolinium-enhancing lesions at 52 weeks (0.3 vs. 1.4, odds ratio [OR] 0.15, 95% CI 0.09-0.25, p<0.0001) and new or enlarging T2 hyperintense lesions at 52 weeks (2.4 vs. 8.1, relative risk reduction [RRR] 70%, 95% CI 59-78%, p<0.0001), but not percentage change in whole brain volume at 52 weeks (-0.79 vs. -0.74, p=0.33). There were also significant improvements in quality of life as measured by the Multiple Sclerosis Impact Scale (MSIS-29) physical score, the EuroQol five dimensions (EQ-5D) summary health index, the EuroQol visual analog scale, and the 12-item short form health survey (SF-12) physical and mental health components for daclizumab compared to placebo. Adverse events (AEs) and serious adverse events (SAEs) were similar in the two groups, but there were more serious infections in the daclizumab group (3% vs. 0%). There were also more reports of liver enzyme elevations > 5 times the upper limit of normal (4% vs. <1%). This is noteworthy as severe hepatic injury is listed as a black box warning for daclizumab.

The DECIDE trial randomized 1,841 patients to daclizumab or interferon β-1a 30 mcg IM each week for up to 144 weeks (median 108.7 weeks for daclizumab; median 111.4 weeks for interferon β-

1a).[83] It is one of the largest and longest randomized trials of the DMTs. The study was judged to be of poor quality primarily because of the large loss to follow-up (23%, > 20% considered a fatal flaw due to risk for selection bias). The primary outcome compared the relapse rate for each arm using negative binomial regression adjusted for baseline relapse rate as well as prior interferon use, baseline EDSS score and age. The ARR for daclizumab was lower (0.22 vs. 0.39, p<0.001, RR 0.55, 95% CI 0.47-0.64) for daclizumab compared to interferon β-1a. The HR for confirmed disability progression sustained for at least 12 weeks was 0.84 (0.66-1.07, p=0.16) and the HR for confirmed disability progression sustained for at least 24 weeks was 0.79 (0.59-1.06, p=0.012). There were also significant reductions in the following MRI outcomes: new gadolinium-enhancing lesions at 96 weeks (0.4 vs. 1.0, OR 0.25, 95% CI 0.20-0.32, p<0.001); new or enlarging T2 hyperintense lesions at 96 weeks (4.3 vs. 9.4, 54% reduction, 95% CI 47-61%, p<0.001), and percentage change in whole brain volume at 96 weeks (-0.56% per year vs. -0.59% per year, p<0.001). There were significant improvements in quality of life as measured by the MSIS-29 physical score and the EQ-5D summary health index for daclizumab compared to interferon β-1a 30 mcg. There were also statistically significant improvements on the MSFC at 96 weeks (0.091 vs. 0.055, p<0.001) as well as its components, the timed 25-foot walk, the 9-hole peg test, and the 3-second paced auditory serial addition test. SAEs were more common in the daclizumab group when MS relapses were excluded (15% vs. 10%) as were discontinuations due to non-MS adverse events (14% vs. 9%). There were more serious infections (4% vs. 2%) and serious hepatic events (1% vs. <1%) in the daclizumab group.

In summary, the SELECT trial found that daclizumab was significantly better than placebo at reducing relapses, disability progression, and MRI lesions. The DECIDE trial found that daclizumab was significantly better than interferon β-1a 30 mcg at reducing relapses and MRI lesions, but not disability progression. There were small improvements in quality of life measures in both trials. There were also more SAEs in the DECIDE trial with an increase in serious infections in both trials, though the increase was small.

Ocrelizumab (Ocrevus)

There are two pivotal phase III randomized trials for ocrelizumab: OPERA I and OPERA II.[14] The investigators randomized 821 and 835 patients, respectively, to either ocrelizumab IV (300 mg on days 1 and 15 and then 600 mg IV once every 24 weeks for 3 doses) or interferon β-1a 44 mcg SC three times a week (TIW) and followed them for 96 weeks. We judged the trials to be of good quality. The primary outcome, ARRs in the ocrelizumab group compared to that of the interferon β-1a, was significantly lower in the ocrelizumab group (46% and 47% ARR reduction, respectively, p<0.001 in both trials). There were also significant reductions in confirmed disability progression sustained for 24 weeks (HR 0.57, 95% CI 0.34-0.95 for OPERA I and HR 0.63, 95% CI 0.40-0.98 for OPERA II through 96 weeks of follow-up). There was a 94-95% reduction in gadolinium-enhancing lesions in the two trials with ocrelizumab compared to interferon β-1a 44 mcg (p<0.001, for both

trials). The number of new or enlarging T2 lesions was reduced with ocrelizumab (77% and 83% respectively, p<0.001 for both trials). The difference in the rate of brain volume loss between weeks 24 and 96 was 23% in OPERA I (p=0.004) and 15% in OPERA II (p=0.09). In OPERA I there was no significant difference between groups in the SF-36 physical component summary score (+0.04 ocrelizumab, -0.66 interferon β-1a, p=0.22, but the difference was significant in OPERA II (+0.33 versus -0.83, p=0.04). SAEs, including infections, and nervous system disorders, were lower in the ocrelizumab group. Overall AEs were similar in the two groups, but patients receiving ocrelizumab were more likely to have infusion-related reactions (34% vs. 10%) and upper respiratory infections (15% vs. 10%).

Interferon β-1a (Avonex vs. Rebif)

Based on stakeholder interest, we also summarized data from the EVIDENCE trial comparing Avonex and Rebif. This trial was a fair quality, open-label study funded by the manufacturer of Rebif that randomized 677 patients with RRMS by the Poser criteria to two forms of interferon β-1a: 44 mcg SC TIW (Rebif) or 30 mcg IM once a week (Avonex). A blinded physician evaluated the participants for all outcomes. The baseline characteristics of trial participants are summarized in Appendix Table C2 and they were similar in both arms of the trial. Follow-up was completed for 96% of participants in both arms at 48 weeks of follow-up. The primary endpoint, proportion free of relapse at 24 weeks, was greater in the 44 mcg TIW group (75% vs. 63%, p=0.0005). The differences remained significant at 48 weeks (62% vs. 52%, p=0.009). The HR for first relapse was 0.70 (95% CI 0.55-0.88, p=0.003) over the course of the study. However, the rate of relapses over 48 weeks did not differ significantly (0.54 vs. 0.64, p=0.093). There were no significant differences in confirmed disability progression sustained for 12 weeks (43 vs. 49 participants, HR 0.87, 95% CI 0.58-1.31, p=0.51) or for 24 weeks (20 vs. 28 participants, HR 0.70, 95% CI 0.39-1.25, p=0.23). The number of combined unique lesions on MRI was lower in the 44 mcg TIW group (24 vs. 37, p<0.001). These finding suggest that the 44 mcg SC TIW dosing of interferon β-1a may be more effective than the 30 mcg IM weekly dosing. However, the trial was too short to adequately address some outcomes that matter to patients (long-term disability progression). The lack of blinding of patients and treating physicians raises the possibility of both differential co-interventions and ascertainment bias, although the outcomes assessment was performed by a blinded physician. These results should be placed in the context of the full set of randomized trial results comparing Avonex to Rebif that will be discussed below as part of the network meta-analysis.

Rituximab (Rituxan)

The HERMES trial was a small, fair quality, phase II study that randomized 104 patients with RRMS in a 2:1 ratio to rituximab or placebo and followed them for 48 weeks.[84] The patient characteristics are summarized in Appendix Table C2. The only important difference in baseline characteristics between the two arms of the trial was a higher proportion of participants with gadolinium-

enhancing lesions in the rituximab group (36% vs. 14%, p=0.02). The primary outcome, number of gadolinium-enhancing lesions, was lower in the rituximab group (mean 0.5 vs. 5.5 lesions per patient, p<0.001). The volume of T2-weighted lesions at 36 weeks was also lower (-10.3 mm^3 vs. +123 mm^3, p=0.004) as was the number of new gadolinium-enhancing lesions (0.2 vs. 4.5, p<0.001). The proportion of patients with relapses was lower in the rituximab group at 24 weeks (14.5% vs. 34.3%, p=0.02) and at 48 weeks (20.3% vs. 40.0%, p=0.04). The ARR was significantly lower at 24 weeks (0.37 vs. 0.84, p=0.04), but not at 48 weeks (0.37 vs. 0.72, p = 0.08). Disability progression was not reported. SAEs were similar in the two groups (13.0% vs. 14.3%) and infection-related SAEs were less common in the rituximab group (2.9% vs. 5.7%). Reactions after the first infusion were more common in the rituximab group (78% vs. 40%). This small trial suggests that anti-CD20 therapy has promise for RRMS, but larger and longer confirmatory studies are needed.

Other Head-to-Head Trials

There are several other head-to-head trials comparing new agents to one of the interferons. The TRANSFORM trial compared fingolimod to interferon β-1a 30 mcg IM every week.[85] Fingolimod had significantly lower ARR (0.16 vs. 0.33, p<0.001), but there were no differences in disability progression. In the TENERE trial, the ARR for teriflunomide 7 mg (0.41) was significantly higher than that of teriflunomide 14 mg (0.26) and interferon β-1a 44 mcg TIW (0.22).[86] Despite the higher relapse rates, patients rated teriflunomide better on the Treatment Satisfaction Questionnaire for Medication domains of Global Satisfaction, Convenience, and Side Effects. In the CONFIRM trial, there were no significant differences between dimethyl fumarate and glatiramer acetate for ARR, though both were more effective than placebo.[87] They also were more effective than placebo in reducing the number of MRI findings including gadolinium-enhancing lesions, new or enlarging T2 lesions, and hypointense T1 lesions. There were no significant differences between any of the groups in confirmed disability progression sustained for 12 weeks. The only difference that was significantly lower for dimethyl fumarate was new or enlarging hyperintense lesions on T2-weighted images.

Finally, in three trials of alemtuzumab versus interferon β-1a 44 mcg TIW, alemtuzumab was consistently better for relapse reduction and sustained disability progression.[88-90] The CAMMS223 phase II study was stopped early after immune thrombocytopenic purpura (ITP) developed in 3 patients and 1 of the 3 died. In that trial alemtuzumab markedly reduced disability progression (HR 0.29, p<0.001), ARR (HR 0.26, p<0.001), and decreased average disability (improved by 0.39 EDSS points in alemtuzumab group, worsened by 0.38 EDSS points in interferon β-1a group, p<0.001). MRI outcomes also were significantly better in the alemtuzumab group. AEs were more common in the alemtuzumab group including autoimmune thyroid disorders (23% vs. 3%), ITP (3% vs. 1%), and infections (66% vs. 47%). In the phase III CARE-MS I and CARE MS II trials, the reduction in relapse rates and disability progression were slightly lower, but highly significant, MRI outcomes were similar, and the pattern of increased autoimmune disease and infections were observed.

In summary, in these head-to-head trials, alemtuzumab was more effective at preventing relapses than interferon β-1a 44 mcg, but alemtuzumab was associated with an increase in autoimmune thyroid and platelet diseases and infections. Fingolimod was more effective at preventing relapses than interferon β-1a 30 mcg. Teriflunomide and dimethyl fumarate were not more effective than interferon β-1a 44 mcg and glatiramer acetate, respectively.

Previous Network Meta-Analyses

There are four published network meta-analyses of DMTs for RRMS.[27-30] Fogarty and colleagues published the most recent NMA.[28] They included 28 RCTs in their analyses, but did not evaluate daclizumab, rituximab, or ocrelizumab. They concluded that all of the DMTs reduced the ARR compared with placebo, but there was greater uncertainty with disability progression. They also concluded that natalizumab and alemtuzumab demonstrated consistently high rankings across all outcomes, while the interferons and glatiramer acetate ranked lowest. The Cochrane review concluded that alemtuzumab, natalizumab, and fingolimod were more effective than other drugs at preventing relapses and that there was insufficient evidence about irreversible disability progression. They also highlighted the lack of evidence for efficacy beyond two years, which is very important for patients with a lifelong disease. Finally, they highlighted the poor reporting of safety data and the fact that most studies were sponsored by pharmaceutical companies, which is a known potential source of bias. The CADTH review concluded that alemtuzumab and natalizumab were the most effective DMTs followed by fingolimod and dimethyl fumarate. They concluded that the interferons, glatiramer acetate, and teriflunomide had lower efficacy. Finally, Tolley and colleagues published a NMA in 2015[27] that only evaluated the interferons and glatiramer acetate. They evaluated ARRs, confirmed disability progression at both 12 and 24 weeks, and safety and tolerability. They included 16 randomized trials and concluded that the interferons and glatiramer acetate demonstrated comparable efficacy and tolerability.

PPMS

Rituximab (Rituxan)

The OLYMPUS trial was a good-quality trial that randomized 439 patients with PPMS in a 2:1 ratio to two 1000 mg infusions of rituximab or placebo 14 days apart every 24 weeks and followed them for 96 weeks.[9] The mean age of the participants was 50 years and 50% were female. The mean duration of disease was 9.1 years and 65% had received no prior therapy. The mean EDSS score was 4.8. On baseline MRI, 25% had gadolinium-enhancing lesions. Only 4 patients were lost to follow-up. There was no significant difference in the time to confirmed disability progression sustained for at least 12 weeks (HR 0.77, 30.2% for rituximab and 38.5% placebo, p=0.14), which was the primary endpoint.

For the predefined secondary endpoints, there was a significant reduction in the T2 lesion volume (p<0.001), but not in the change in brain volume (p=0.62). Additional outcomes found that patients randomized to rituximab performed significantly better on the MSFC timed 25-foot walk, but results were not significantly different for the overall MSFC, the 9-Hole peg test, paced auditory serial testing, or confirmed disability progression sustained for 24 weeks. Preplanned subgroup analyses found that rituximab significantly delayed the time to progression for patients aged < 51 years (HR 0.52, p=0.01) and in those patients with gadolinium-enhancing lesions at baseline (HR=0.41, p=0.007). SAEs were more common in the rituximab group (16.4% vs. 13.6%). In particular, infection-associated SAEs were more common with rituximab (4.5% vs. <1%). There were 3 deaths (1 in rituximab group, 2 in placebo group). The most common AEs were pruritus, flushing, headache, fatigue, chills, nausea and fever associated with the drug infusion. These reactions decreased with repeated infusions, but still occurred in 7.8% of participants receiving rituximab at the 7th infusion (compared to 5.6% in the placebo infusion group). In summary, the trial did not meet its primary endpoint, but suggested that rituximab shows promise for younger patients with PPMS who have gadolinium-enhancing lesions on MRI; additional study is required, however, to confirm rituximab's benefits in this PPMS population.

Ocrelizumab (Ocrevus)

The ORATORIO study was a good-quality study published in January 2017.[91] The study randomized 732 patients ages 18-55 years with PPMS in a 2:1 ratio to two 300 mg infusions of ocrelizumab or placebo every 24 weeks and followed them for 120 weeks. The mean age of the participants was 45 years and 49% were female. The mean duration of disease was 6.5 years and 90% had received no MS therapy in the prior 2 years. The mean EDSS score was 4.7. On baseline MRI, 26% had gadolinium-enhancing lesions. Only 4 patients were lost to follow-up. Confirmed disease progression sustained for at least 12 weeks, the primary endpoint of the trial, was significantly lower in the ocrelizumab group (HR 0.76, 95% CI 0.59 - 0.98, p=0.032). Confirmed disease progression sustained for at least 24 weeks was also significantly lower in the ocrelizumab group (HR 0.75, 95% CI 0.58 - 0.98, p=0.04). As with rituximab, there was a significant reduction in the T2 lesion volume (p<0.001) and faster performance of the 25-foot walk (p=0.04). In addition, there was a significant improvement in the change in brain volume (p=0.02). There was no significant difference between groups in the SF-36 physical component summary score (-0.73 ocrelizumab, -1.11 placebo, p=0.60. SAEs were less common in the ocrelizumab group (20.4% vs. 22.2%) and infection-associated SAEs nearly identical (6.2% vs. 5.9%). There were more deaths (0.8% vs. 0.4%) and more malignancies (2.3% vs. 0.8%) in the ocrelizumab group. The most common AEs were mild to moderate reactions associated with the drug infusion. In summary, the trial demonstrated a significant 24-25% reduction in the rate of disability progression sustained at 12 and 24 weeks as well as a reduction in brain volume loss and in the rate of decline in walking speed. The difference in malignancies is concerning particularly given similar reports in patients with B-cell lymphomas treated with rituximab, but it may be a chance finding.

The relative rate reduction in relapses demonstrated for ocrelizumab in the ORATORIO study (26%) is similar to that observed for ocrelizumab in the OLYMPUS trial (23%), and may represent a class effect for anti-CD20 therapies. The OLYMPUS trial had fewer participants and shorter follow-up and thus was underpowered to detect a 20% to 25% reduction in disability progression. The ORATORIO study also enrolled a younger population, perhaps based on the subgroup analysis in OLYMPUS that demonstrated a significant reduction in disability progression in younger patients. No subgroup analyses have as yet been reported for the ORATORIO study.

Clinical Benefits

Relapse Rate

In the survey performed by the MS Coalition for this review, preventing relapses was felt to be as important to patients as preventing disability progression. Relapses take patients and their caregivers away from work, school, and other important life responsibilities, and symptoms can last for months. Twenty head-to-head studies, five of which also included a placebo arm, and an additional 13 placebo-controlled studies contributed results to the NMA of ARR (see Appendix Figure D1 for the Network Diagram and Appendix Table C4 for the results from each trial contributing to the NMA).

The ARR in the placebo group ranged from 0.34 to 1.38 relapses per year across studies. As noted earlier, there is a trend towards lower relapse rates in the placebo groups in more recent trials compared with earlier trials. For example, the ARR in the placebo group of the 5 trials published before 2000 ranged from 0.82 to 1.38[13,80,92-95], while those published since 2010 ranged from 0.34-0.50.[81,82,86,87,96-101] The explanation for the change in ARR over time has been studied, but no conclusive reason has been identified.[22,23,25,26] Possible explanations include the age of participants, the number of pre-enrollment relapses in the prior 1 to 2 years, the length of time since their first symptoms of MS, the use of differing diagnostic criteria for MS, the length of follow-up in the trials, and the country of origin for patients enrolled in the trials. None of these factors, however, fully explain the observed trend.

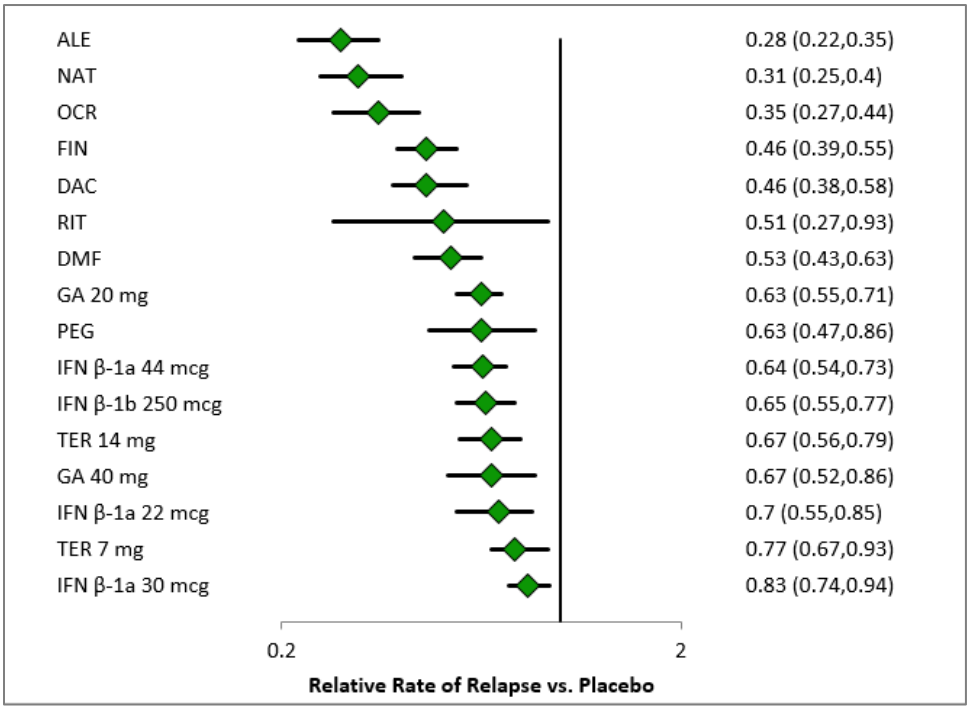
The average age of the study participants was about 36 years across the trials and approximately 70% were women (Appendix Table C2). The participants were predominantly white (~90%). The average duration of MS ranged from 1.1 to 10.5 years across the trials, but most averaged 5-6 years. Their mean EDSS grade at baseline ranged from 2.0 to 3.0 and the mean number of relapses in the prior year ranged from 1.0 to 2.2. Finally, the average number of gadolinium-enhancing lesions on MRI, which was not reported in 17 of the trials, ranged between 1.3 and 4.3.

In the early trials of the interferons and glatiramer acetate the DMTs reduced the ARR by 20% to 40% compared to placebo, with the exception of the early trial by Bornstein and colleagues, published in 1987, which reported a 76% reduction in ARR with glatiramer acetate. The newer

generation drugs, such as dimethyl fumarate, fingolimod, rituximab, daclizumab, ocrelizumab, and natalizumab all report greater than a 50% reduction in ARR compared to placebo.[32,81,82,84,87,99] The one exception is teriflunomide, which reduced ARR by 20%-40% compared to placebo.[97,100] . There are no placebo controlled trials of alemtuzumab; all three of the alemtuzumab randomized trials used interferon β-1a 44 mcg as an active control.

In our NMA, alemtuzumab, natalizumab, and ocrelizumab had the greatest reduction in ARR (approximately 70% reduction compared to placebo). The 95% credible interval for the first two drugs did not include 1 when compared to any of the other drugs with the exception of rituximab (Table 5). Fingolimod, daclizumab, rituximab, and dimethyl fumarate were the next most effective (47% to 54% reduction). The interferons, glatiramer acetate 20 mg, and teriflunomide were less effective (17% to 37% reduction). All of the drugs were significantly better than placebo. A forest plot summarizing the relative risks and 95% credible intervals for each drug compared to placebo is presented below (Figure 3).

Figure 3. Forest Plot of DMTs vs. Placebo for Annualized Relapse Rate



Legend: The diamonds represent the point estimate from the NMA for the relative risk of relapse rate for each drug compared to placebo and the horizontal bars represent the 95% credible intervals. Any numbers less than 1 indicate a reduction in the relapse rate compared to placebo.

The forest plot graphically demonstrates the superiority of alemtuzumab, natalizumab, and ocrelizumab to the other agents. The study of rituximab was underpowered compared to the other studies (much wider credible intervals, greater uncertainty), but the point estimate was similar to

that of fingolimod, daclizumab, and dimethyl fumarate. The interferons, glatiramer acetate, and teriflunomide appear to be less effective at reducing relapse rates than the other drugs. Nevertheless, interferon β-1a 30 mcg, which was the least effective drug in the NMA, is still superior to placebo.

Table 5 below includes the complete set of pairwise comparisons for all drugs included in the network. Comparisons with statistically-significant results are highlighted in bold. Consistent with the forest plot presented previously, significant reductions in relapse rate were generally observed for the most effective agents versus the next most-effective group, and again for the "middle" group in comparison to the interferons, glatiramer acetate, and teriflunomide.

We compared our NMA random-effects estimates to those obtained using a fixed-effects model, those from a direct meta-analysis, and performed meta-regression to evaluate the effect of trial-level baseline patient characteristics (duration of MS, EDSS score at baseline, relapses in the prior year) on the NMA results (Appendix Tables D1). There were no direct meta-analysis results for alemtuzumab or ocrelizumab because neither drug has been studied in placebo controlled trials. The remaining sensitivity analyses produced values and rank ordering of DMTs that were similar to the base-case estimates.

We also performed subgroup analyses to evaluate the effect of prior treatment, study size, the criteria used to define clinically-definite MS (Poser vs. McDonald criteria), study quality, length of follow-up, and excluding open label trials and there were no important changes in the ordering of drugs or the estimated efficacy versus placebo (Appendix Table D2).

The results from our NMA for ARR are in line with those reported in four earlier NMAs (see Table 6 below).[27-30] The Cochrane NMA estimated the relative rates over both 12- and 24-month follow-up periods. The Fogarty NMA is the most recent, so their results are most similar to those in the ICER NMA.

Table 5. League Table for Annualized Relapse Rate, Base Case

ALE																
0.92 (0.63-1.23)	NAT															
0.82 (0.61-1.05)	0.89 (0.65-1.29)	OCR														
0.61 (0.45-0.80)	**0.67 (0.51-0.91)**	0.76 (0.56-1.01)	FIN													
0.61 (0.44-0.81)	**0.67 (0.49-0.93)**	0.75 (0.54-1.01)	0.99 (0.76-1.29)	DAC												
0.56 (0.29-1.08)	0.62 (0.32-1.22)	0.69 (0.36-1.35)	0.91 (0.48-1.75)	0.93 (0.48-1.78)	RIT											
0.54 (0.39-0.71)	**0.59 (0.44-0.81)**	**0.66 (0.48-0.90)**	0.88 (0.67-1.13)	0.88 (0.67-1.18)	0.97 (0.50-1.83)	DMF										
0.45 (0.35-0.57)	**0.49 (0.39-0.66)**	**0.55 (0.43-0.71)**	**0.74 (0.60-0.91)**	**0.74 (0.59-0.94)**	0.79 (0.43-1.51)	0.84 (0.68-1.04)	GA 20 mg									
0.45 (0.30-0.64)	**0.50 (0.34-0.72)**	**0.56 (0.37-0.80)**	0.74 (0.51-1.02)	0.74 (0.51-1.05)	0.80 (0.39-1.56)	0.83 (0.57-1.18)	1 .00 (0.71-1.36)	PEG								
0.44 (0.37-0.53)	**0.49 (0.38-0.66)**	**0.55 (0.45-0.67)**	**0.73 (0.59-0.91)**	**0.73 (0.58-0.95)**	0.79 (0.42-1.50)	0.83 (0.66-1.06)	0.99 (0.85-1.16)	0.98 (0.73-1.42)	IFNß-1a 44 mcg							
0.44 (0.33-0.56)	**0.48 (0.37-0.65)**	**0.54 (0.41-0.71)**	**0.71 (0.57-0.90)**	**0.72 (0.57-0.93)**	0.77 (0.41-1.47)	0.82 (0.61-1.04)	0.97 (0.83-1.13)	0.97 (0.71-1.39)	0.99 (0.81-1.18)	IFNß-1b 250 mcg						
0.43 (0.31-0.56)	**0.47 (0.35-0.63)**	**0.52 (0.39-0.69)**	**0.69 (0.55-0.88)**	**0.70 (0.54-0.91)**	0.76 (0.39-1.44)	0.79 (0.61-1.02)	0.95 (0.76-1.15)	0.95 (0.68-1.36)	0.96 (0.76-1.17)	0.97 (0.77-1.21)	TER 14 mg					
0.42 (0.29-0.59)	**0.46 (0.33-0.67)**	**0.52 (0.36-0.74)**	**0.69 (0.51-0.94)**	**0.69 (0.50-0.97)**	0.75 (0.39-1.47)	0.79 (0.57-1.08)	0.94 (0.70-1.24)	0.94 (0.64-1.41)	0.95 (0.70-1.26)	0.97 (0.71-1.30)	1.00 (0.74-1.35)	GA 40 mg				
0.41 (0.3-0.54)	**0.45 (0.34-0.63)**	**0.5 (0.38-0.68)**	**0.66 (0.52-0.89)**	**0.67 (0.51-0.91)**	0.73 (0.38-1.42)	0.76 (0.58-1.02)	0.91 (0.72-1.15)	0.91 (0.65-1.34)	0.92 (0.74-1.14)	0.94 (0.73-1.21)	0.96 (0.75-1.27)	0.96 (0.70-1.36)	IFNß-1a 22 mcg			
0.37 (0.27-0.48)	**0.40 (0.30-0.53)**	**0.45 (0.33-0.59)**	**0.59 (0.46-0.75)**	**0.60 (0.46-0.77)**	0.65 (0.34-1.22)	**0.68 (0.52-0.86)**	**0.82 (0.65-0.98)**	0.82 (0.58-1.15)	**0.83 (0.65-0.99)**	0.84 (0.65-1.03)	0.86 (0.72-1.01)	0.86 (0.63-1.15)	0.89 (0.67-1.14)	TER 7 mg		
0.34 (0.26-0.43)	**0.37 (0.29-0.49)**	**0.42 (0.32-0.53)**	**0.56 (0.46-0.67)**	**0.56 (0.46-0.68)**	0.61 (0.32-1.14)	**0.63 (0.51-0.79)**	**0.76 (0.65-0.87)**	0.76 (0.56-1.06)	**0.77 (0.65-0.88)**	**0.78 (0.65-0.96)**	**0.80 (0.66-0.98)**	0.80 (0.61-1.06)	0.84 (0.65-1.04)	0.94 (0.77-1.15)	IFNß-1a 30 mcg	
0.28 (0.22-0.35)	**0.31 (0.25-0.40)**	**0.35 (0.27-0.44)**	**0.46 (0.39-0.55)**	**0.46 (0.38-0.58)**	**0.51 (0.27-0.93)**	**0.53 (0.43-0.63)**	**0.63 (0.55-0.71)**	**0.63 (0.47-0.86)**	**0.64 (0.54-0.73)**	**0.65 (0.55-0.77)**	**0.67 (0.56-0.79)**	**0.67 (0.52-0.86)**	**0.70 (0.55-0.85)**	**0.77 (0.67-0.93)**	**0.83 (0.74-0.94)**	Placebo

Legend: The DMTs are arranged from most effective (top left) to least effective (bottom right) Each box represents the estimated rate ratio and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in bold signify that the 95% credible interval does not contain 1

Table 6. Rate Ratio Estimates for ARR in Network Meta-Analyses of DMTs Compared to Placebo for RRMS

Drug	Cochrane 12-month	Cochrane 24-month	CADTH	Tolley	Fogarty	ICER
Interferon β-1a 30 mcg (Avonex)	0.93	0.89	0.87	0.74	0.85	0.83
Interferon β-1b 250 mcg (Betaseron)	0.98	0.85	0.67	0.68	0.67	0.65
Glatiramer acetate (Copaxone)						
20 QD	0.80	0.83	0.67	0.64	0.65	0.63
40 TIW					0.65	0.67
Interferon β-1a (Rebif)	0.87	0.86				
22 mcg			0.71	0.71	0.72	0.70
44 mcg			0.67	0.66	0.67	0.64
Peginterferon β-1a (Plegridy)	0.89	NR	NR	0.65	0.64	0.63
Daclizumab (Zinbryta)	0.79	NR	NR	NR	NR	0.46
Fingolimod (Gilenya)	0.63	0.72	0.44	NR	0.47	0.46
Teriflunomide (Aubagio)	0.84	0.88		NR		
7 mg			0.69		0.67	0.77
14 mg			0.68			0.67
Dimethyl fumarate (Tecfidera)	0.78	0.89	0.50	NR	0.50	0.53
Natalizumab (Tysabri)	0.56	0.56	0.32	NR	0.31	0.31
Alemtuzumab (Lemtrada)	0.40	0.46	0.30	NR	0.31	0.28
Ocrelizumab (Ocrevus)	NR	NR	NR	NR	NR	0.35
Rituximab (Rituxan)	NR	NR	NR	NR	NR	0.51

NR: not reported

Disability Progression

A primary long-term goal for patients is to avoid progressive and permanent disability as this has the greatest impact on their ability to work, participate in family life, and contribute to society. Ideally, studies would measure disability progression over at least five years.[15] Unfortunately, all but two of the studies were two years or less in duration and many studies did not report the preferred measure: the number of patients with confirmed disability progression sustained for a minimum of 24 weeks. We identified 27 trials that reported dichotomous results for disability progression, including 16 head-to-head studies (4 of which also had a placebo arm) and an additional 11 placebo-controlled studies, all of which contributed results to the NMA of disability progression (see Appendix Figure D2 for the Network Diagram and Appendix Tables C5-C6 for the results from each trial contributing to the NMA). Six studies did not contribute data to the NMA of disability progression because they did not report these data (Appendix Tables C5 and C6 specify which trials were included or excluded from the base-case analysis).

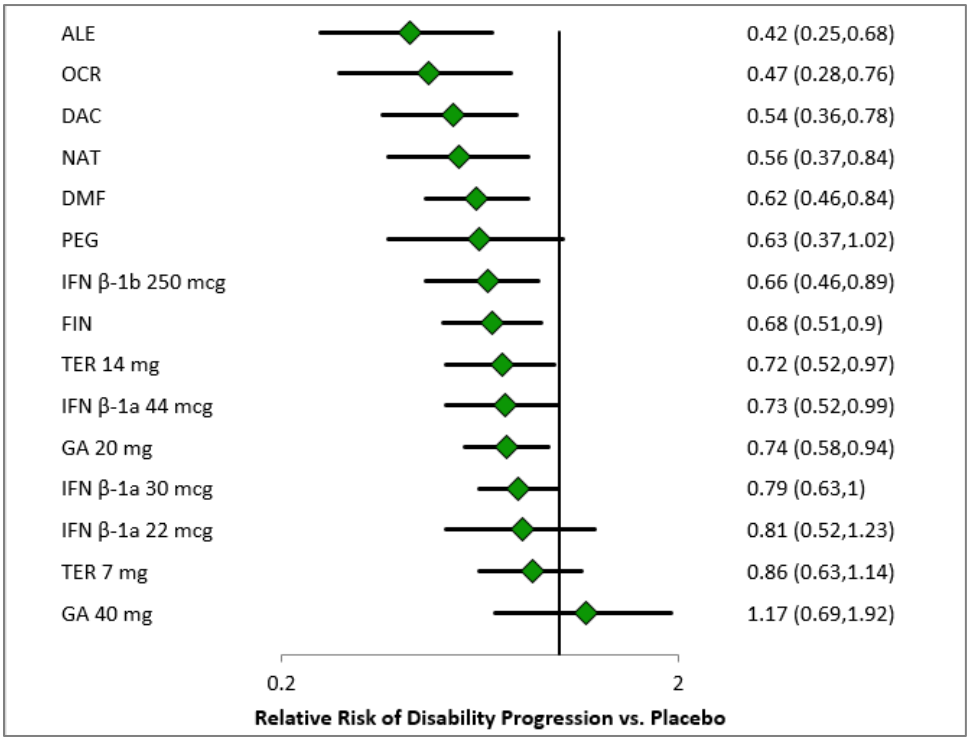
Studies reported confirmed disability progression sustained for 12 or 24 weeks (Appendix Tables C6 and C5), and as noted earlier, disability progression sustained for 24 weeks was the preferred outcome. In studies the reported both outcomes, the relative risk for disability progression was usually lower for the 24-week outcome than for the 12-week outcome. Examples include the FREEDOMS study of fingolimod versus placebo (RR 0.63 for confirmed disability progression sustained for 24 weeks vs. 0.70 for 12 weeks), the CONFIRM study of dimethyl fumarate versus placebo (RR 0.62 and 0.79), the CAMMS223 study of alemtuzumab versus interferon β-1a 44 mcg (RR 0.25 and 0.42) and the DECIDE study of daclizumab versus interferon β-1a 30 mcg (RR 0.79 and 0.84). For the NMA, we used the number of patients with confirmed disability progression at 24 weeks as the primary outcome, but used the 12-week outcome when the study did not report the number of patients with confirmed progression at 24-weeks, which may underestimate the true benefit of DMTs that lack these data (i.e., interferon β -1a 22 mg, teriflunomide 7/14 mg, dimethyl fumarate, glatiramer acetate 40 mg, peginterferon β-1a).

The incidence of disability progression was lower than that of relapses, so the confidence intervals for the relative risk of disability progression are wider than those of the rate ratios for ARR. The observed reduction in disability progression ranged from 19% to 37% for the interferons and glatiramer acetate compared to placebo and 14% to 58% for the newer DMTs, though with widely overlapping confidence intervals for most agents.

In our NMA, ocrelizumab and alemtuzumab had the greatest reduction in disability progression (53% to 58% reduction compared to placebo respectively), closely followed by daclizumab (46%) and natalizumab (44%). Dimethyl fumarate, peginterferon β-1a, interferon β-1b 250 mcg, and fingolimod were next (32% to 38%). Teriflunomide, glatiramer acetate, and the remaining interferons were less effective (14% to 28%). Four of the drugs were not significantly better than placebo (interferon β-1a 30 mcg, interferon β-1a 22 mcg, teriflunomide 7 mg, and glatiramer acetate 40 mg; credible interval contains 1.0). In the only trial of glatiramer acetate 40 mg (GALA trial), there was a non-significant trend towards greater disability progression in the glatiramer acetate 40 mg group.[16] It is unlikely that glatiramer acetate 40 mg increases disability progression. Indeed, in the three-year open-label extension of the same GALA trial, there was a trend towards a reduction in disability in the glatiramer acetate 40 mg arm, although this also was not statistically significant (HR 0.76, 95% CI 0.55-1.04, p=0.09).[17]

A forest plot summarizing the relative risks and 95% credible intervals for each drug compared to placebo is below (Figure 4). The credible intervals for most of the drugs are quite wide, highlighting the limitations of indirect evidence to distinguish one drug or set of drugs from the others. This also reflects the small number of patients with disability progression due to the relatively short follow-up and small size of most of the trials. In the league table (Table 7), which compares each DMT to the others, alemtuzumab, ocrelizumab, and daclizumab, are significantly better than at least one other DMT aside from glatiramer acetate 40 mg (interferon β-1a 30 mcg).

Figure 4. Forest Plot of DMTs vs. Placebo for Disability Progression



Legend: The diamonds represent the point estimate from the NMA for the relative risk of disability progression for each drug compared to placebo and the horizontal bars represent the 95% credible intervals. Any numbers less than 1 indicate a reduction in disability progression compared to placebo.

The credible intervals for each of the drugs in the EDSS progression forest plot above are wider than the corresponding credible intervals for relapse rates. Thus, it is difficult to distinguish between the drugs based on disability progression with a high level of certainty. Alemtuzumab and ocrelizumab appear to be most effective, but the relative risk for disability progression is not statistically significant for alemtuzumab compared to ocrelizumab, daclizumab, natalizumab, dimethyl fumarate, peginterferon β-1a, interferon β-1b 250 mcg, fingolimod, and teriflunomide 14 mg (see Table 7). Alemtuzumab is superior to interferon β-1a (22, 44, and 30 mcg doses), teriflunomide 7 mg, and glatiramer acetate (20 and 40 mg doses).

Table 7 below includes a complete set of pairwise comparisons for all agents included in the network.

Table 7. League Table for Disability Progression, Base Case

ALE															
0.91 (0.54-1.51)	OCR														
0.78 (0.43-1.42)	0.86 (0.47-1.60)	DAC													
0.76 (0.39-1.43)	0.84 (0.43-1.59)	0.97 (0.54-1.7)	NAT												
0.68 (0.38-1.17)	0.75 (0.41-1.31)	0.87 (0.53-1.38)	0.89 (0.53-1.49)	DMF											
0.67 (0.33-1.36)	0.74 (0.37-1.51)	0.86 (0.45-1.64)	0.88 (0.47-1.73)	0.99 (0.56-1.83)	PEG										
0.64 (0.37-1.14)	0.71 (0.40-1.27)	0.83 (0.52-1.33)	0.85 (0.51-1.47)	0.95 (0.64-1.49)	0.96 (0.53-1.77)	IFNß-1b 250 mcg									
0.62 (0.35-1.07)	0.68 (0.38-1.20)	0.79 (0.50-1.24)	0.82 (0.49-1.36)	0.91 (0.61-1.38)	0.92 (0.51-1.63)	0.97 (0.62-1.43)	FIN								
0.59 (0.33-1.04)	0.65 (0.36-1.17)	0.76 (0.46-1.22)	0.78 (0.46-1.32)	0.87 (0.56-1.35)	0.88 (0.48-1.57)	0.92 (0.57-1.41)	0.95 (0.63-1.45)	TER 14 mg							
0.58 (0.40-0.82)	**0.64 (0.44-0.92)**	0.75 (0.46-1.17)	0.77 (0.46-1.30)	0.86 (0.57-1.32)	0.86 (0.47-1.56)	0.90 (0.59-1.35)	0.94 (0.62-1.42)	0.99 (0.63-1.54)	IFNß-1a 44 mcg						
0.57 (0.34-0.92)	0.63 (0.37-1.04)	0.73 (0.47-1.10)	0.75 (0.46-1.22)	0.84 (0.60-1.19)	0.85 (0.47-1.47)	0.89 (0.63-1.17)	0.92 (0.64-1.32)	0.97 (0.65-1.44)	0.98 (0.70-1.35)	GA 20 mg					
0.53 (0.32-0.86)	**0.59 (0.35-0.97)**	**0.68 (0.48-0.94)**	0.70 (0.43-1.12)	0.79 (0.54-1.13)	0.79 (0.45-1.36)	0.83 (0.57-1.15)	0.86 (0.62-1.18)	0.90 (0.61-1.32)	0.92 (0.65-1.27)	0.93 (0.71-1.23)	IFNß-1a 30 mcg				
0.52 (0.29-0.90)	0.57 (0.32-1.01)	0.67 (0.38-1.15)	0.69 (0.38-1.25)	0.77 (0.46-1.29)	0.78 (0.40-1.47)	0.81 (0.47-1.34)	0.84 (0.51-1.40)	0.88 (0.52-1.50)	0.89 (0.58-1.38)	0.91 (0.58-1.47)	0.98 (0.62-1.56)	IFNß-1a 22 mcg			
0.49 (0.28-0.86)	**0.54 (0.30-0.95)**	0.63 (0.39-1.01)	0.65 (0.39-1.08)	0.73 (0.48-1.11)	0.73 (0.40-1.30)	0.77 (0.48-1.16)	0.80 (0.53-1.19)	0.83 (0.61-1.14)	0.85 (0.55-1.30)	0.86 (0.59-1.27)	0.92 (0.64-1.35)	0.95 (0.56-1.58)	TER 7 mg		
0.36 (0.18-0.73)	**0.40 (0.20-0.81)**	**0.46 (0.24-0.88)**	**0.48 (0.25-0.93)**	**0.54 (0.30-0.98)**	0.54 (0.26-1.10)	0.56 (0.30-1.02)	0.58 (0.33-1.06)	0.61 (0.34-1.12)	0.62 (0.34-1.13)	0.63 (0.36-1.13)	0.68 (0.39-1.21)	0.69 (0.36-1.36)	0.73 (0.41-1.34)	GA 40 mg	
0.42 (0.25-0.68)	**0.47 (0.28-0.76)**	**0.54 (0.36-0.78)**	**0.56 (0.37-0.84)**	**0.62 (0.46-0.84)**	0.63 (0.37-1.02)	**0.66 (0.46-0.89)**	**0.68 (0.51-0.90)**	**0.72 (0.52-0.97)**	**0.73 (0.52-0.99)**	**0.74 (0.58-0.94)**	0.79 (0.63-1.00)	0.81 (0.52-1.23)	0.86 (0.63-1.14)	1.17 (0.69-1.92)	Placebo

Legend: The DMTs are arranged from most effective (top left) to least effective (bottom right) Each box represents the estimated rate ratio and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in bold signify that the 95% credible interval does not contain 1.

We performed subgroup analyses to evaluate the effect of study quality, length of follow-up, trial size, the criteria used to define clinically-definite MS (Poser vs. McDonald), and the definition of confirmed disability progression (12-week, 24-week) (Appendix Table D5-D6). There were several DMTs (interferon β-1a 44 mcg, alemtuzumab, ocrelizumab) with substantial changes in the summary estimates for the relative risk for disability progression in the subgroup analysis of trials using the McDonald criteria for MS. The summary relative risk for interferon β-1a 44 mcg increased from 0.73 to a non-significant 1.15 under the McDonald criteria. This is due to the exclusion of the earlier placebo controlled trials that demonstrated the effectiveness of interferon β-1a 44 mcg. This change also affected the estimates for alemtuzumab and ocrelizumab because the phase III trials of the two drugs were head-to-head trials with interferon β-1a 44 mcg. When open-label trials are excluded, the estimate for alemtuzumab substantially improved (RR 0.19 instead of 0.42). These differences may represent chance findings because of the small numbers of trials in the network for each drug, but add uncertainty to comparisons of older trials that used the Poser diagnostic criteria to the results of trials that used newer criteria to recruit participants.

We also performed meta-regression to evaluate the effect of trial-level baseline patient characteristics (duration of MS, EDSS score at baseline, relapses in the prior year) on the NMA results. There were no important changes identified (Appendix Table D5), although there were some small changes in the ordering of DMTs. For example, daclizumab and natalizumab sometimes switched rank order.

The results from our NMA for disability progression are similar to those reported in four earlier NMAs despite somewhat different definitions of disability progression (see Table 8 below).[27-30] The Cochrane and CADTH NMAs used confirmed disability progression sustained at 24 weeks for their analyses.[29,30] Tolley et al. and Fogarty et al. reported separate analyses for confirmed disability progression sustained at 12 weeks and 24 weeks. As described earlier, our analysis preferentially used confirmed disability progression sustained at 24 weeks, but included confirmed disability progression sustained at 12 weeks when the preferred outcome was not available. There are modest differences which reflect the different approaches used for the analysis (frequentist versus Bayesian, the choice of outcomes, and the set of included studies). The Cochrane review was done in 2014 and is the only NMA that used a frequentist approach. CADTH included fewer trials because they reviewed DMTs that were approved in Canada at the time of the review and it is the oldest of the NMAs (2013). The Tolley analysis limited studies to the interferons and glatiramer acetate. The Fogarty NMA was the most recent NMA so its results are generally closer to the ICER results for relapses because many of the same trials were included in both NMAs. The estimates for disability progression differ by definition of confirmed disability progression (12 versus 24 weeks).

Table 8. Relative Risk Estimates for Disability Progression in Network Meta-Analyses of DMTs Compared to Placebo for RRMS

Drug	Cochrane	CADTH	Tolley 12-week	Tolley 24-week	Fogarty 12-week	Fogarty 24-week	ICER 24/12
Interferon β-1a 30 mcg (Avonex)	0.93	0.87	0.79	0.81	0.81	0.71	0.79
Interferon β-1b 250 mcg (Betaseron)	0.79	0.74	0.82	0.54	0.83	0.31	0.66
Glatiramer acetate (Copaxone)							
20 mg QD	0.77	0.83	0.82	0.70	0.81	0.75	0.74
40 mg TIW							1.17
Interferon β-1a (Rebif)	0.86						
22 mcg		0.89	0.77	NR	0.81	NR	0.81
44 mcg		0.84	0.69	0.78	0.72	0.77	0.73
Peginterferon β-1a (Plegridy)	0.89	NR	NR	0.43	0.62	0.45	0.63
Daclizumab (Zinbryta)	0.79	NR	NR	NR	NR	NR	0.54
Fingolimod (Gilenya)	0.86	0.76			0.75	0.69	0.68
Teriflunomide (Aubagio)	0.87						
7 mg		0.85	NR	NR	0.72	NR	0.86
14 mg		0.80	NR	NR	NR	NR	0.72
Dimethyl fumarate (Tecfidera)	0.80	0.73	NR	NR	0.62	0.65	0.62
Natalizumab (Tysabri)	0.64	0.67	NR	NR	0.55	0.46	0.56
Alemtuzumab (Lemtrada)	0.35	0.56	NR	NR	0.32	0.41	0.42
Ocrelizumab (Ocrevus)	NR	NR	NR	NR	NR	NR	0.47
Rituximab (Rituxan)	NR	NR	NR	NR	NR	NR	NR

NR: not reported

It is worth highlighting again the many sources of uncertainty that underlie the results of the NMA. The confidence intervals provide one measure of uncertainty, but don't fully reflect the uncertainty introduced by the assumptions that underlie the analysis. As we noted earlier, the populations in the trials vary somewhat, with the clearest difference represented by the decrease in the ARR over time. Patients at lower risk for relapses are now being included in the trials. In addition, the diagnostic criteria for MS have evolved over time; the trials use different definitions for relapses and confirmed disability over time; MRI technology has improved; and the individual trials vary in quality. All of these factors can introduce inconsistency in the network. These concerns apply to both NMAs (relapse rates, disability progression).

MRI Outcomes

MRI findings are used in the diagnosis and management of MS; many clinicians also feel they have the potential to serve as surrogate outcomes for relapse rates and disability progression. It is, however, difficult to compare MRI findings across trials because of variability in how MRI measures

were performed and reported. Many of the early trials did not report MRI outcomes, and the trials that did reported a variety of outcomes, including: gadolinium-enhancing T1 lesions, new T2 lesions, new and expanding T2 lesions, the volume of T2 lesions, the cumulative total number for lesions, and brain volume changes. In some studies, MRIs were performed monthly, while in others they were performed annually or not at all. Study centers used different machines, with different protocols for image acquisition and processing, all of which can change the appearance of lesions. There is also a lack of data from trials demonstrating that MRI changes predict patient outcomes.

Sormani and colleagues conducted a comprehensive meta-analysis of MRI outcomes in 54 comparative randomized trials in more than 25,000 patients with RRMS, which updated a prior meta-analysis.[102,103] The authors highlighted a strong correlation between the ratio of the average number of MRI lesions in the experimental and control groups with the ratio of the ARR in the experimental and control groups (R^2=0.74). The investigators did not rank order the studied drugs based on this analysis; rather, they argued that regulatory agencies should allow the use of MRI outcomes as a surrogate for relapse rates in RRMS trials, which would allow for shorter, less expensive trials and the more rapid approval of new therapies. They acknowledged the possibility of the ecological fallacy in this analysis, but pointed to examples of clinical trials that performed analyses at the individual patient level that reported about 60% of the drug's effect on relapse rates was mediated through MRI findings.

In contrast, the evidence that MRI findings predict disability progression is relatively weak. For example, in the 16-year follow-up of the pivotal interferon β-1b trial, MRI changes during the trial explained none of the variability in disability progression.[104] MRI technology has evolved significantly since the start of that trial, but validation of the clinical utility of a standardized approach to MRI assessment in MS remains a work in progress.

Quality of Life / Patient-Centered Outcomes

Quality of life is worse in patients with MS compared to age- and sex-matched individuals in the general population.[18,19] Quality of life correlates with EDSS scores: as EDSS scores increase, quality of life declines. In general, studies of DMTs for MS have focused on reducing relapses and disability progression, not quality of life. The depression, fatigue, musculoskeletal, and urinary symptoms that patients with MS experience are usually managed by other interventions. Treatments for depression in MS include conventional antidepressant medications, cognitive behavioral therapy, and mindfulness. Treatments for fatigue include amantadine, methylphenidate, and modafinil. Physical therapy, anti-spasticity drugs, medical devices, and botulinum toxin are all employed to help address musculoskeletal and urologic needs. At high-quality MS centers, multidisciplinary teams employ multiple modalities to help improve these outcomes.

Quality of life outcomes were sparsely reported in the pivotal randomized trials of DMTs. Trials reporting QoL outcomes used a variety of instruments including the European Quality of Life 5

Dimensions (EQ-5D) Index and Visual Analog Scale, the Short Form 12 and 36 questionnaires (SF-12, SF-36), the Multiple Sclerosis Impact Scale (MSIS-29), the Beck Hopelessness scale, the Center for Epidemiologic Studies depression mood scale, the Global Health Questionnaire, the Treatment Satisfaction Questionnaire, and the Fatigue Impact Scale. The studies that reported outcomes using these instruments are summarized in Table 9 below. The measures that were statistically significant are noted with an asterix. No one measure was used consistently across the trials. The most commonly reported measures were the EQ-5D and the SF-36. Most of the trials reporting SF-36 results found significant improvements in the Physical Component Summary Scale (PCS), but not the Mental Component Summary Scale. The same trend appears on the MSIS-29, though there are fewer studies. During relapses, quality of life decreases. Thus, the primary intermediate-term quality of life benefits from the DMTs appear to be physical and correlates with changes in level of disability. The few trials that reported fatigue and depression measures did not find consistent improvements with DMTs compared to placebo.

Since there was no quality of life measure used consistently in the trials, no summary estimates or comparisons across DMTs are possible. The magnitude of the benefit, when found, was generally small. For example, in the AFFIRM study, 25% of patients randomized to natalizumab had a clinically important improvement of the PCS subscale of the SF-36 compared to 17% of patients randomized to placebo; 18% of patients randomized to natalizumab had a clinically important worsening of the PCS compared to 25% of patients randomized to placebo.

Table 9. Patient Reported and Quality of Life Outcomes

Measure	GA 20 mg	IFN β-1a 22, 44 mcg	PEG	FIN	TER 7, 14 mg	DMF	DAC	NAT	ALE	OCR
EQ-5D Index	CONFIRM		ADVANCE	FREEDOMS II	TEMSO	CONFIRM DEFINE	SELECT* DECIDE*		CARE MS I CARE MS II	
EQ-5D VAS			ADVANCE	FREEDOMS II		DEFINE*	SELECT* DECIDE*		CARE MS I CARE MS II*	
SF-36	CONFIRM - PCS* - MCS				TOWER - PCS 7, 14 - MCS 7, 14*	CONFIRM - PCS* - MCS DEFINE - PCS* - MCS		AFFIRM - PCS* - MCS*	CARE MS I - PCS - MCS CARE MS II - PCS* - MCS	OPERA I - PCS OPERA II - PCS* ORATORIO - PCS
SF-12			ADVANCE				SELECT* DECIDE			
MSIS-29			ADVANCE				SELECT Physical* Mental DECIDE Physical* Mental*			
FIS				FREEDOMS II	TEMSO TENERE 7*, not 14 TOWER					
PRIMUS				FREEDOMS II						
Beck HS		PRISMS								
CES-D		PRISMS								
GHQ		PRISMS								
TSQM					TENERE*					
GWB VAS	CONFIRM*					CONFIRM* DEFINE*		AFFIRM*		
FAMS									CARE MS I* CARE MS II*	

* p<0.05

EQ-5D: European Quality of Life 5 Dimensions; VAS: Visual Analog Scale; SF-36: Short Form 36; PCS: Physical Component Summary; MCS: Mental Component Summary; SF-12: Short Form 12; MSIS-29: xxx; MSQOL 54: Multiple Sclerosis Quality of Life 54; FIS: Fatigue Impact Scale; SIP: Sickness Impact Profile; PRIMUS: Patient Reported Indices in Multiple Sclerosis; Beck HS: Beck Hopelessness Scale; CES-D: Center for Epidemiologic Studies Depression Scale; GHQ: Global Health Questionnaire; TSQM: Treatment Satisfaction Questionnaire for Medication; GWB VAS: Global Well Being Visual Analog Scale; FAMS: Functional Assessment of Multiple Sclerosis.

Harms

The harms of the DMTs are summarized in Table 10. In the randomized trials, specific SAEs were generally uncommon (<1% of treated patients) and not statistically different from the control group, whether active or placebo. However, a number of potentially life-threatening harms have been identified from post-marketing data leading to Black Box warnings for five of the DMTs. For non-serious AEs, flu-like symptoms were more common in patients treated with interferons, injection site reactions were more common for all of the injectable agents, and infusion reactions were more common for the infused agents. Fingolimod has first dose cardiac effects that must be monitored. However, it is the less common, more serious AEs that cause the greatest concerns for both patients and their treating providers.

Table 10. Harms of DMTs

Drug (Brand name)	Major safety concerns	D/C rates	SAEs
Subcutaneous injections			
Interferon β-1a 30 mcg (Avonex)	Depression, suicide, psychosis, liver toxicity, seizures, allergic reactions, CHF, ↓ peripheral blood counts, thrombotic microangiopathy, flu-like symptoms are common (49%)	4%	14%
Interferon β-1b 250 mcg (Betaseron, Extavia)	Liver toxicity, allergic reactions, depression, suicide, CHF, injection site necrosis (4%), leukopenia, thrombotic microangiopathy, flu-like symptoms are common (57%)	6%	11%
Glatiramer acetate (Copaxone, Glatopa)	Post-injection reaction (16%), transient chest pain (13%), lipoatrophy, skin necrosis, injection site reactions	3%	13%
Interferon β-1a 22/44 mcg (Rebif)	Depression, suicide, livery injury, allergic reactions, ↓ peripheral blood counts, thrombotic microangiopathy, seizures, injection site reactions common (~90%), injection site necrosis (3%), flu-like symptoms are common (59%)	5%	16%
Peginterferon β-1a (Plegridy)	Liver toxicity, depression, suicide, seizures, allergic reactions, CHF, ↓ peripheral blood counts, thrombotic microangiopathy, flu-like symptoms are common (47%)	5%	11%
Daclizumab (Zinbryta)	↑ risk of infection and skin reactions. Hypersensitivity reactions, depression, and suicide. Boxed warning: significant hepatic injury (0.7%), autoimmune hepatitis (0.3%), other immune mediated disorders. Serious immune-mediated reactions in 5% of patients. Only available through **REMS**.*	15%	22%
Oral agents			
Fingolimod (Gilenya)	1st dose bradycardia, ↑ risk of serious infection, PML, macular edema, PRES, ↓ respiratory function (↓FEV1), liver toxicity, ↑BP, basal cell carcinoma (2%). **REMS requirement lifted in late 2016.***	12%	10%

Drug (Brand name)	Major safety concerns	D/C rates	SAEs
Teriflunomide (Aubagio)	Boxed warning for hepatotoxicity (including fatal liver failure) and teratogenicity. ↓ WBC, possible infection risk, peripheral neuropathy (1.4 – 1.9%); ↑ BP (3-4%). Hair thinning.	13%	13%
Dimethyl fumarate (Tecfidera)	Anaphylaxis, angioedema, PML, ↓ WBC, liver injury, flushing (40%)	14%	18%
Intravenous infusions			
Natalizumab (Tysabri)	Boxed warning for PML. ↑ risk for herpes encephalitis and meningitis, liver toxicity, hypersensitivity (including anaphylaxis) reactions, ↑ risk of infection. Only available through **REMS.***	6%	19%
Alemtuzumab (Lemtrada)	Boxed warning for serious (sometimes fatal) autoimmune conditions such as ITP, life-threatening infusion reactions, may ↑ risk of malignancies. Infusion reactions (92%), rash (53%), lymphopenia (99.9%). Only available through **REMS**.*	2%	13%
Ocrelizumab (Ocrevus)	It is unknown if there will be a Boxed Warning as ocrelizumab is not yet FDA approved. Risk of infection, possible ↑ risk for PML (due to similarity in mechanism to rituximab and ofatumumab)[20]	4%	7%
Rituximab (Rituxan)	Boxed warning for fatal infusion reactions within 24 hours of infusion, severe mucocutaneous reactions (including fatalities), HBV reactivation, PML (all for non-MS indications). ↑ risk of infection, ↑ risk of cardiac arrhythmia, bowel obstruction, cytopenias	4%	13%

BP: blood pressure, CHF: congestive heart failure, D/C rates: discontinuation due to adverse events, FEV1: forced expiratory volume in 1 second, HBV: hepatitis B virus, ITP: idiopathic thrombocytopenic purpura, PRES: posterior reversible encephalopathy syndrome, PML: progressive multifocal leukoencephalopathy, WBC: white blood cell count

*REMS: Risk Evaluation and Mitigation Strategy

Because of the very serious potential AEs, four of the drugs have been prescribed under the FDA's Risk Evaluation and Mitigation Strategy (REMS). A REMS is a safety strategy to manage a known or potential serious risk associated with a drug in order to allow patients continued access to the drug by managing its safe use. The goal is to ensure that the benefits of the drug outweigh the risk. Because the risk profile for each drug is different, the REMS for each drug is also different. The REMS for natalizumab focuses on the risk for PML. The REMS for alemtuzumab focuses on the risks for autoimmune blood, thyroid and kidney diseases, infusion reactions, and malignancies. The REMS for fingolimod has been lifted, but focused on bradyarrythmias, herpes virus infections, liver injury, pulmonary function, and macular edema. Finally, the REMS for daclizumab focuses on liver toxicity and autoimmune skin, gastrointestinal, and lymph diseases.

Three of these four drugs carry black box warnings (natalizumab, alemtuzumab, and daclizumab. Two other DMTs carry black box warnings: teriflunomide for hepatotoxicity and teratogenicity; and

rituximab for fatal infusion reactions, hepatitis B virus (HBV) reactivation, and PML based on its use for the treatment of B-cell lymphomas. It is not known whether the FDA will require a black box warning or REMS for ocrelizumab.

There are case reports of PML with several of the DMTs (fingolimod, dimethyl fumarate, natalizumab, rituximab), but natalizumab is the only FDA-indicated DMT with a black box warning for PML due to the much greater risk associated with its use. Studies have identified three risk factors for PML in patients treated with natalizumab: positive antibodies for the JC virus, prior immunosuppressive therapy (e.g., mitoxantrone, methotrexate, azathioprine, cyclophosphamide, mycophenolate), and length of time on natalizumab (> 2 years).[21] The incidence of PML varies from < 0.09 per 1000 patients for JC virus antibody-negative patients to 11.1 per 1000 patients for JC virus antibody-positive patients on natalizumab for 2 to 4 years with prior exposure to immunosuppressive drugs (~120-fold difference in risk).[21]

Follow-up studies of alemtuzumab confirm the high risk for autoimmune disease. In one cohort, 47% of participants developed autoimmune disease over an average of 6.1 years of follow-up.[20] This included autoimmune thyroid disease in 35% of all patients and idiopathic thrombocytopenic purpura in 3%. No cases of PML were observed in this study. The most common infections were urinary tract infections (12%) and herpes zoster (8%). In the extension of the TRANSFORMS study of fingolimod beyond one year, the AEs were similar to those observed in the original trial.[105] Two patients met formal criteria for hepatotoxicity and discontinued the drug. Basal cell carcinoma (9 patients) and lymphopenia (9 patients) were the other two common AEs leading to drug discontinuation. The 15-year extension trial of glatiramer acetate and the 21-year extension trial of interferon β-1b did not identify any new significant adverse events.

Because of the risk for serious adverse events, both alemtuzumab and daclizumab's FDA indications state that they "should generally be reserved for patients who have had an inadequate response to two or more drugs indicated for the treatment of MS. Similarly, the FDA indication for natalizumab originally stated "Tysabri is generally recommended for patients who have had an inadequate response to, or are unable to tolerate, an alternate MS therapy." It now reads "Tysabri increases the risk of PML. When initiating and continuing treatment with Tysabri, physicians should consider whether the expected benefit of Tysabri is sufficient to offset this risk. "

Balancing the benefits and harms is challenging for both patients and their providers, as the more powerful drugs are more effective, but carry with them higher risks for life-threatening complications.

Controversies and Uncertainties

Several limitations to the evidence base reduced our ability to make confident judgments about the comparative net health benefits of DMTs for MS. First, the evolving diagnostic criteria for clinically-

definite MS over the decades of clinical trials of DMTs caused important variation among the studied patient populations. Many patients enrolled in trials that used the McDonald criteria would have been diagnosed with CIS under the Poser criteria. Prior analyses have also demonstrated a decrease in ARRs and risk of disability progression in the clinical trial populations over the past 25 years.[22-26] There is not consensus about the reason or reasons for the observed change in rates. However, the relative benefits of DMTs appear similar across these different populations. There is no convincing evidence of effect modification by risk for relapse.

A second limitation was the short follow-up of the randomized trials. The important clinical impacts of MS must be measured over decades and European research guidelines recommend 5-year trials. However, the majority of the RCTs followed patients for 1 or 2 years before unblinding. While long-term extension trials demonstrate continued DMT efficacy over time, the true impact of individual drugs is difficult to assess because loss to follow-up introduces selection bias and unblinding introduces measurement bias and differential co-interventions. The short follow-up time in the trials most directly impacted the estimates of sustained disability progression, as demonstrated by the wide credible intervals that often included 1 in the ICER NMA.

Ideally, comparative effectiveness assessments are informed by information from large, high-quality, head-to-head trials. Although NMAs may be performed in the absence of such evidence, the assumptions that are necessary to perform indirect comparisons through common comparators introduce additional uncertainty. In general, our NMA results mirror the findings of the available head to head trials. Additionally, many of the trials were not double-blinded so the ascertainment of both relapses and disability progression required judgments on the part of patients and clinicians that could be influenced by knowledge of treatment group.[106,107] The open-label trials were also potentially subject to ascertainment bias.

It would also have been preferable to compare first-line therapies to each other and second-line therapies to each other, but the lack of conclusive FDA indications, clinical guidelines, or RCT entry criteria precluded those types of comparisons. Several drugs, by virtue of their potentially life-threatening side effects (e.g., natalizumab, alemtuzumab, fingolimod, daclizumab) are often considered second- or third-line agents, but many patients and clinician organizations have advocated for their first-line use due to their higher efficacy than the interferons and glatiramer acetate. Furthermore, the clinical trials for these drugs largely recruited treatment-naïve patients. Several trials included a mix of treatment naïve and experienced patients, but only one of the 33 reviewed RCTs studied a population in which 100% of the participants had been treated with at least one DMT.[90]

Similarly, there is no widely accepted definition for a patient who is at high risk for rapid progression of their MS, despite the identification of many risk factors. Experts have suggested that the highly effective, but risky medications such as alemtuzumab and natalizumab should be used

early in high-risk patients. The lack of a clear definition of high risk raises the possibility for significant practice variation in the use of highly effective agents that is not supported by evidence. Some patients may not receive appropriate treatment and others will be treated who are unlikely to benefit from the higher-risk agents.

In the NMA and in the model below, we treated all of the DMTs equally, as if each could be used as first line therapy. In reality, most insurance plans support using one of the interferons or glatiramer acetate as first line therapy and the FDA indications for alemtuzumab, daclizumab, and natalizumab discourage their use as first line therapy.

Finally, the results of the randomized trials of ocrelizumab for patients with RRMS and PPMS are encouraging, but ocrelizumab has not yet received FDA approval. Thus, there is no real-world data to assess uncommon, serious adverse events and to corroborate the findings of the clinical trials performed for regulatory approval. In addition, the independent review of the full set of clinical trial data performed by the FDA will be invaluable in assessing the balance of risks and benefits for ocrelizumab. Furthermore, the limited numbers of patients and short follow-up among those treated with ocrelizumab add to the uncertainty about rare, but serious adverse events that may not be fully appreciated until post-marketing data are available. It is the only DMT under consideration in this review that has no real-world data on safety.

Summary

RRMS: DMTs Compared to Best Supportive Care

From the patient perspective, the most important outcome is the prevention of disability progression, followed by a reduction in relapses. Patient-centered outcomes such as quality of life are also of great interest to patients, though they are sparsely and inconsistently reported in the pivotal trials, and we were unable to arrive at any judgments of the comparative effectiveness of DMTs on these outcomes. The data on relapse rates and disability progression are most robust comparing DMTs to placebo. Of all the agents included in this review, alemtuzumab, natalizumab, and ocrelizumab were the most effective drugs in reducing relapses and they were significantly better than the other DMTs. They were also three of the top four most effective drugs at reducing disability progression, although the separation from other DMTs was not as substantial. The differences in efficacy between the alemtuzumab, natalizumab, and ocrelizumab were relatively small and non-significant. We gave alemtuzumab and natalizumab an "A" rating - high certainty of a moderate to large net health benefit. The primary factor distinguishing the two drugs, apart from mechanism of action, is their unique risks for adverse events. Patients treated with natalizumab are at high risk for PML and must be monitored closely for its signs and symptoms of PML and other infections. Patients treated with alemtuzumab are at risk for life-threatening ITP, infusion reactions, and less severe, but common autoimmune thyroid diseases. Among JC virus antibody negative patients, who are at lower risk for PML, natalizumab is safer and equally effective. For JC

virus antibody-positive patients, the risk for PML generally precludes the use of natalizumab. We gave ocrelizumab a B+ rating (incremental or better net health benefits when compared to placebo) because of additional uncertainty with pending FDA approval and the lack of real-world experience with the drug.

The next most effective group for relapse reduction included daclizumab, rituximab, fingolimod, and dimethyl fumarate. There is only one small trial of rituximab with no data on disability progression, but impressive MRI data, so we judge the evidence on rituximab to be promising, but inconclusive (P/I). We judge daclizumab, fingolimod, and dimethyl fumarate to produce incremental or better net health benefits ("B+"); although point estimates of their benefits may be slightly less than those of ocrelizumab, there is substantial overlap of all four agents' credible intervals compared with one another in both ARR and disability progression NMAs. Daclizumab, fingolimod, and dimethyl fumarate have some real-world experience, but substantially less than the interferons and glatiramer acetate. Of the three, dimethyl fumarate may have a lower risk for very serious adverse events because it does not carry a black box warning, nor is its use monitored under a REMS program.

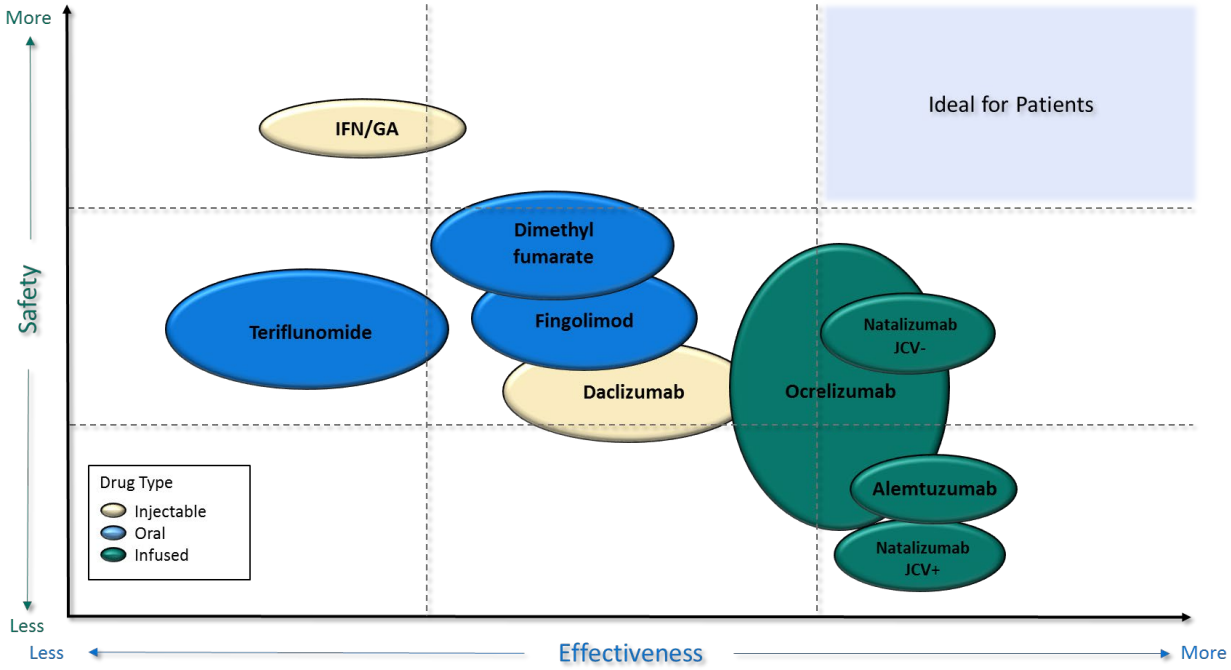
Finally, our NMA suggested that the interferons, glatiramer acetate, and teriflunomide were substantially similar with respect to their effects on ARR and disability progression. Each of the four prior NMAs came to the same conclusion either about the interferons and glatiramer acetate[27], or those agents plus teriflunomide.[28-30] In addition, a 2017 systematic review of 36 observational trials with data from more than 32,000 patients concluded that the interferons show similar effectiveness in real world practice.[31] All are effective at reducing relapses and have good safety profiles with decades of treatment experience to support their safety. There are small differences among the agents. For instance, the higher doses of interferon β-1a and teriflunomide are consistently more effective than the lower doses. Some of the injectable DMTs can be dosed less frequently and teriflunomide is taken orally. These differences be important for patients when choosing among different options, but the clinical differences in important outcomes are small. As such, we judged with high certainty that these nine DMTs provide incremental net health benefits compared to best supportive care ("B").

Table 11. ICER rating on the Comparative Net Health Benefit of DMTs for RRMS Compared to Best Supportive Care

Drug	ICER rating
Injectable Agents	
Interferon β-1a 30 mcg (Avonex)	B
Interferon β-1b 250 mcg (Betaseron, Extavia)	B
Glatiramer acetate 20 mg (Copaxone)	B
Glatiramer acetate 40 mg (Copaxone)	B
Interferon β-1a 22 mcg (Rebif)	B
Interferon β-1a 44 mcg (Rebif)	B
Peginterferon β-1a (Plegridy)	B
Daclizumab (Zinbryta)	B+
Oral Agents	
Fingolimod (Gilenya)	B+
Teriflunomide 7 mg (Aubagio)	B
Teriflunomide 14 mg (Aubagio)	B
Dimethyl fumarate (Tecfidera)	B+
Infused Agents	
Natalizumab (Tysabri)	A
Alemtuzumab (Lemtrada)	A
Ocrelizumab (Ocrevus)	B+
Rituximab (Rituxan)	P/I

Figure 5 below qualitatively summarizes the relative safety and effectiveness of the DMTs for RRMS. Each drug or group of drugs is represented by an oval. The width of the oval reflects uncertainty about its overall effectiveness and the height of the oval represents uncertainty about the safety of the drug. The safest drugs are highest on the graph and the most effective are to the right. Thus alemtuzumab, which was consistently the most effective drug, is on the right side of the figure but relatively low. The interferon/glatiramer acetate group is on the upper left as those DMTs are among the safest, but least effective. The ideal DMT, both safe and highly effective, would be to the upper right.

Figure 5. Safety and Effectiveness of DMTs for RRMS



Wider and taller shapes indicate greater uncertainty. Not drawn to scale.

RRMS: Newer DMTs Compared to Interferons and Glatiramer Acetate

The comparison of the newer agents to the interferons and glatiramer acetate is of greater interest to many stakeholders (Table 12). Alemtuzumab significantly reduces relapses and disability progression compared to the early injectable DMTs, but carries significant risks for life-threatening complications. We judge it to incremental or better compared to the earlier DMTs (B+). Natalizumab also significantly reduces relapse rates compared to the early injectable agents, but is not significantly better than most for disability progression. The AFFIRM trial demonstrated a large decrease in disability progression compared with placebo, but there are no large randomized trials comparing natalizumab to another DMT. Given the lack of direct comparative trial results, the availability of data from only a single trial, and the additional harms associated with natalizumab, we judge it to be incremental or better when compared to the injectable DMTs (B+). Daclizumab, fingolimod, and dimethyl fumarate significantly reduced relapses compared to the early injectable DMTs, but are not significantly better at reducing disability progression. They all have greater risks for life-threatening adverse events than the earlier DMTs. Thus, we judge them to be comparable or better when compared to the injectable DMTs (C+).

As noted above, there is only one small trial of rituximab compared to placebo with no data on disability progression, but impressive MRI data. We judge the evidence on rituximab to be promising, but inconclusive (P/I). Ocrelizumab significantly reduces relapses and disability

progression compared to the interferons and glatiramer acetate. To date, it has few know severe adverse events. However, there is no real-world evidence supporting its efficacy. Thus, we judge it to produce incremental or better net health benefits when compared to the earlier agents, a "B+" rating. The ARR and disability progression for teriflunomide were not significantly different compared with the interferons and glatiramer acetate. It has the advantage of being an oral agent, but has a boxed warning for hepatotoxicity and has other important side effects. Overall, we judge that teriflunomide has comparable net health benefits (C) to the interferons and glatiramer acetate.

Table 12. ICER Rating on the Comparative Net Health Benefit of Newer DMTs for RRMS Compared to the Interferons and Glatiramer Acetate

Drug	ICER rating
Injectable Agents	
Daclizumab (Zinbryta)	C+
Oral Agents	
Fingolimod (Gilenya)	C+
Teriflunomide 7 mg (Aubagio)	C
Teriflunomide 14 mg (Aubagio)	C
Dimethyl fumarate (Tecfidera)	C+
Infused Agents	
Natalizumab (Tysabri)	B+
Alemtuzumab (Lemtrada)	B+
Ocrelizumab (Ocrevus)	B+
Rituximab (Rituxan)	P/I

RRMS: Additional Key Comparisons

We were aware of specific interest in the comparative effectiveness of interferon β-1a 44 mcg SC TIW (Rebif) to interferon β-1a 30 mcg IM once weekly (Avonex) because of differing judgments about the head-to-head EVIDENCE trial. In the NMA, Rebif had a significantly lower relapse rate than Avonex (RR 0.77, 95% CrI 0.65-0.88) and a non-significantly lower disability progression (RR 0.92, 95% CrI 0.65-1.27). In the EVIDENCE trial, which compared these two different formulations head to head, there were non-significant trends towards lower relapse rates (RR 0.84, 95% CI not reported, p=0.093) and disability progression (RR 0.70, 95% CI 0.39-1.25) that were similar to the findings of the NMA. The primary endpoint in the EVIDENCE trial, the proportion of patients remaining free from relapse, was lower with Rebif (HR 0.70, 95% CI 0.55-0.88, p=0.003). In addition, the MRI outcomes (number of combined unique active lesions, T1 gadolinium-enhancing lesions, and active T2 lesions) were significantly better in the patients treated with Rebif (P<0.001 for all 3 comparisons). SAEs and discontinuations due to AEs were almost identical in the two groups, but patients in the Rebif group reported more injection site reactions, liver enzyme abnormalities, and white blood cell abnormalities. Overall the differences in harms were small.

Based on these data we judge there to be moderate certainty of a small-to-substantial net health benefit for Rebif compared to Avonex, with high certainty of at least a small net health benefit (B+).

There are insufficient data to compare rituximab to ocrelizumab. The two drugs target the same molecule (CD20), but ocrelizumab is a humanized monoclonal antibody and may have fewer serious infusion reactions than rituximab. The only randomized trial of rituximab for patients with RRMS was small, short, and did not report disability progression. The reduction in relapses observed was comparable to that observed with ocrelizumab, but the confidence interval was wide. Thus, there is insufficient evidence to estimate the comparative clinical effectiveness of the two DMTs (ICER rating: I).

There are observational data suggesting that rituximab deserves further study. A Swedish study evaluated patients with RRMS treated with natalizumab who needed to change to a different DMT because they tested positive for antibodies to the JC virus.[108] Using a propensity score matched analysis, the investigators compared outcomes in patients treated with rituximab to those of patients treated with fingolimod. Over 1.5 years, 1.8% of patients treated with rituximab had a relapse compared to 17.6% of patients treated with fingolimod (HR 0.10, 95% CI 0.002-0.43). Adverse events (5% vs. 21%) and treatment discontinuation (2% vs. 28%) were also lower in the rituximab treated group. Finally contrast enhancing lesions on MRI were also lower in the rituximab group (1.4% vs. 24.2%, OR 0.05, 95% CI 0.00-0.22). These results are from an observational study, not a randomized trial, so they may be subject to selection bias and confounding by indication, but the large effect sizes and the robustness of the outcomes adjusted for known potential confounders and propensity score adjustment suggest that rituximab deserves further study.

PPMS

As described in detail in the Key Studies section, there is one placebo controlled trial of ocrelizumab (ORATORIO) and one of rituximab (OLYMPUS). For ocrelizumab, confirmed disability progression sustained for at least 12 weeks, the primary endpoint of the trial, was significantly lower than placebo (HR 0.76, 95% CI 0.59 - 0.98, p=0.03). Confirmed disability progression sustained for at least 24 weeks was also significantly lower (HR 0.75, 95% CI 0.58-0.98, p=0.04), and there was a significant reduction in the T2 lesion volume (p<0.001), faster performance of the 25-foot walk (p=0.04) and a significant improvement in the change in brain volume (p=0.02). There was no excess of adverse events associated with ocrelizumab. We judge there to be moderate certainty of small to substantial net benefit, tempered primarily by the lack of real-world experience with the drug (ICER rating B+).

For rituximab, the OLYMPUS trial was a good-quality trial that did not find a significant difference in the time to confirmed disease progression sustained for at least 12 weeks (HR 0.77, p=0.14). There was a significant reduction in the T2 lesion volume (p<0.001), but not in the change in brain volume (p=0.62). Preplanned subgroup analyses found that rituximab significantly delayed the time to

progression for patients aged < 51 years (HR 0.52, p=0.01) and in those patients with gadolinium-enhancing lesions at baseline (HR=0.41, p=0.007). Infection-associated SAEs were more common with rituximab. In summary, the trial did not meet its primary endpoint, but suggested that rituximab shows promise for younger patients with PPMS who have gadolinium-enhancing lesions on MRI. We judge the evidence for the effectiveness of rituximab in PPMS to be promising, but inconclusive (P/I).

Table 13. ICER Rating on the Comparative Net Health Benefit of DMTs for PPMS Compared to Best Supportive Care

Drug	ICER rating
Ocrelizumab (Ocrevus)	B+
Rituximab (Rituxan)	P/I

5. Other Benefits or Disadvantages

Our reviews seek to provide information on other benefits or disadvantages offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. Examples include but are not limited to:

1. Methods of administration that improve or diminish patient acceptability and adherence
2. A public health benefit, e.g., reducing new infections
3. Treatment outcomes that reduce disparities across various patient groups
4. More rapid return to work or other positive effects on productivity (if not considered a benefit as part of comparative clinical effectiveness)
5. New mechanisms of action for treatments of clinical conditions for which the response to currently available treatments varies significantly among patients for unknown reasons (substantial heterogeneity of treatment effect)

One consistent message that we heard from the patient community is the value of choice. They value choice in the route of administration, choice in the mechanism of action, and choice in the balance of risks and benefits.

The route of administration is important for patients.[33,34] For many years, their only option was regular subcutaneous injections. Many patients would prefer to take one to two pills each day rather than inject themselves with medication or be required to visit the doctor for a drug infusion, particularly when starting therapy. However, many patients who have been stable on daily injectable therapy for years choose to continue daily injections rather than switch to another agent with less frequent injections or oral administration, suggesting that once patients are comfortable with an effective drug for them, the route of administration may be less important.

Similarly, the travel and time commitment posed by an office visit to receive an IV infusion may discourage some patients from treatment with the infused agents. Conversely, avoiding regular injections or daily pills may appeal to some patients. In addition, the required contact with neurology professionals on a regular basis may enhance the overall care of their MS.

It is also important to recognize the value of having drugs with multiple mechanisms of action. MS is a heterogeneous disease, with some patients remaining stable for years while others progress rapidly. The availability of more potent drugs for those who appear to have aggressive disease is reassuring. Similarly, patients value the ability to switch to a drug with a different mechanism of action when their current therapy is not working. Currently there is no way to match an individual patient to the drug with the most appropriate mechanism of action for their individual form of MS,

but there is hope that research into the underlying mechanisms of MS will allow physicians to personize therapy in the future.

A reduction in relapse rates and disability progression also has non-medical benefits for patients, their caregivers, and society. Patients with MS are commonly in their most productive years at home, work and volunteering in the community. Relapses cause absence from work and other important life tasks. Progressive disability leads to early retirement with associated loss of income, both for the patient and for caregivers who devote time to caring for the affected individual. Improved outcomes lead to increased productivity in each of these areas. Clinical trial results do not capture these benefits of therapy.

The stress that caregivers experience in supporting patients with MS is not captured in any of the clinical trial results and is an important benefit of improvement in therapy. Relapses and progressive disability have important effects on the quality of life of the caregivers in addition to that experienced by the patient.

Ocrelizumab will likely be the first drug to receive FDA approval for the treatment of PPMS, which is an important benefit.

6. Comparative Value

6.1 Overview

The primary aim of this analysis was to estimate the lifetime cost-effectiveness of various DMTs for patients initiating treatment for 1) RRMS and 2) PPMS. The model structures for this assessment are depicted in Figure 6. The two models were developed in Microsoft Excel.

The models estimated the average amount of time that patients spent in each health state, defined by EDSS category. Unadjusted and utility-adjusted time spent in each health state were summed over a patient's remaining lifetime to provide estimates of life expectancy and quality-adjusted life expectancy; the RRMS model further estimated the frequency of relapses in each state. For pairwise comparisons in the RRMS model, generic glatiramer acetate 20 mg (Glatopa) was chosen as the universal comparator. This DMT was chosen because glatiramer acetate is the most commonly used DMT, the generic version is the lowest priced version, and there is no existing evidence to support any difference in efficacy between branded and generic versions. Cost-effectiveness ratios were also calculated versus no DMT (i.e., best supportive care). For best supportive care, we used data on the natural history progression, regression, relapse rates, and mortality from publicly available sources. Costs for best supportive care were based a previous analysis that modeled costs by EDSS state and included inpatient and outpatient admissions, office visits to physicians and other health professionals, examinations, medical devices, non-DMT drugs, and over the counter medicines. Best supportive care was used as the comparator in the PPMS model, as no medications have yet received FDA approval for this indication.

Model outcomes of interest included:

- By intervention:
    - Quality-adjusted life expectancy
    - Life expectancy
    - Relapses (RRMS model only)
- Pairwise comparisons:
    - Costs per additional QALY versus no DMT / best supportive care
    - Costs per additional QALY versus generic glatiramer acetate 20 mg
    - Costs per additional life-year versus no DMT / best supportive care
    - Costs per additional life-year versus generic glatiramer acetate 20 mg
    - Cost per relapse avoided versus no DMT / best supportive care (RRMS model only)
    - Cost per relapse avoided versus generic glatiramer acetate 20 mg (RRMS model only)

6.2 Cost-Effectiveness Model: Methods

Model Structure

We developed two Markov models, one for RRMS and one for PPMS (Figure 6), with health states based on the EDSS,[48] which has been widely used to describe MS progression in clinical trials.[109] RRMS patients may progress to secondary progressive MS (SPMS) over their lifetime; therefore, SPMS states were included in the RRMS model. The models were adapted from previously published work evaluating the cost-effectiveness of MS treatments.[110-117]

We used a natural history transition matrix and applied a relative risk for each therapy to derive DMT-specific transition probabilities between health states. This relative risk, based on the comparative clinical effectiveness analysis described above, was applied to progression probabilities for increasing EDSS states. The same relative risk was applied to progression probabilities for conversion from RRMS to SPMS, under the assumption that patients' EDSS score increased by 1 at the time of conversion from RRMS to SPMS. A rate ratio for each DMT was applied to the natural history EDSS-specific ARRs, also based on the comparative clinical effectiveness analysis described above.

The RRMS model consisted of 20 health states: EDSS 0–9 for RRMS patients, EDSS 1–9 for SPMS patients, and death (Figure 6). At baseline, a cohort of patients was distributed among the 10 RRMS health states according to the expected distribution of newly diagnosed MS patients.[87,99,118-120] These patients then transitioned between states during each one-year cycle over a lifetime time horizon, from treatment initiation until death. Patients entering the model were treatment-naïve, and began first-line treatment with one of the DMTs of interest upon entering the model. After discontinuation of the initial DMT in an RRMS or SPMS state, patients continued to a second-line treatment; after discontinuation from second-line therapy, patients transitioned to best supportive care. For patients with RRMS, EDSS scores could increase, decrease, or remain the same at each cycle; or the patient could transition to SPMS. In SPMS, EDSS scores could increase or remain the same, but were assumed not to decrease. A patient could progress to death or have a relapse from any state.

Though some DMT labels suggest use later in treatment sequences, no label precludes use as a first-line agent. Therefore, all DMTs were modeled as such for completeness. In the case of MS, there is no standard recommended treatment sequence in DMT labels, published literature, or clinical guidelines. It is not feasible to model every potential combination of DMTs over time; therefore we chose a more parsimonious model structure. We chose to use an average second-line approach, described below, that aggregates second-line treatments over all patients. Additionally, although patients may not often move to supportive care after only two DMTs, there is limited data with

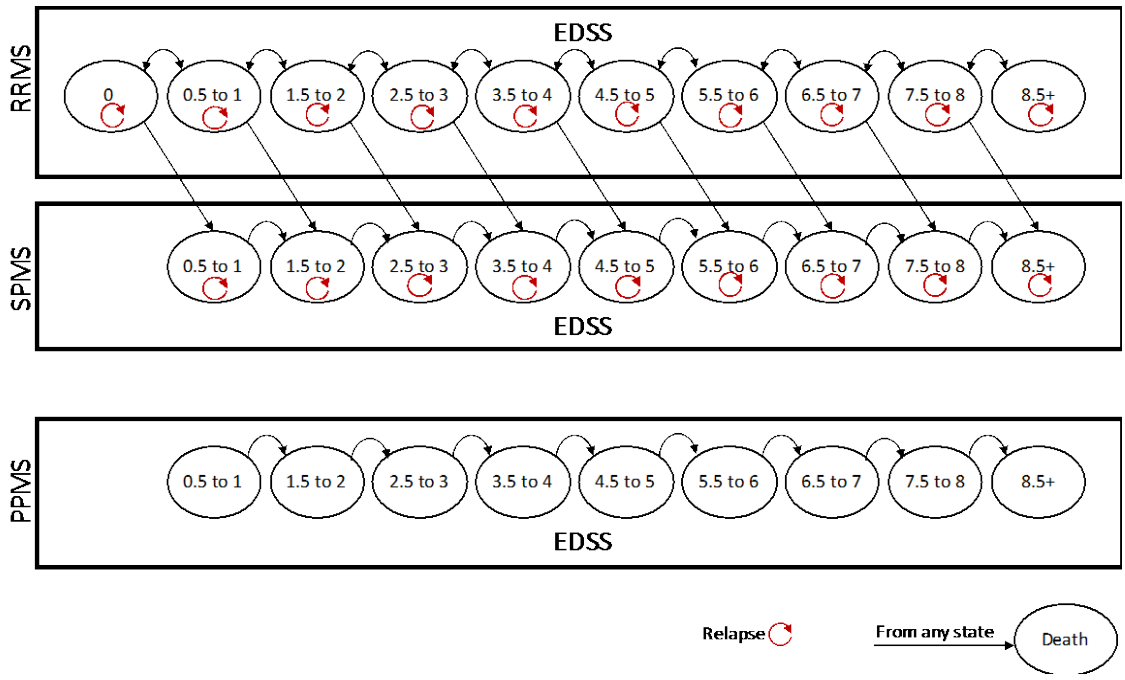
which to model the efficacy of DMTs in third- and later-lines of therapy. This approach should not substantially bias the estimated cost-effectiveness toward any particular DMT or the class overall.

The PPMS model consisted of 10 health states: EDSS 1-9 and death (Figure 6). As with the RRMS model, patients were distributed among the 10 PPMS health states, could transition between states during each one-year cycle over a lifetime time horizon, and were assumed to be treatment-naïve at the start of DMT therapy. After discontinuation of a DMT in a PPMS state, the patient received best supportive care, given the lack of an approved drug for this indication. For patients with PPMS, EDSS scores could increase or remain the same, but were assumed not to decrease. A patient could progress to death from any state.

Utilities and costs were applied to each health state. Additionally, utility decrements and costs were applied for each relapse event, as well as for SAEs. Outcomes and costs were dependent on time spent in each health state, drug treatment, numbers of relapse events, and SAEs. For each DMT, a total drug cost was calculated including acquisition, administration, and monitoring costs.

The model outcomes were drug costs, adverse event costs, total costs, quality-adjusted life-years (QALYs), life-years, and relapses over a lifetime time horizon. Costs were inflated to 2016 US dollars using the US consumer price index (CPI) for medical care.[121]

Figure 6. Markov Model Structure for RRMS and PPMS



Target Population

The populations for these analyses were adults ages 18 years and older in the United States with: 1) RRMS and 2) PPMS. Both populations were previously naïve to DMTs.

The modeled population for RRMS had an assumed mean age at onset of disease of 29 years (range for sensitivity analysis [SA] 23-35 years) and was 25% male (range for SA 20%-30%).[122] The modeled population for PPMS had an assumed mean age at onset of disease of 42 years (range for SA 33-50 years) and was 47% male (range for SA 38%-56%).[123]

Treatment Strategies

The interventions for RRMS assessed in this model were the same as those assessed in the evidence review and NMA, with the exception of rituximab and glatiramer acetate 40 mg, as there was insufficient evidence on disability progression to include them in the model. The intervention for PPMS assessed in this model was ocrelizumab.

Key Model Choices and Assumptions

The model used a US health system perspective (i.e., focus on direct medical care costs only) with a 3% discount rate for costs and health outcomes over a lifetime time horizon. The model was informed by several assumptions, which are listed in Table 14 along with the rationale for each assumption.

Table 14. Key Model Assumptions

Assumption	Rationale
Costs and mortality risks for the different EDSS-defined disease stages were assumed to be the same for patients with 1) RRMS and 2) SPMS or PPMS.	EDSS stages are used to characterize disability for all types of MS. There is little to no evidence that costs or mortality rates differ between these disease states.
Patients continued treatment after transitioning to SPMS states.	Current clinical opinion supports the continued use of treatment after transitioning to SPMS.
Patients receiving DMTs were assumed to stop treatment when their EDSS score reached 7 or above.	While there is no clinical consensus, stopping treatment at EDSS 7 or above is commonly done in clinical practice. Note that EDSS transitions were based on confirmed disability progression; therefore temporary EDSS increases did not influence discontinuation. We conducted a scenario analysis in which treatment was continued beyond EDSS 7.
Patients who discontinued on initial treatment for RRMS or SPMS were assumed to initiate second-line treatment.	Utilization data and clinical opinion suggest that most RRMS and SPMS patients initiate second-line treatment.
We assumed that second-line treatment was evenly distributed across natalizumab, fingolimod, alemtuzumab, daclizumab, and dimethyl fumarate. In the case that the first-line DMT was one of these, the second line treatment was distributed equally over the remaining DMTs.	These DMTs are commonly used for second-line treatment in clinical practice. Our approach aggregates future treatments to apply averages to all patients. This approach would not substantially bias toward any particular DMT, or the class overall.
Patients who discontinued on second-line treatment were assumed to follow the natural history progression of disease.	Current evidence does not suggest that untreated disease progression rates differ after discontinuation of active therapy.
No vial sharing was assumed.	This is in line with common clinical practice.
Patients had the same transition probabilities per health state regardless of the patient's disease history.	Markov model assumption

Clinical Inputs

Clinical Probabilities

Treatment effectiveness with DMTs was included in the model in two ways: 1) treatment effect on disability progression to higher EDSS states, and 2) treatment effect on ARR (Appendix Table E5). These results were based on the NMA (methods and results presented in Section 4). The treatment effect of ocrelizumab on disability progression to higher EDSS states in PPMS was acquired from the ORATORIO trial.[91]

The annual discontinuation probability for each DMT was derived from 28 of the 33 studies included in the base case network meta-analyses (Appendix Table C1); the rituximab trial was not

included, and 4 studies were excluded because they did not include reasons for discontinuation.[13,80,92,124] For each study, we extracted the total number of study participants, the total number of participants who discontinued, and the number who discontinued due to non-protocol-related reasons. Reasons for discontinuation that were excluded from our final discontinuation probability include death, refusal to sign re-consent form, withdrawing consent, protocol violation, administrative problems, or deviation from protocol. All other reasons for discontinuation were included. Additional patient-level data was provided by the manufacturer of teriflunomide for discontinuation reasons in the 'other' category of the TOWER study.[120] The percent of the total number of study participants who discontinued for qualified reasons was then annualized according to study time period or median time if follow-up was variable. For each DMT, we took an average of the annualized discontinuation probability with each study weighted based on the total study participants (Table 15). After discontinuation, all patients transitioned to second line treatment or supportive care (see methods below).

Table 15. Annual Discontinuation Probability for Each DMT

DMT	Annual Discontinuation Probability
Interferon β-1a 30 mcg (Avonex)	5.3%
Interferon β-1b 250 mcg (Betaseron)	4.4%
Interferon β-1b 250 mcg (Extavia)	4.4%
Glatiramer Acetate 20 mg (Copaxone)	5.2%
Glatiramer Acetate 20 mg (Glatopa)	5.2%
Interferon β-1a 22 mcg (Rebif)	5.6%
Interferon β-1a 44 mcg (Rebif)	8.6%
Peginterferon β-1a 125 mcg (Plegridy)	4.9%
Daclizumab 150 mg (Zinbryta)	9.1%
Fingolimod 0.5 mg (Gilenya)	8.4%
Teriflunomide 7 mg (Aubagio)	12.3%
Teriflunomide 14 mg (Aubagio)	12.7%
Dimethyl Fumarate 240 mg (Tecfidera)	13.3%
Natalizumab 20 mg (Tysabri)	4.9%
Alemtuzumab 12 mg (Lemtrada)	2.3%
Ocrelizumab (Ocrevus)	5.0%

To evaluate progression of MS disease without a DMT, we modelled the natural history of RRMS, SPMS, and PPMS. The initial distribution of patients with RRMS was aggregated from several data sources to create a summary measure for implementation in the model (Appendix Table E6).[87,99,118-120] For the PPMS population, the initial distribution of EDSS states from the ORATORIO[91] trial was used (Appendix Table E6).

The transition probabilities between EDSS states in the absence of DMTs for RRMS, from RRMS to SPMS, and within SPMS are presented in Appendix Tables E8-E10; these were based on a previous study[117] that used data from the DEFINE and CONFIRM clinical trial supplementary data, along with London, Ontario, cohort data.[39,87,99] As there was not sufficient data available on PPMS transition probabilities, we assumed that PPMS transition probabilities were the same as SPMS transition probabilities. The relative risks for each DMT were then applied to the progression probabilities (Appendix Table E5). Because patients transitioning from RRMS to SPMS were assumed to simultaneously increase EDSS states, the relative risks were applied to these probabilities as well.

ARRs in the absence of DMTs were based on an existing study[117] that extrapolated from observational data in Patzold and Pocklington (Appendix Table E8).[125] It is difficult to select a representative data source for ARRs for untreated patients, as significant variation exists between populations, in relapse diagnoses, and over time. Therefore, we selected a data source with mid-range estimates for relapse rates, and performed scenario analyses using data sources with higher and lower rates, as well as one-way sensitivity analyses on each input. Rate ratios for ARR resulting from the NMA described above were applied to each baseline ARR (Appendix Table E5). For patients who experience relapses, 18.7% were assumed to be severe, with the remainder being mild/moderate in severity.[126] We assumed that PPMS patients did not experience relapses.

Background mortality rates were based on age-specific US life tables for males and females and weighted by the gender distribution for RRMS or PPMS.[127] These were adjusted for MS-specific mortality using an EDSS-specific mortality multiplier calculated from Pokorski et al.[128] via the following equation, $Multiplier=0.0219*EDSS^3-0.1972*EDSS^2+0.6069*EDSS+1$, and are presented in Table 16. More recent data sources stratified by severity could not be identified.

Table 16. Calculated Mortality Multipliers of All-Cause General Population Mortality, by EDSS State (Applied to Age-specific Mortality Rates)

EDSS State	Mortality Multiplier* [128]	Range for SA
0	1.00	0.80-1.20
1	1.43	1.15-1.72
2	1.60	1.28-1.92
3	1.64	1.31-1.96
4	1.67	1.34-2.01
5	1.84	1.47-2.21
6	2.27	1.82-2.73
7	3.10	2.48-3.72
8	4.45	3.56-5.34
9	6.45	5.16-7.74

*Calculated using the equation: Multiplier = $0.0219*EDSS^3-0.1972*EDSS^2+0.6069*EDSS+1$

Utilities

Annual utility values per EDSS state were based on previously published estimates that were derived from patient-reported health states scored using the EQ-5D[117], and that used data from the DEFINE and CONFIRM trials for RRMS and a UK survey for SPMS (Table 17).[87,99,125] Each mild/moderate relapse event was associated with a one-cycle disutility of 0.091, and each severe relapse event was associated with a one-cycle disutility of 0.302.[129] We assumed that utility values for PPMS EDSS states were the same as for SPMS in the absence of available data. Note that for EDSS states that indicate the most severe levels of disability, the negative utility values indicate that patients consider quality of life to be so poor that they rate these health states to be worse than death. Such ratings are not uncommon in conditions featuring pronounced disability or inability to provide basic self-care.[130]

Table 17. Utility Scores by Health State[117]

EDSS State	Annual Utility, RRMS*	Annual Utility, SPMS/PPMS*
0	0.8752	--
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	0.0023	-0.0413
9	-0.1701	-0.2138
Death	0	0

*Varied ± 20% in sensitivity analysis

Adverse Events

For each DMT, we included associated SAEs, as severe events tend to differ between treatments and have effects on costs and/or health outcomes. We included data on adverse events when rates were provided in the label. No data on SAE risks for all DMTs could be identified from observational sources. Therefore, to evaluate SAE rates for each DMT, we collected SAE rates from all clinical trials. We included only SAEs that occurred in at least 1% of patients in clinical trials. We included PML for natalizumab, as that was the only DMT with available population-based rates. While PML has been reported for other drugs, this has been limited to case reports.

For each SAE, we applied a cost based on an assumed diagnosis related group (DRG) code, ICD-9 code, or resource utilization (Appendix Table E4). Source costs for utilization can be found in Appendix Table E2. We also applied an annualized disutility for each SAE (Appendix Table E4).

To calculate an expected SAE cost and disutility for each DMT, we multiplied the rates from trials by the costs and disutilities listed in Table 18. These resulting totals were applied for the first year of treatment with the relevant DMT (Appendix Table E4). SAE rates for the two brands of interferon β-1b (Betaseron and Extavia) and for branded and generic glatiramer acetate 20 mg (Copaxone and Glatopa, respectively) were assumed to be the same. When SAE rates from the lower dose of a given DMT were greater than SAE rates for the higher dose, we used SAE rates from the lower dose. For sensitivity analyses, all expected SAE disutilities were varied from 0 to 0.05, and all expected SAE costs were varied from $0 to $1000.

Table 18. Utilities and Costs Associated with Severe Adverse Events

Severe AE	Cost		Disutility	
	Per Event	Utilization	Per Event	Source
Lymphopenia	$126.38	blood count; 1 specialist visit	0	Jakubowiak 2016[131]
ALT increased	$284.30	2 specialist visits; 4 liver function tests	0	Mauskopf 2016[117]
Cholelithiasis	$4,476.85	DRG 446	0.005	Cook 1994[132]
Influenza	$5,687.24	DRG 194	0.016	Mauskopf 2016[117]
Serious infection	$11,176.56	DRG 177	0.005	Jakubowiak 2016[131]
Trigeminal neuralgia	$7,829.06	DRG 073	0.44	Tölle 2006[133]
Depression	$3,884.28	DRG 881	0.56	Mauskopf 2016[117]
PML	$23,444.88	ICD diagnosis code 046.3	0.4	Campbell 2013[134]

Economic Inputs

Drug Acquisition Costs

Each DMT was associated with an annual cost based on the wholesale acquisition cost (WAC), dosing, administration, and monitoring. Average discounts applied to each drug are shown in Table 19. These estimates were derived using data from SSR Health that combined data on net US dollar sales with information on unit sales to derive net pricing at the unit level across all payer types. In general, this net price reflects total discounts and rebates. Companies retain discretion over which price concessions are included in reported net sales, but in financial filings typically describe them as encompassing "all usual and customary items." Data on the approved agents of interest were current through the third quarter of 2016.[135] We estimated net prices for these agents by comparing the four-quarter rolling averages (i.e., fourth quarter 2015 through third quarter 2016) of both net prices and WAC prices per unit to arrive at an average discount from WAC. Finally, we applied this average discount from WAC (rounded to the nearest 5%) to the most current WAC price[136] for each medication to arrive at an estimated net price. WAC prices used were current at the time of this report, though these prices change rapidly and did increase over the course of this analysis.

For alemtuzumab, costs were applied as calculated for year 1 and year 2. For years 3-6, the year 2 cost was applied to 19%, 13%, 16%, and 9% of patients who received an additional course in that year.[120] After this time, patients on alemtuzumab no longer incurred drug acquisition costs, but continued to benefit from the efficacy of alemtuzumab until they transitioned to second-line treatment or natural history. As no price was available for ocrelizumab, we did not calculate or model projected drug costs for this DMT. We assumed dosing of each DMT was consistent with the

FDA labeled indication, except for ocrelizumab and rituximab, which were dosed as in the clinical trials.

Table 19. DMT Acquisition Costs

Drug Name and Labeled Dose	Package Dose	WAC Package Cost*	Discount Applied to WAC	Annual Acquisition Cost†	
				Year 1	Subsequent years
Interferon β-1a 30 mcg (Avonex)	30 mcg	$6,287 / 4EA	20%	$65,654	$65,654
Interferon β-1b 250 mcg (Betaseron)	300 mcg	$6,648/ 14EA	35%	$60,958	$56,328
Interferon β-1b 250 mcg (Extavia)	300 mcg	$5,947 / 15EA	35%	$50,899	$47,033
Glatiramer Acetate 20 mg (Copaxone)	20 mg/1 ml	$7,114 / 30EA	15%	$73,571	$73,571
Glatiramer Acetate 20 mg (Glatopa)	20 mg/1 ml	$5,194 / 30EA	35%	$41,075	$41,075
Interferon β-1a 22/44 mcg (Rebif)	22/44 mcg/0.5 ml	$6,629 / 0.5ml 12EA	15%	$73,454	$73,454
Peginterferon β-1a 125 mcg (Plegridy)	125 mcg/0.5 ml	$6,287 / 1ml	10%	$73,760	$73,760
Daclizumab 150 mg (Zinbryta)	150 mg/1 ml	$6,833 / 1ml	5%	$77,900	$77,900
Fingolimod 0.5 mg (Gilenya)	0.5 mg	$6743 / 30EA	10%	$73,839	$73,839
Teriflunomide 7/14 mg (Aubagio)	7/14 mg	$5,877 / 28EA	10%	$68,951	$68,951
Dimethyl Fumarate 240 mg (Tecfidera)	240 mg	$6,820 / 60EA	10%	$74,679	$74,679
Natalizumab 20 mg (Tysabri)	20 mg/1 ml	$6,000 / 15ml	5%	$74,304	$74,304
Alemtuzumab 12 mg (Lemtrada)	10 mg/1 ml	$20,749 / 1.2ml	5%	$98,562	$59,137

EA: each

*Redbook accessed on January 13th, 2017

†Varied ± 20% in sensitivity analysis

Drug Administration Costs

For each DMT that is administered by intravenous infusion, we applied an annual administration cost corresponding to the infusion time (see Appendix Table E1). Utilization was calculated based on CPT codes for infusions (Appendix Table E2). All other products were assumed to have no administration costs.

Laboratory and Clinic Visit Costs

Several categories of administration, laboratory, and healthcare costs were used as model inputs for various calculations described below. Relevant costs and sources are shown in Appendix Table E2.

Drug Monitoring Costs

Most DMTs have laboratory monitoring recommended in the package insert. These instructions are summarized in Appendix Table E3. Any pre-treatment monitoring costs were included in the first year of treatment. Note that all monitoring costs for alemtuzumab are directly billed to the manufacturer by the laboratory. Because this program covers all monitoring costs, is used by 97% of patients including those with Medicare, and is expected to continue in perpetuity, we assumed no monitoring costs from the payer perspective for alemtuzumab.[120] Daclizumab has additional monitoring after the final dose, which was captured in the first year after discontinuation. In addition to DMT-specific monitoring, we included a physician visit when a patient discontinues a first- or second-line regimen. Although MRIs are often used for MS monitoring, there are no consistent guidelines for frequency of periodic MRIs; we therefore chose not to explicitly model it. These costs should be captured in underlying costs, and would not substantially influence relative comparisons between DMTs.

Annual Costs by EDSS State

An annual cost of care was associated with each EDSS state. Costs for each EDSS state were assumed to be the same for RRMS, SPMS, and PPMS. EDSS state-specific costs were calculated based on an interpolation of data from Figure 2 in Kobelt et al.[137] Data from the figure was extracted for direct costs (direct costs and other drugs from the figure) as well as indirect costs (indirect costs and informal care from the figure). Direct costs included inpatient and outpatient admissions, office visits to physicians and other health professionals, examinations, medical devices, non-DMT drugs, and over the counter medicines. Indirect costs, evaluated as part of a separate scenario analysis, included productivity losses based on short-term work absence, changes in working situation leading to reduction in income, and early retirement, all related to MS only. The extracted values were extrapolated using the following equations: direct costs = 1,594.1*EDSS +2,217.5, and indirect costs = 3,094.5*EDSS + 8,407.5. Results were inflated from 2004 to 2016 USD.

Table 20. Annual costs per EDSS state

EDSS State	Annual Direct Costs (2016 $)[137]*	Annual Indirect Costs (2016 $)[137]*
0	$2,825	$10,711
1	$4,856	$14,653
2	$6,887	$18,595
3	$8,917	$22,537
4	$10,948	$26,480
5	$12,979	$30,422
6	$15,010	$34,364
7	$17,041	$38,306
8	$19,071	$42,249
9	$21,102	$46,191

*Extrapolated from Figure 2 of Kobelt et al.;[137] varied ± 20% in sensitivity analysis

As cost data were not available stratified by relapse severity, we assumed an average relapse cost for all relapse severities of $2,692 in direct costs and $2,339 in indirect costs.[129] Direct costs included inpatient care (hospitalization and nursing home care); emergency room and outpatient services such as diagnostic tests for MS; ambulatory visits to healthcare professionals; medications (prescription, non- prescription, and alternative medicines); and home care services, as well as alterations and adaptations to home or car and the purchase of assistive medical devices. Indirect costs, evaluated as a separate scenario analysis, included short-term absence, reduced working time, reduced productivity, and informal care.[129]

Second-Line Treatment

For the RRMS model, we assumed that all patients would continue to an average second-line therapy after discontinuation from a first line DMT. This average therapy was comprised of natalizumab, fingolimod, alemtuzumab, daclizumab, and dimethyl fumarate, which are all commonly used as later-line agents.[138] These DMTs were assumed to be equally distributed in the second line. In the case where one of natalizumab, fingolimod, alemtuzumab, daclizumab, or dimethyl fumarate was the first-line DMT, the second-line average was comprised of the remaining four. Patients discontinued second-line treatment at a constant rate of 10% annually until they reached EDSS 7, at which point all patients discontinued. Patients who discontinued second-line treatment then followed the natural history progression.

The effectiveness of second-line treatment was based on the average effectiveness of included DMTs as described above. The annual costs for second-line therapy were based on the average annual net cost of the included DMTs. To include alemtuzumab costs for second-line treatment, we calculated a constant annual cost by averaging the year 1 and year 2 costs, then dividing by the

expected time on second-line treatment. The SAE costs and disutilities for second-line treatment were based on the averages of the included DMTs.

Sensitivity Analyses

We ran one-way sensitivity analyses to identify the key drivers of model outcomes, using the ranges for each input described in the model inputs section above. Probabilistic sensitivity analyses were also performed by jointly varying all model parameters over 5,000 simulations, then calculating 95% credible range estimates for each model outcome based on the results. To demonstrate the results of this analysis, we calculated the probability that each DMT was cost-effective at the $150,000 per QALY threshold compared to both supportive care and glatiramer acetate 20 mg. We used normal distributions for costs, rates, multipliers, and ages; log-normal for relative risks; gamma distributions for negative utilities; and beta distributions for probabilities and utilities (with the exception of SAE costs and disutilities, for which we used gamma distributions). Finally, we systematically altered the WAC of each DMT (with no discount) to estimate the maximum prices that would correspond to given willingness to pay (WTP) thresholds.

Scenario Analyses

We conducted several scenario analyses, listed below:

1. Higher untreated ARR by EDSS states[117] (based on trial data, Appendix Table E7)
2. Lower untreated ARR by EDSS states[139] (based on data presented in Appendix Table E7)
3. NMA results for relative risk of EDSS progression using only 12-week results
4. NMA results for relative risk of EDSS progression using only 24-week results
5. Inclusion of indirect costs
6. Patients continue DMTs without stopping at EDSS 7
7. Higher AE rates for all DMTs: 50 per 1,000 incidence, with a utility decrement of 0.5 and cost of $30,000 per event.
8. Inclusion of all DMTs, equally distributed, in the aggregate second-line calculation, except for the DMT being modelled as first-line.
9. Constant discontinuation rate for all DMTs of 10% for the first 2 years and 3% annual thereafter.
10. Removal of studies with variable follow-up time from calculations of DMT discontinuation rates.

Model Validation

We used several approaches to validate the model. First, we provided information on the preliminary model approach, inputs, and results to the manufacturers of DMTs. Feedback from these companies resulted in the identification of an error in one SAE rate and cost, an error in the

calculation of ocrelizumab cost, and revisions to the model, including DMT dosing and monitoring specifications, age of PPMS patients, removal of second-line treatment for PPMS patients, categorization of relapses by severity, and identification of additional data sources. Second, we compared our results to nine independently developed models, both published and unpublished, since 2010[110,114,115,117,139-143]. Lastly, we conducted both probabilistic and one-way sensitivity analyses to assess model behavior.

6.3 Cost-Effectiveness Model: Results

Base Case Results

Total discounted costs, relapses, life-years, and QALYs over the lifetime time horizon are shown in Table 21, with results arranged in order of increasing QALYs. Among patients with RRMS, discounted costs for DMT therapy, SAEs, and MS-related healthcare over the projected lifetime were approximately $341,100 for supportive care, and ranged from approximately $601,100 for alemtuzumab to $1.3 million for natalizumab. The projected number of relapses was 16.72 for supportive care, and ranged from 11.40 for alemtuzumab to 15.94 for interferon β-1a 30 mcg. Discounted life expectancy from age of DMT initiation (age 29 years for RRMS) was 21.82 years for supportive care, and ranged narrowly from 22.25 years for teriflunomide 7 mg to 23.38 years for alemtuzumab. Finally, projected discounted QALYs were 5.67 for supportive care, and ranged from 7.76 for teriflunomide 7 mg to 12.46 for alemtuzumab.

Among patients with PPMS, projected discounted costs, life-years, and QALYs for supportive care were approximately $264,800, 15.61 years, and 2.75 QALYs, respectively, compared to approximately 16.11 years and 3.33 QALYs for ocrelizumab.

Table 21. Results for Base-case Analysis

Drug	Cost	Relapses	Life-Years	QALYs
RRMS				
Supportive Care	$341,120	16.72	21.82	5.67
Teriflunomide 7 mg	$986,499	15.21	22.25	7.76
Interferon β-1a 22 mcg (Rebif)	$1,125,894	14.94	22.28	7.88
Interferon β-1a 30 mcg (Avonex)	$1,078,976	15.94	22.32	7.92
Teriflunomide 14 mg	$1,005,404	15.11	22.39	8.41
Interferon β-1a 44 mcg (Rebif)	$1,088,038	14.88	22.40	8.43
Glatiramer acetate 20 mg (Copaxone)	$1,169,725	14.68	22.41	8.43
Glatiramer acetate 20 mg (Glatopa)	$871,708	14.68	22.41	8.43
Fingolimod	$1,104,382	13.96	22.49	8.94
Dimethyl fumarate	$1,033,081	14.63	22.50	8.97
Interferon β-1b 250 mcg (Betaseron)	$1,061,275	15.16	22.58	9.07
Interferon β-1b 250 mcg (Extavia)	$965,217	15.16	22.58	9.07
Peginterferon β-1a	$1,230,613	15.12	22.63	9.30
Daclizumab	$1,148,145	14.32	22.66	9.64
Natalizumab	$1,273,664	12.62	22.78	10.17
Ocrelizumab	-	13.19	22.98	10.94
Alemtuzumab	$601,053	11.40	23.38	12.46
PPMS				
Supportive Care	$264,760	N/A	15.61	2.75
Ocrelizumab	-	N/A	16.11	3.33

Life-years and QALYs inversely correlated with relative risk for progression, as expected, with the exception of teriflunomide 14 mg and dimethyl fumarate. The rankings for these drugs are not directly ordered with relative risk for progression because of differences in rankings of the rate ratio for relapses, which negatively affected quality of life.

Projected relapses did not directly correlate with rate ratios for relapse because the underlying ARR changed with EDSS state, with the highest rate of relapses occurring in the middle EDSS states and lower rates at higher and lower EDSS states. Because of this underlying trend, number of relapses was affected by the relative risk for progression as well as the rate ratio for relapse rate. As a result, DMTs with particularly high or low relative risks for progression did not show direct correlation between rate ratios for relapse rate and number of projected relapses. For example, interferon β-1a 22 mcg had fewer projected relapses than peginterferon β-1a despite having a

higher rate ratio for relapses (0.70 vs. 0.63) because interferon β-1a 22 mcg had a higher relative risk for progression (0.81 vs. 0.63) and therefore more interferon β-1a 22 mcg patients were in higher EDSS states with low ARRs.

We also calculated the cost per additional QALY, cost per additional life-year, and cost per relapse avoided for each DMT compared to supportive care and compared to generic glatiramer acetate 20 mg (Tables 22 and 23). Again, DMTs were ordered according to the projected QALYs. When compared to supportive care for RRMS, costs per additional QALY ranged from approximately $38,300 per QALY for alemtuzumab to $355,100 for interferon β-1a 22 mcg; costs per additional life-year ranged from approximately $166,100 per year for alemtuzumab to $1.7 million for interferon β-1a 22 mcg; and costs per relapse avoided ranged from approximately $48,800 for alemtuzumab to $942,000 for interferon β-1a 30 mcg.

Table 22. Pairwise Results for DMTs Compared to Supportive Care for RRMS

Drug	Cost per Additional QALY	Cost per Additional Life-Year	Cost per Relapse Avoided
Teriflunomide 7 mg	$309,236	$1,511,475	$425,498
Interferon β-1a 22 mcg (Rebif)	$355,115	$1,684,239	$439,473
Interferon β-1a 30 mcg (Avonex)	$327,639	$1,479,572	$942,036
Teriflunomide 14 mg	$242,043	$1,162,876	$411,786
Interferon β-1a 44 mcg (Rebif)	$270,883	$1,285,688	$405,626
Glatiramer acetate 20 mg (Copaxone)	$300,171	$1,411,303	$405,493
Glatiramer acetate 20 mg (Glatopa)	$192,211	$903,711	$259,652
Fingolimod	$232,983	$1,128,922	$276,208
Dimethyl fumarate	$209,327	$1,010,592	$330,591
Interferon β-1b 250 mcg (Betaseron)	$211,444	$951,083	$459,962
Interferon β-1b 250 mcg (Extavia)	$183,240	$824,222	$398,609
Peginterferon β-1a	$244,802	$1,101,324	$555,894
Daclizumab	$203,375	$959,547	$335,738
Natalizumab	$206,934	$972,577	$227,149
Alemtuzumab	$38,277	$166,077	$48,787

When compared to generic glatiramer acetate 20 mg, five DMTs were less effective and more costly for cost per additional QALY and cost per additional life-year, and eight were less effective and more costly for cost per relapse avoided. This indicates that the DMT had higher projected costs and worse or equal projected health outcomes (fewer QALYs or life-years, or more relapses). As branded and generic glatiramer acetate 20 mg were assumed to have equivalent effectiveness, the more expensive branded product would be considered cost-increasing in a cost-minimization

analysis. Among those DMTs with better health outcomes compared to generic glatiramer acetate 20 mg, costs per additional QALY ranged from approximately $144,900 per QALY for interferon β-1b 250 mcg (Extavia) to approximately $451,300 per QALY for fingolimod; costs per additional life-year ranged from approximately $549,800 per year for interferon β-1b 250 mcg (Extavia) to $2.6 million per life-year for fingolimod; and costs per relapse avoided ranged from approximately $195,000 for natalizumab to $3.3 million for dimethyl fumarate. The incremental results that are particularly high are because the health outcomes are very close to those for generic glatiramer acetate 20 mg, while the costs are higher. Alemtuzumab was more effective and less costly for cost per additional QALY, cost per additional life-year, and cost per relapse avoided, meaning that projected costs were lower, projected QALYs and life-years were higher, and projected relapses were lower than glatiramer acetate.

Table 23. Pairwise Results for DMTs Compared to Generic Glatiramer Acetate 20 mg for RRMS

Drug	Cost per Additional QALY	Cost per Additional Life-Year	Cost per Relapse Avoided
Teriflunomide 7 mg	Less effective and more costly	Less effective and more costly	Less effective and more costly
Interferon β-1a 22 mcg (Rebif)	Less effective and more costly	Less effective and more costly	Less effective and more costly
Interferon β-1a 30 mcg (Avonex)	Less effective and more costly	Less effective and more costly	Less effective and more costly
Teriflunomide 14 mg	Less effective and more costly	Less effective and more costly	Less effective and more costly
Interferon β-1a 44 mcg (Rebif)	Less effective and more costly	Less effective and more costly	Less effective and more costly
Glatiramer acetate 20 mg (Copaxone)	Cost increasing*	Cost increasing*	Cost increasing*
Fingolimod	$451,265	$2,614,993	$323,202
Dimethyl fumarate	$295,984	$1,653,617	$3,250,242
Interferon β-1b 250 mcg (Betaseron)	$293,696	$1,114,615	Less effective and more costly
Interferon β-1b 250 mcg (Extavia)	$144,873	$549,813	Less effective and more costly
Peginterferon β-1a	$411,079	$1,627,413	Less effective and more costly
Daclizumab	$228,893	$1,088,649	$767,288
Natalizumab	$230,210	$1,081,350	$194,938
Alemtuzumab	More effective and less costly	More effective and less costly	More effective and less costly

*Cost increasing indicates that the DMT had higher projected costs and equal projected effectiveness compared to glatiramer acetate 20 mg (Glatopa).

Validation Results

Predicted costs across therapies were generally similar to previous models. We noted that our model used a younger age of drug initiation (29 years) than most available models (37-38 years) and used a longer time horizon, and that our projected life-years and QALYs were similar when using the same ages and time horizon. We note that our undiscounted life expectancy estimates (range: 64-69 years) are in line with observed and published MS life expectancy estimates. [144,145]. The projected number of relapses in our model is consistent with previous models when adjusted for age and time horizon [140].

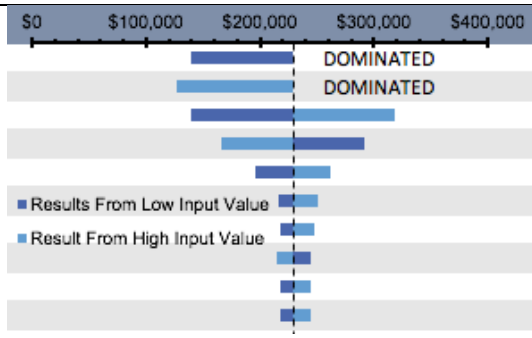
Sensitivity Analysis Results – One Way

To demonstrate effects of uncertainty on both costs and health outcomes, we varied input parameters across the ranges defined above to evaluate changes in the cost per additional QALY for each DMT compared to generic glatiramer acetate 20 mg. As an illustrative example, the impacts of varying each of the parameters in the model over ranges reflecting their uncertainty are shown in Figure 7 for daclizumab compared to generic glatiramer acetate 20 mg for RRMS. For those DMTs that were either more effective and less costly or less effective and more costly compared to generic glatiramer acetate 20 mg, we evaluated the changes in both incremental costs and incremental QALYs. Full results for all DMTs can be found in Appendix Table E11. Uncertainty in the costs of DMTs and relative risks for progression had the largest impact on model results.

Figure 7. One-way Sensitivity Analysis: Cost per Additional QALY for Daclizumab Compared to Generic Glatiramer Acetate 20 mg for RRMS

Cost per additional QALY

RRMS DAC vs GA 20 mg (Glatopa)



Parameter	Low Value	High Value
Relative Risk, Progression, DAC	0.36	0.78
Relative Risk, Progression, GA 20 mg (Glatopa)	0.58	0.94
WAC, DAC	$5,467	$8,200
WAC, GA 20 mg (Glatopa)	$4,155	$6,233
Discount, GA 20 mg (Glatopa)	0.28	0.42
Relative Risk, Progression, NAT	0.37	0.84
Relative Risk, Progression, ALE	0.25	0.68
Annual Utility, RRMS, EDSS 2	0.62	0.94
Relative Risk, Progression, FIN	0.51	0.90
Relative Risk, Progression, DMF	0.46	0.84

Sensitivity Analysis Results – Probabilistic

The results of our probabilistic sensitivity analysis can be found in Appendix Tables E12-E16. Wide variability in the incremental cost-effectiveness ratios was observed, especially when agents were compared to generic glatiramer acetate 20 mg rather than to supportive care. For example, the cost

per additional QALY for daclizumab ranged from approximately $143,500 to $281,100 when compared to supportive care and from $85,500 to less effective and more costly when compared to generic glatiramer acetate 20 mg. The probability that each DMT was below the $150,000 per QALY threshold is shown in Table 24. Only alemtuzumab had a greater than a 50% chance of meeting the $150,000 per QALY threshold compared to supportive care, and interferon β-1b 250 mcg (Extavia) and alemtuzumab had a greater than 50% chance of meeting the $150,000 per QALY willingness-to-pay level when compared to generic glatiramer acetate.

Table 24. Probability of Each DMT Costing Less than $150,000 per QALY Compared to Supportive Care and Generic Glatiramer Acetate 20 mg

DMT	Compared to Supportive Care	Compared to Glatiramer Acetate 20 mg (Glatopa)
Teriflunomide 7 mg	0.0%	3.4%
Interferon β-1a 22 mcg (Rebif)	0.1%	2.8%
Interferon β-1a 30 mcg (Avonex)	0.0%	1.7%
Teriflunomide 14 mg	0.2%	11.9%
Interferon β-1a 44 mcg (Rebif)	0.1%	4.6%
Glatiramer acetate 20 mg (Copaxone)	0.0%	--
Glatiramer acetate 20 mg (Glatopa)	18.4%	--
Fingolimod	0.5%	10.6%
Interferon β-1b 250 mcg (Betaseron)	9.6%	30.3%
Interferon β-1b 250 mcg (Extavia)	28.8%	52.4%
Dimethyl fumarate	2.4%	24.3%
Peginterferon β-1a	3.1%	12.4%
Daclizumab	5.4%	26.2%
Natalizumab	7.0%	21.6%
Alemtuzumab	100.0%	99.6%

Sensitivity Analysis Results – Scenarios

Results from the scenario analyses can be found in Appendix Tables E17-E26. For the majority of pairwise comparisons, the scenario analyses did not yield major differences in conclusions from the base case. However, when using only 24-week NMA results, we note that the cost per QALY compared to generic glatiramer acetate for interferon β-1b 250 mcg (Extavia and Betaseron) decreased to approximately $74,000 and $127,000, respectively. Of note, including indirect costs did decrease resulting pairwise comparisons for costs per QALY and costs per life-year, but not substantially enough to change conclusions. Similarly, increased AE rates did not influence results.

Threshold Analysis Results

Prices for each drug that would achieve cost-effectiveness thresholds ranging from $50,000 to $150,000 per QALY gained are presented in Table 25, along with the wholesale acquisition cost per package. It was not possible to calculate a threshold price for ten of the DMTs at $50,000/QALY, and for two of the DMTs at $100,000/QALY. This was because even if the price of the DMT were $0, the patient still accrued costs from second-line drugs and other care. As those other costs are particularly high relative to supportive care, it was not possible to decrease the WAC enough to reach the threshold. Note that the price of alemtuzumab would increase to reach these cost-effectiveness thresholds, as its cost-effectiveness at WAC is below $50,000/QALY. The net price with SSR discount was higher than the $150,000 threshold prices for all DMTs except alemtuzumab (net price $19,712).

Table 25. Resulting Package Prices for Each DMT to Reach Cost per QALY Thresholds

DMT	WAC (per package)	$50,000	$100,000	$150,000
Interferon β-1a 30 mcg (Avonex)	$6,287	N/C; at $0 WAC, ICER is $70,003	$586	$1,562
Interferon β-1b 250 mcg (Betaseron)	$6,648	$239	$1,504	$2,768
Interferon β-1b 250 mcg (Extavia)	$5,947	$256	$1,611	$2,965
Glatiramer Acetate 20 mg (Copaxone)	$7,114	N/C; at $0 WAC, ICER is $55,746	$1,095	$2,332
Glatiramer Acetate 20 mg (Glatopa)	$5,194	N/C; at $0 WAC, ICER is $55,746	$1,095	$2,332
Interferon β-1a 22 mcg (Rebif)	$6,629	N/C; at $0 WAC, ICER is $72,919	$541	$1,539
Interferon β-1a 44 mcg (Rebif)	$6,629	N/C; at $0 WAC, ICER is $78,710	$624	$2,090
Peginterferon β-1a	$6,287	$230	$1,623	$3,017
Daclizumab	$6,833	N/C; at $0 WAC, ICER is $54,813	$1,975	$4,159
Fingolimod	$6,743	N/C; at $0 WAC, ICER is $63,186	$1,316	$3,103
Teriflunomide 14 mg	$5,877	N/C; at $0 WAC, ICER is $96,456	$129	$1,945
Teriflunomide 7 mg	$5,877	N/C; at $0 WAC, ICER is $121,549		$802
Dimethyl Fumarate	$6,820	N/C; at $0 WAC, ICER is $79,176	$982	$3,340
Natalizumab	$6,000	$485	$2,147	$3,808
Alemtuzumab	$20,750	$28,322	$65,047	$101,771
Ocrelizumab (RRMS)*	--	$9,861	$34,235	$58,608
Ocrelizumab (PPMS)*	--	$4,208	$9,288	$14,367

*Annual prices are presented for ocrelizumab because package prices are not currently available.
N/C: Not calculable; there is no price that can achieve a given cost-effectiveness threshold, even at $0

6.4 Prior Published Evidence on Costs and Cost-Effectiveness of DMTs for MS

We reviewed several cost-effectiveness models comparing different MS therapies and have summarized those that most closely resembled our model in structure, population, perspective, and setting.

A manufacturer-funded study by Hernandez et al. (2016) compared the cost-effectiveness of peginterferon β-1a 125 mcg versus interferon β-1a 44 mcg and glatiramer acetate 20 mg in RRMS patients.[139] Peginterferon β-1a resulted in a slower rate of EDSS progression and more time spent in EDSS states below 7 versus the two comparators. Peginterferon β-1a dominated (i.e., had lower cost and better effectiveness) both interferon β-1a 44 mcg and glatiramer acetate 20 mg, and had the smallest EDSS change from baseline. While both the ICER and Hernandez models were similar in structure, one of the key differences between the two models was the time horizon: 10 years for the Hernandez model versus lifetime for the ICER model. When the time-horizon in the Hernandez model was extended to lifetime, peginterferon β-1a resulted in a cost-effectiveness ratio of approximately $29,000 versus glatiramer acetate 20 mg (Copaxone). While there were other differences in model estimation (e.g., discontinuation rates, utilities), these findings are directionally consistent with those of the ICER model (i.e., effectiveness of peginterferon β-1a [9.3 QALYs] was greater than that of interferon β-1a 44 mcg and glatiramer acetate 20 mg [8.43 QALYs each, respectively]).

Another manufacturer-funded study by Mauskopf et al. (2016) compared dimethyl fumarate to glatiramer acetate 20 mg and fingolimod in RRMS patients.[117] Dimethyl fumarate dominated both comparators, with an incremental QALY gain of 0.45 and 0.36 and lower total costs by approximately $71,000 and $33,000 over glatiramer acetate and fingolimod, respectively. This model was similar to the ICER model in most aspects; however, there were several key differences between the two models. The Mauskopf model population was composed of 60% treatment-naïve and 40% treatment-experienced patients, whereas the ICER model population included only treatment-naïve patients. In addition, second-line DMT therapy was not included in the Mauskopf model, while it was included in the ICER model. Finally, Mauskopf et al. modeled treatment over a 20-year time horizon whereas ICER modeled treatment over a lifetime.

We reviewed three other US studies, all of which were modeled from a societal perspective and had shorter time horizons (maximum 10 years) compared to our model. Noyes et al. modeled a cohort of RRMS and SPMS patients over 10 years using data from a longitudinal MS study.[142,146-148] Indirect costs included those associated with unemployment periods, part-time employment, interruption in schooling, and absenteeism from work and school. The study included interferon β-1a 30 mcg, interferon β-1a (Rebif, dose unspecified), interferon β-1b 250mcg, and glatiramer acetate 20 mg. Ten-year costs were similar for all agents, ranging from $467,000 to $492,000. Other than supportive care, glatiramer acetate 20 mg had the lowest number of QALYs accrued (6.5) over the 10 years, while interferon β-1a 30 mcg had the highest QALYs gained (6.7). Our model showed that interferon β-1a 22 mcg had the lowest number of QALYs gained (7.88), and interferon β-1b 250 mcg had the highest QALYs gained (9.07). This discrepancy may be a result of varying approaches to the two available dose strengths of Rebif (22 and 44 mcg); our model analyzed the doses separately, while it is unclear how Noyes approached the two doses. Furthermore, the QALY difference

between drugs is greater in our model compared to the Noyes model due to the longer time horizon in our model.

Lee at al. developed a Markov model comparing fingolimod to interferon β-1a 30 mcg in RRMS patients over a 10-year time horizon.[140] As in our model, fingolimod generated approximately 1 additional QALY versus interferon β-1a 30 mcg (6.77 versus 5.95) and was also more expensive. Finally, Zhang et al. modeled RRMS patients over a five-year time horizon, comparing fingolimod, interferon β-1a 30 mcg, teriflunomide 14 mg, and dimethyl fumarate.[143] While a societal perspective was employed in this model, productivity costs were not included, under the assumption that these effects were captured in the QALY estimate. Drug costs in the model were obtained from the Federal Supply Schedule list. When the four drugs are ranked by cost, fingolimod was the most expensive of the four in both, this model and the ICER model, while the least expensive was dimethyl fumarate in the Zhang model as opposed to teriflunomide in ours.

6.5 Potential Budget Impact

We used the cost-effectiveness model to estimate the potential budget impact of two new treatments in the RRMS patient population: daclizumab, which received FDA approval in 2016, and ocrelizumab, for which FDA approval is pending. As the price of ocrelizumab is currently unknown, we used prices required to achieve WTP thresholds of $150,000, $100,000 and $50,000 per QALY in our estimates of budget impact. We also assessed the potential budget impact of ocrelizumab as the first agent likely to secure FDA approval in PPMS, using the threshold prices listed above. We did not include other therapies modeled above in this potential budget impact analysis, given their established presence in the market.

Potential Budget Impact Model: Methods

We used results from the same model employed for the cost-effectiveness analyses to estimate total potential budget impact, calculating incremental health care costs (including drug costs) minus any offsets in these costs from averted health care events. In the RRMS cohort, potential budget impact was defined as the total incremental net cost of using daclizumab versus natalizumab for the treated population, as clinical input suggested that natalizumab was the most likely competitor for daclizumab market share in the near term. Although daclizumab has been available in the market for several months, we considered its budget impact from an *ex ante* perspective for this analysis; that is, treating it as new to market. We also estimated the potential budget impact of using ocrelizumab, using prices required to achieve WTP thresholds of $150,000, $100,000, and $50,000 per QALY. For RRMS patients, we assumed that the share of patients using ocrelizumab would be drawn equally from three existing competitors: natalizumab, fingolimod, and dimethyl fumarate. For the PPMS population, we analyzed the potential budget impact of using ocrelizumab rather than best supportive care, as there is no DMT currently approved for these patients. 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.

The potential budget impact analysis included the entire candidate population for treatment, which consisted of adults with RRMS, whether DMT treatment-naïve or -experienced. We recognize that in reality, both new treatments and the drugs they are displacing will have only a share of the potential market; in the absence of any rigorous projection on what changes in market share would look like, we felt it best to document the percentage of all possible patients who would have access to new medications without crossing the budget impact threshold in order to compare new interventions on a consistent scale. Because no DMT has been approved for use in PPMS patients, we assumed all patients in this cohort to be DMT treatment-naïve. To estimate the size of the potential candidate population for treatment with daclizumab or ocrelizumab in the RRMS cohort, we first determined the estimated prevalence of MS in the US, which has been reported as 142.9 cases per 100,000 persons.[35] We estimated the proportion of MS patients following the RRMS disease course to be 85%, with the remaining 15% following the PPMS disease course.[1] Applying these proportions to the projected 2016 US population resulted in an estimate of 410,900 RRMS patients and 72,500 PPMS patients in the US over a five-year period.

ICER's methods for estimating potential budget impact are described in detail elsewhere and have recently been updated. 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 or device 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. In this analysis, we assumed that in the RRMS population, daclizumab would take market share entirely from natalizumab, and that ocrelizumab would take market share from natalizumab, fingolimod and dimethyl fumarate in equal shares. In the PPMS population, we assumed ocrelizumab would take market share from supportive care in the absence of other treatments for PPMS. For daclizumab, we tested the potential budget impact by assuming different unit price points – namely WAC, discounted WAC as calculated from the SSR database, and prices to reach WTP thresholds of $50,000/QALY, $100,000/QALY and $150,000/QALY, against the calculated discounted price of natalizumab. We assumed daclizumab to take market share from natalizumab based on expert opinion that its most likely place in therapy is among patients who are positive for the JC virus and would otherwise be candidates for natalizumab. For ocrelizumab, we assumed only prices to reach the WTP thresholds given that the drug is not yet approved and no price has been set, and compared against the calculated discounted prices of natalizumab, fingolimod and dimethyl fumarate as the drugs it is most likely to displace in the RRMS population, and against the cost of supportive care in the PPMS population.

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 (http://icer-review.org/wp-content/uploads/2016/02/Value-Assessment-Framework-slides-for-July-29-webinar-FINAL-corrected-8-22-1.pdf), 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 each year, and the contribution of spending on retail and facility-based drugs to total health care spending. The original annual threshold was $904 million, which has now been updated to $915 million for 2017-18. Calculations are performed as shown in Table 26.

For 2017-18, therefore, the five-year annualized potential budget impact threshold that should trigger policy actions to manage affordability is calculated to total approximately $915 million per year for new drugs.

Table 26. Calculation of Potential Budget Impact Threshold

Item	Parameter	Estimate	Source
1	Growth in US GDP, 2017 (est.) +1%	3.20%	World Bank, 2016
2	Total health care spending, 2016 ($)	$2.71 trillion	CMS NHE, 2014
3	Contribution of drug spending to total health care spending (%)	17.7%	CMS National Health Expenditures (NHE), 2016; Altarum Institute, 2014
4	Contribution of drug spending to total health care spending ($) (Row 2 x Row 3)	$479 billion	Calculation
5	Annual threshold for net health care cost growth for ALL new drugs (Row 1 x Row 4)	$15.3 billion	Calculation
6	Average annual number of new molecular entity approvals, 2013-2014	33.5	FDA, 2016
7	Annual threshold for average cost growth per individual new molecular entity (Row 5 ÷ Row 6)	$457.5 million	Calculation
8	Annual threshold for estimated potential budget impact for each individual new molecular entity (doubling of Row 7)	$915 million	Calculation

Potential Budget Impact Model: Results

When treating the eligible RRMS cohort with daclizumab at discounted WAC price, the potential budget impact was estimated to be approximately $2,200 per patient over 5 years. Using threshold prices, the potential budget impact was estimated to be cost-saving over 5 years, ranging from

approximately $71,400 when using the price ($4,159) to reach the $150,000 per QALY WTP threshold, to approximately $140,500 when using the price to reach the $100,000 per QALY WTP threshold ($1,975). When using WAC, the annual potential budgetary impact exceeded the threshold of $915 million by 32%. As shown in the Figure 8 below, 100% of patients could be treated in a given year without crossing the ICER budget impact threshold at the three WTP threshold prices as well as discounted WAC, while 76% of the population could be treated without crossing the threshold at the full WAC. The disparate findings between full and discounted WAC are somewhat surprising on initial review, as there is only an approximate $350 difference between WAC and discounted WAC per dose; however, this translates into a greater than $4,000 difference on an annual basis and is compounded further by both total population size and the 5-year time horizon.

Figure 8. Budgetary Impact of Daclizumab in RRMS Patients

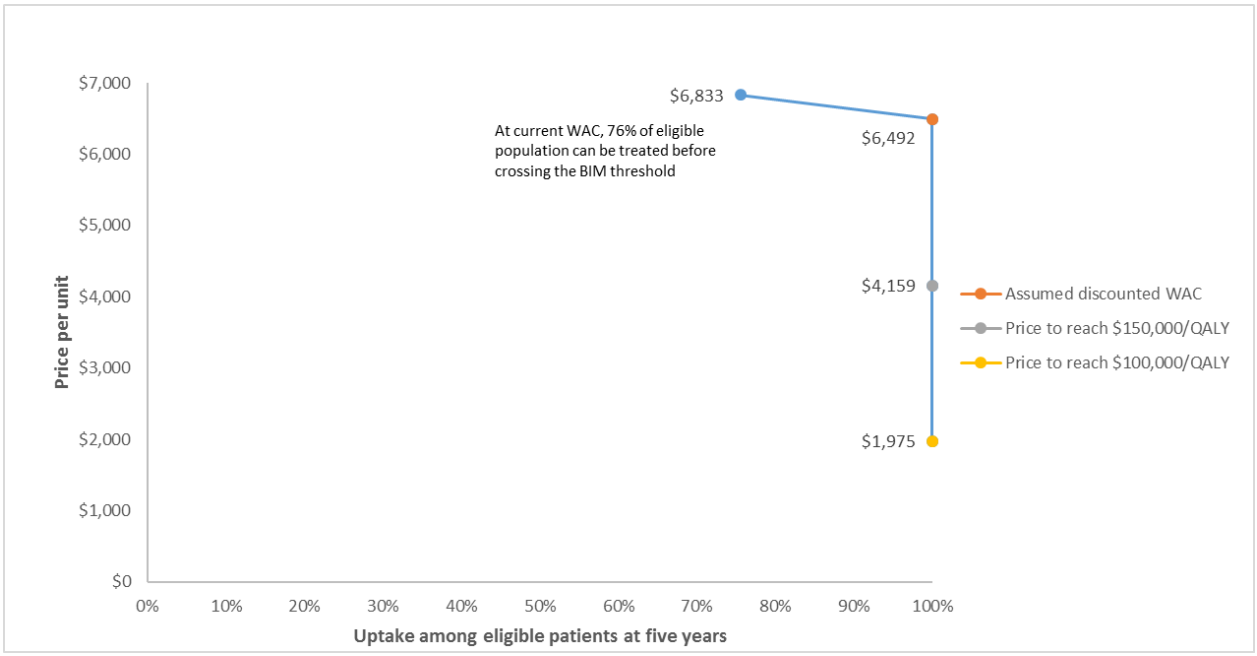


Table 27 below illustrates the per-patient budget impact calculations for ocrelizumab in more detail, based on the price ($58,608) to achieve a WTP threshold of $150,000/QALY for ocrelizumab and the DMTs it would displace. At that price, ocrelizumab would result in cost-savings relative to the displaced DMTs; cost savings would increase at threshold prices to achieve $50,000 and $100,000 per QALY gained.

Table 27. Per-Patient Potential Budget Impact of Ocrelizumab in RRMS Population, Using Price to Reach WTP Threshold of $150,000/QALY Gained

	Avg. Annual Per-Patient Budget Impact (Over 5-year Time Horizon)	Weighted† Avg. Annual Per-Patient Budget Impact (over 5-year Horizon)
Ocrelizumab	$66,985	$200,371
Natalizumab+Fingolimod+Dimethyl fumarate*	$81,600	$242,605
Net	-$14,615†	-$42,234‡

*Weighted equally among all three drugs

†For five-year horizon, drug costs and cost offsets apportioned assuming 20% of patients in uptake target initiate therapy each year. Those initiating in year 1 receive full drug costs and cost offsets, those initiating in year 2 receive 80% of drug costs and cost offsets, etc.

‡Indicates cost-saving

Finally, when treating the eligible PPMS cohort with ocrelizumab, the annual average potential budgetary impact per-patient over 5 years ranged from approximately $18,300 using the price ($4,208) to achieve a WTP threshold of $50,000/QALY to approximately $44,200 using the price ($14,367) to achieve a WTP threshold of $150,000/QALY. However, the annual budgetary impact of treating the entire PPMS cohort across all WTP threshold prices did not exceed the $915 million threshold, reaching 29% of the budget impact threshold at the price to reach $50,000/QALY, 50% at the $100,000/QALY price, and 70% at the $150,000/QALY price, due to the assumed small size of the candidate population for PPMS treatment in any given year (14,500 patients).

6.6 Value-based Benchmark Prices

Our value-based benchmark prices for each MS treatment are provided in Table 28. As noted in the ICER methods document, the value-based benchmark price for a drug is defined as the price range that would achieve cost-effectiveness ratios between $100,000 and $150,000 per QALY gained. Because the estimated cost-effectiveness of alemtuzumab was well below $100,000 per QALY in our base case, its price could be increased substantially before reaching $100,000 per QALY or $150,000 per QALY WTP thresholds. For all other DMTs, the discounts required to achieve both WTP threshold prices are greater than the current discounted WAC (Table 28). As mentioned above, there was no price for which teriflunomide 7mg dose would achieve a $100,000/QALY threshold.

Table 28. Value-based Price Benchmarks for MS Disease-Modifying Therapies

DMT	WAC (per package)	Cost to achieve $100,000/QALY	Cost to achieve $150,000/QALY	Discount from WAC to reach WTP threshold
Interferon β-1a 30 mcg (Avonex)	$6,287	$586	$1,562	75% to 91%
Interferon β-1b 250 mcg (Betaseron)	$6,648	$1,504	$2,768	58% to 77%
Interferon β-1b 250 mcg (Extavia)	$5,947	$1,611	$2,965	50% to 73%
Glatiramer Acetate 20 mg (Copaxone)	$7,114	$1,095	$2,332	67% to 85%
Glatiramer Acetate 20 mg (Glatopa)	$5,194	$1,095	$2,332	55% to 79%
Interferon β-1a 22 mcg (Rebif)	$6,629	$541	$1,539	77% to 92%
Interferon β-1a 44 mcg (Rebif)	$6,629	$624	$2,090	68% to 91%
Peginterferon β-1a	$6,287	$1,623	$3,017	52% to 74%
Daclizumab	$6,833	$1,975	$4,159	39% to 71%
Fingolimod	$6,743	$1,316	$3,103	54% to 81%
Teriflunomide 14 mg	$5,877	$129	$1,945	67% to 98%
Teriflunomide 7 mg	$5,877	N/C	$802	86%
Dimethyl Fumarate	$6,820	$982	$3,340	51% to 86%
Natalizumab	$6,000	$2,147	$3,808	37% to 64%
Alemtuzumab	$20,750	$65,047	$101,771	213% to 390% increase
Ocrelizumab (RRMS)*	--	$34,235	$58,608	--
Ocrelizumab (PPMS)*	--	$9,288	$14,367	--

*Annual prices are presented for ocrelizumab because package prices are not currently available.
N/C: Not calculable; there is no price that can achieve a given cost-effectiveness threshold, even at $0

6.7 Summary and Comment

We estimated the cost-effectiveness of various DMTs over a lifetime time horizon for adult patients with RRMS and PPMS. Patient time spent in EDSS-defined health states was summed to provide estimates of life expectancy and quality-adjusted life expectancy. Annual net health care costs, including drug acquisition, administration, and monitoring costs, were summed to estimate lifetime costs for each DMT. We used a natural history transition matrix and applied a relative risk for each therapy to derive DMT-specific transition probabilities between EDSS states, and included each treatment's effect on relapse rates.

Compared to supportive care for RRMS, costs per additional QALY were estimated to total approximately $38,300 for alemtuzumab, but exceeded the commonly-cited threshold of $150,000 per QALY for all other DMTs (range: $183,200 for Interferon β-1b 250 mcg [Extavia] to $355,100 for interferon β-1a 22 mcg). Alemtuzumab provided the highest number of QALYs gained while costing

less than all other treatments except supportive care. The newest approved agent, daclizumab, produced an estimate of approximately $203,400 per QALY gained. Among patients with PPMS, ocrelizumab was estimated to produce an additional 0.58 QALY or an additional 0.50 life year compared to supportive care, based on relatively modest clinical benefits in this more difficult-to-treat population.

When compared to generic glatiramer acetate 20 mg, six DMTs were more costly and less effective or cost-increasing (i.e., more costly with the same effectiveness). Among those DMTs with better health outcomes compared to generic glatiramer acetate 20 mg, costs per additional QALY ranged from approximately $144,900 per QALY for interferon β-1b 250 mcg (Extavia) to approximately $451,300 for fingolimod. Alemtuzumab was more effective and less costly, meaning that projected costs were lower and projected QALYs and life-years were higher than for glatiramer acetate. The cost-effectiveness of daclizumab was estimated to be approximately $228,900 per QALY gained.

Our budget impact estimates for daclizumab suggest that its use in RRMS will not increase costs to a level that raises concerns regarding short-term affordability for the health-care system at our assumed discounted price, but that only 76% of the population could be treated without crossing the threshold at the full WAC. Our potential budget impact estimates indicate that all eligible RRMS and PPMS patients could be treated with ocrelizumab at its $150,000 per QALY gained price without exceeding the budget impact threshold.

We have attempted to model MS treatment to both reflect clinical practice and accommodate the limits of available data. The latter has placed some restrictions on how accurately we can model MS treatment. There were several key limitations of our analysis.

First, 24-week disability progression data were not available for all clinical trials. Second, natural history data for RRMS and SPMS patients by EDSS state are from older studies. The populations from this dataset may not represent current MS populations due to differences in diagnostic and treatment practices. As a high-quality data source does not exist for untreated patients beginning DMTs, we were limited to mixed populations of DMT-naïve and DMT-experienced patients to capture the most generalizable population. Third, clinical practice guidelines have not yet reached consensus on treatment sequencing for RRMS. Though some DMTs are more often used for later lines of therapy, none of their indications exclude first-line use, and there is no single treatment pattern for later lines of therapy. For these reasons, we chose to model an aggregate of the most commonly used second-line treatments to reflect continued costs and health gains after discontinuing first-line treatment. However, given the variety of second-line treatment options, this may not be representative of the treatment patterns for all patients. Fourth, limited data exist for PPMS patients, including natural history data in a format relevant to our model structure, costs by EDSS state, and utilities by EDSS state. For these inputs, we assumed PPMS to be similar to SPMS. If there are major differences between these patient populations beyond relapse rates, the relevance

of our findings for PPMS may be limited. In addition, the net prices used in our analysis are meant to reflect an estimate of average discount from WAC, but it should be noted that discounts vary widely across payers and that specific discount information is usually not publicly available. Finally, the cost of ocrelizumab has not yet been released; we therefore were not able to calculate a base case estimate of cost-effectiveness for this DMT.

Conclusions

In summary, our analyses indicate that the DMTs of interest in this evaluation uniformly and substantially improved health outcomes compared to best supportive care, but demonstrated mixed results compared to generic glatiramer acetate. These outcomes come at a high relative cost. In almost all cases, pairwise results were well above commonly cited thresholds for cost-effectiveness. The notable exception to this finding was alemtuzumab, which consistently demonstrated improved health outcomes and good value compared to both supportive care and generic glatiramer acetate 20 mg. The costs of alemtuzumab were much lower than other DMTs, as it does not require continuous dosing over time and the manufacturer covers the costs of laboratory monitoring, which led to lower incremental cost-effectiveness ratios. Caution in considering the cost-effectiveness findings for alemtuzumab is required, however, given the safety concerns relevant to this DMT described in Section 4 of this report and elsewhere.

7. Summary of the Votes and Considerations for Policy

7.1 About the CTAF Process

During CTAF public meetings, the CTAF Panel deliberates and votes on key questions related to the systematic review of the clinical evidence, an economic analysis of the applications of treatments under examination, and the supplementary information presented. Panel members are not pre-selected based on the topic being addressed and are intentionally selected to represent a range of expertise and diverse perspectives.

Acknowledging that any judgment of evidence is strengthened by real-life clinical and patient perspectives, subject matter experts are recruited for each meeting topic and provide input to CTAF Panel members before the meeting to help clarify their understanding of the different interventions being analyzed in the evidence review. The same clinical experts serve as a resource to the CTAF Panel during their deliberation, and help to shape recommendations on ways the evidence can apply to policy and practice.

After the CTAF Panel votes, a policy roundtable discussion is held with the CTAF Panel, clinical experts, patient advocates, payers, and when feasible, manufacturers. The goal of this discussion is to bring stakeholders together to apply the evidence to guide patient education, clinical practice, and coverage and public policies. Participants on policy roundtables are selected for their expertise on the specific meeting topic, are different for each meeting, and do not vote on any questions.

At the February 16, 2017 meeting, the CTAF Panel discussed issues regarding the application of the available evidence to help patients, clinicians, and payers address important questions related to the use of disease-modifying therapies for relapsing-remitting and primary-progressive multiple sclerosis (RRMS and PPMS, respectively). Following the evidence presentation and public comments (public comments from the meeting can be accessed here, starting at minute 1:24:10), the CTAF Panel voted on key questions concerning the comparative clinical effectiveness and comparative value of treatment options for RRMS and PPMS. These questions are developed by the ICER research team for each assessment to ensure that the questions are framed to address the issues that are most important in applying the evidence to support clinical practice, medical policy decisions, and patient decision-making. The voting results are presented below, along with comments reflecting considerations mentioned by CTAF Panel members during the voting process.

In its deliberations and votes related to value, the CTAF Panel made use of a value assessment framework with four different components of “long term value for money,” a concept that

represents the long-term perspective, at the individual patient level, on patient benefits with a given intervention and the incremental costs to achieve those benefits. The four components of long term value for money are comparative clinical effectiveness, estimated incremental cost-effectiveness, other benefits or disadvantages, and contextual considerations regarding the illness or therapy.

There are four elements to consider when deliberating on long term value for money:

1. Comparative clinical effectiveness is a judgment of the overall difference in clinical outcomes between two interventions (or between an intervention and placebo), tempered by the level of certainty possible given the strengths and weaknesses of the body of evidence. CTAF uses the ICER Evidence Rating Matrix as its conceptual framework for considering comparative clinical effectiveness.

2. Estimated incremental cost-effectiveness is the average per-patient incremental cost of one intervention compared to another to achieve a desired "health gain," such as an additional stroke prevented, case of cancer diagnosed, or gain of a year of life. Alternative interventions are compared in terms of cost per unit of effectiveness, and the resulting comparison is presented as a cost-effectiveness ratio. Relative certainty in the cost and outcome estimates continues to be a consideration. As a measure of cost-effectiveness, ICER follows common academic and World Health Organization (WHO) standards by using cost per quality-adjusted life years (QALYs) and adopting thresholds at $100,000 per QALY and $150,000 per QALY as guides to reasonable ratios for cost-effectiveness.

3. Other benefits or disadvantages refers to any significant benefits or disadvantages offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. Examples of other benefits include better access to treatment centers, mechanisms of treatment delivery that require fewer visits to the clinician's office, treatments that reduce disparities across various patient groups, and new potential mechanisms of action for treating clinical conditions that have demonstrated low rates of response to currently available therapies. Other disadvantages could include increased burden of treatment on patients or their caregivers. For each intervention evaluated, it will be open to discussion whether other benefits or disadvantages such as these are important enough to factor into the overall judgment of care value. There is no quantitative measure for other benefits or disadvantages.

4. Contextual considerations include ethical, legal, or other issues (but not cost) that influence the relative priority of illnesses and interventions. Examples of contextual considerations include whether there are currently any existing treatments for the condition, whether the

condition severely affects quality of life or not, and whether the condition affects priority populations. There is no quantitative measure for contextual considerations.

7.2 Voting Results

1) For patients with RRMS, is the evidence adequate to demonstrate that the net health benefit of dimethyl fumarate (Tecfidera®, Biogen Inc.) is greater than that of teriflunomide 14 mg (Aubagio®, Sanofi-Genzyme, Inc.)?

Yes: 2 votes	***No: 12 votes***

Comments: Panelists who voted "no" noted that while dimethyl fumarate demonstrated a slightly superior effect on annualized relapse rate (ARR), there was no statistical difference between dimethyl fumarate and teriflunomide's effects on disability progression. While safety profiles differ between the two drugs, most panelists noted that these variations were not substantial enough to differentiate between the two agents. One panelist, however, noted that the lack of a black box warning for dimethyl fumarate indicated a more favorable risk profile, but that these safety considerations were outweighed by the lack of a demonstrated difference in disability progression results.

2) For patients with RRMS, is the evidence adequate to demonstrate that the net health benefit of fingolimod (Gilenya®, Novartis, Inc.) is greater than that of teriflunomide 14 mg?

Yes: 7 votes	No: 7 votes

Comments: All Panel members noted the statistical superiority of fingolimod on ARR when compared to teriflunomide, but that there were not statistical differences between the two drugs on disability progression. Several Panel members who voted "no" judged the safety profiles and discontinuation rates of the two drugs to be comparable. Others who voted "yes" judged fingolimod to have a slightly more favorable safety profile. One panelist who voted "yes" remarked that although the disability progression results were not statistically significant, they were directionally consistent with the ARR results.

3) For patients with RRMS, is the evidence adequate to distinguish the net health benefit between dimethyl fumarate and fingolimod?

Yes: 2 votes	***No: 12 votes***

Comments: Panel members who voted "no" highlighted the lack of statistically significant differences between dimethyl fumarate and fingolimod on ARR and disability progression. As in question 1, several panelists underscored that the three drugs have comparable safety profiles, though specific adverse events may differ from one drug to another. One panelist

noted that a head-to-head randomized controlled trial would be necessary to determine whether there is any difference in net health benefit between dimethyl fumarate and fingolimod.

4) For patients with RRMS, is the evidence adequate to demonstrate that the net health benefit of daclizumab (Zinbryta®, Biogen Inc. and AbbVie Inc.) is greater than that of dimethyl fumarate or fingolimod?

Yes: 0 votes	***No: 14 votes***

Comments: Panel members voiced nearly identical considerations as in the previous question. There were no significant differences among the three drugs for ARR or disability progression, and their safety profiles were considered comparable.

5) For patients with RRMS, is the evidence adequate to demonstrate that the net health benefit of daclizumab is greater than that of generic glatiramer acetate 20 mg (Glatopa®, Sandoz, Inc.)?

Yes: 7 votes	No: 7 votes

Comments: All panel members noted daclizumab's statistical superiority to glatiramer acetate 20 mg on ARR, but that there was no significant difference in regards to disability progression. In oral remarks at the meeting, Panel members noted that glatiramer acetate has a more favorable safety profile, while daclizumab carries greater risks and may be more difficult to use in clinical practice due to requirements for monthly office visits. Panelists who voted "yes" judged the superior effect of daclizumab on ARR sufficient to demonstrate an improved net health benefit, while panelists who voted "no" judged the safety risks to outweigh a reduction in relapses.

6) For patients with RRMS, is the evidence adequate to demonstrate that the net health benefit of ocrelizumab (Ocrevus®, Roche Genentech Inc.) is greater than that of generic glatiramer acetate 20 mg?

Yes: 12 votes	No: 2 votes

Comments: Panelists who voted "yes" highlighted the marked superiority of ocrelizumab on ARR, while many also noted that ocrelizumab was not statistically superior to glatiramer acetate in terms of disability progression. Several panelists noted some uncertainty in their affirmative votes due to the lack of real-world experience with ocrelizumab, as rare adverse events may be discovered post-approval. One panelist who voted "no" did so primarily because of uncertainty regarding long-term outcomes that could not be measured in a 96-week trial.

7) Given the available evidence for patients with RRMS, what is the long-term value for money of treatment with daclizumab versus treatment with generic glatiramer acetate 20 mg?

Low: 12 votes	Intermediate: 2 votes	High: 0 votes

Comment: Panelists who voted that daclizumab represents "low" long-term value for money when compared to generic glatiramer acetate 20 mg judged the *comparative clinical effectiveness* of daclizumab to be incrementally better or comparable to glatiramer acetate 20mg. These panelists noted that daclizumab's superior effectiveness at reducing ARR was mitigated by the greater safety risks and monitoring requirements associated with the drug, and that there was high loss to follow-up (>20%) in the DECIDE clinical trial.[83] All panelists noted that the *incremental costs per QALY gained* versus glatiramer acetate exceeded $150,000. Panel members who voted "low" long-term value for money determined that there were no significant *other benefits or disadvantages* and *contextual considerations* for daclizumab that would warrant a judgment of "intermediate" long-term value for money. One Panel member who judged daclizumab to represent "intermediate" long-term value for money found it to offer superior net health benefits when compared to glatiramer acetate 20mg.

8) For patients with primary-progressive multiple sclerosis (PPMS), is the evidence adequate to demonstrate that the net health benefit of treatment with ocrelizumab is greater than that of best supportive care?

Yes: 11 votes	No: 3 votes

Comments: Panel members who voted "yes" noted that the ORATORIO trial demonstrated a reduction in relapse rates for ocrelizumab compared to best supportive care, but highlighted some uncertainty in their overall judgment due to the drug's lack of FDA approval at the time of the meeting and the absence of real-world experience or long-term data with the drug. One panel member who voted "no" judged ocrelizumab to represent promising but inconclusive benefit for PPMS due to the relatively small number of patients in the trial and the lack of long-term data or real-world experience with the drug.

7.3 Roundtable Discussion and Key Policy Implications

Following its deliberation on the evidence, the CTAF Panel engaged in a moderated discussion with a policy roundtable about how best to apply the evidence on disease-modifying therapies for MS to policy and practice. The policy roundtable members included two patient advocates, two clinical experts, two private payers, and a representative from a pharmaceutical manufacturer. The discussion reflected multiple perspectives and opinions, and therefore, none of the statements below should be taken as a consensus view held by all participants. The names of the Policy Roundtable participants are shown below, and conflict of information disclosures for all meeting participants can be found in Appendix H.

Table 29. Policy Roundtable Members

Sara B. Alvarez, PharmD, BCPS	Manager of Pharmacoeconomic Evaluations, UnitedHealthcare Pharmacy
Peter S. Chin, MD, MSHS	Group Medical Director for Neuroscience, US Medical Affairs, Genentech, Inc.
David E. Jones, MD	Assistant Professor of Neurology, University of Virginia Health System; MS Section Chair, American Academy of Neurology
Annette Langer-Gould, MD, PhD	Research Scientist, Kaiser Permanente Department of Research and Evaluation; MS Specialist, Los Angeles Medical Center
Bari Talente, JD	Executive Vice President, Advocacy, National Multiple Sclerosis Society
Philip Posner, PhD	MS Patient
John Yao, MD, MPH, MBA, MPA, FACP	Staff Vice President of Medical Policy and Technology Assessment, Anthem, Inc.

The roundtable discussion was facilitated by Dr. Steven Pearson, MD, MSc, President of ICER. The main themes and recommendations from the discussion are organized by audience and summarized below.

Manufacturers

***Link launch prices of new disease modifying therapies (DMTs) to the added value they bring to patients compared to existing clinical options. Cease annual price increases that exceed medical inflation without new evidence of improved outcomes*.**

The cost of current therapies for MS was a primary topic of conversation during the policy roundtable. Most DMTs did not meet commonly accepted thresholds for cost-effectiveness in the US and the rate of cost increases for the MS drugs has consistently exceeded the medical inflation rate. If the current net costs of MS drug therapies were rolled back to their 2011 net costs, the price for several drugs would be aligned with ICER's value-based price benchmarks. As noted in the recommendations for payers, this would relax the pressure on payers to impose restrictive step therapy and prior authorization criteria and would improve access for patients.

Leverage clinical trial data to identify characteristics that determine which patients are likely to respond best to specific drugs.

Current MS therapies have different mechanisms of action. Given the heterogeneity of MS, it is likely that there are measurable patient factors that predict which drug or class of drugs would be most appropriate. Studies nested within randomized trials of drugs represent the ideal design to identify the predictors of response to therapy necessary to provide targeted therapy to patients with MS.

Prioritize the development of drugs that have a finite treatment duration.

Patients prefer treatments that do not require a lifetime of ongoing therapy because these agents offer reduced treatment burden and lower ongoing costs. Such therapies are also more likely to be cost-effective over the long-term. For example, drugs like alemtuzumab, which is typically administered for only one to two years, are more cost-effective than drugs with similar outcomes but which require ongoing administration. As discussed in the full report, however, treatment choice must also include discussions of risk, given the safety concerns associated with alemtuzumab.

Payers

In line with recommendations from key patient groups, implement policies to allow patients to remain on a treatment that works regardless of coverage or formulary changes, and without onerous prior authorization documentation required of providers each year.

As noted in the National MS Society "Make MS Medications Accessible" report, patients face challenges with remaining on the MS therapy that has been effective for them when their insurance changes or when the formulary changes within their current plan. Payers indicated that coverage policy generally "grandfathers" in therapies that have been effective for patients, but patients and providers highlighted examples of treatment interruption due to inefficient and burdensome prior authorization requirements as well as examples of denial of therapy.

If drug prices come into alignment with the value they bring to patients, reduce step therapy barriers to these therapies.

United Healthcare recently negotiated lower prices for several MS drugs and relaxed step therapy and prior authorization requirements. Any pricing concessions that payers negotiate should be shared with patients, who face high out-of-pocket costs for their MS care and treatment that are based on the list price for drugs. Better alignment of costs with value should also be translated into more favorable tiering of treatment options.

Develop policies to allow clinicians to prescribe rituximab for appropriate patients with MS.

Despite the limited randomized trial evidence and lack of FDA approval, several organizations, including Kaiser Permanente in the United States and the national health care system in Sweden, routinely utilize rituximab for patients with high-risk MS. Eligible patients include those who are at risk for rebound disease following discontinuation of natalizumab and patients for whom natalizumab would be recommended, but are deemed ineligible because they are positive for the JC virus or have other contraindications to natalizumab. Observational data strongly support the superiority of rituximab over fingolimod in preventing relapses following discontinuation of natalizumab.

Patient Advocacy Organizations

Engage with manufacturers in the design and conduct of pre- and post-approval studies of MS therapies.

Patients highlighted the lack of comparative effectiveness results on patient centered outcomes such as fatigue, cognitive function, and overall quality of life. To help solve this knowledge gap, patient advocacy organizations can advocate for consistent patient-centered outcomes to be integrated into the pivotal clinical trials. They also can contribute to the development of high-quality MS patient registries and participate in them to answer questions about long-term outcomes, such as disability progression over 5 or more years, that are not addressed by most trials. Examples of ongoing efforts supported by patient advocacy organizations and manufacturers include Optimizing Treatment and Understanding Progression (OPT-UP), North American Research Committee on Multiple Sclerosis (NARCOMS), North American Registry for Care and Research in Multiple Sclerosis (NARCRMS), Patient Informed Clinical Trials, and Patient Reported Outcomes Measurement Information System (PROMIS).

Advocate for value-based pricing of MS therapies.

One of the consistent messages from patients was the desire for their physicians to have access to the full range of disease-modifying treatments in order to tailor the choice of therapy to the patient's individual disease characteristics, risk tolerance, and dosing preference. However, the primary reason that payers limit access is cost. Patient advocacy organizations can balance calls for expanded access to medications with increased pressure on pricing; as unrestricted access is likely to cause further price escalation. They can advocate for pharmaceutical companies to cease price increases that are not directly linked to improvements in outcomes.

Specialty Societies

Develop guidelines that include treatment sequencing and a definition of patients at high risk for more aggressive disease. Consider including assessments of value as part of the guideline development process.

Payers primarily base coverage policy on clinical guidelines. The lack of clear guidelines for the use of disease modifying therapies in MS contributes to the heterogeneity in coverage across health plans. There are at least three different treatment paradigms in use today. The traditional approach has been to start with the either the interferons or glatiramer acetate and to advance to agents with greater potential risks following treatment failure with one or more of these agents. Some clinicians now advocate for starting all patients on highly active therapy at diagnosis, while others recommend initial risk stratification with low-risk patients treated with the traditional approach and high-risk patients started on treatment with highly active, but riskier therapies. Current guidelines are not clear on the preferred approach nor do they clearly define criteria to identify patients who are at high risk for rapidly progressive or aggressive disease, despite general agreement on characteristics of high risk patients. In addition, MS clinical guidelines should consider including an assessment of value as part of the guideline development process similar to the approaches taken by the American College of Cardiology / American Heart Association and the American Society for Clinical Oncology. If specialty societies include assessments of value in their guideline development, they will be better positioned to advocate for improved alignment of drug prices with the clinical value they bring to patients.

Clinicians

Discuss potential cost burdens with patients as part of the shared decision-making process.

In the survey performed by the MS Coalition for this report, two-thirds of patients reported out of pocket costs as important or very important in their choice of MS Therapy. High costs lead some patients to skip doses or stop taking their medication altogether, leading to ineffective therapy. Patients and their providers need a frank discussion of cost when choosing the most appropriate therapy.

Regulators

Require that pivotal trials of MS agents be conducted against an active comparator.

Given the evidence that early treatment impacts long-term outcomes for patients with MS, many feel it is unethical to randomize patients with MS to placebo therapy. Indeed, most patients and providers in the US and Europe are unwilling to allow patients to be randomized to placebo, so the trials are increasingly conducted in Eastern Europe and other countries, which limits the

generalizability of these data to the American population. Clinicians and patients wrestle with the question of which therapy is right for the patient. Head-to-head trials provide clinically actionable information about which therapy is more effective. Placebo-controlled trials more directly answer the question of whether to initiate or delay initiation of therapy, which is no longer clinically relevant.

Researchers

Work with patients to standardize the patient-centered outcomes that are included in trials of MS drugs.

As noted above, the lack of consistently reported patient-centered outcomes limits the ability to fully assess the comparative effectiveness of the MS drugs. Experts highlighted two instruments that may be appropriate for use in all MS trials: the Short Form 36 (SF-36), a generic health-related quality of life instrument validated in multiple populations around the world, or the Multiple Sclerosis Quality of Life-54 (MSQOL-54), which includes the SF-36 along with additional MS-specific measures. Ongoing work by the Multiple Sclerosis Outcome Assessment Consortium and the National Institute of Neurologic Disorders and Stroke Common Data Elements initiative are efforts that may address this recommendation. Continued investment in comparative effectiveness research organizations, such as the Patient-Centered Outcomes Research Institute (PCORI), that require the involvement of patients in all phases of study development from the initial study design, patient recruitment and retention, and data analysis also supports this recommendation. Research conducted by these organizations is needed to help patients and clinicians hold more informed discussions about the comparative benefits and risks of the numerous available DMTs.

Conduct studies of new drugs for MS that include long-term data on disability progression.

MS is a chronic disease with disability progression measured over decades, but the current clinical trial evidence base is dominated by trials lasting two years or less, which is insufficient to confidently assess the comparative effectiveness of current MS therapies on disability progression. Extension studies following patients after completion of the randomized trials required for drug approval are insufficient to address this need because of pervasive issues of selection bias. Randomized trials should be designed comparing active therapies with defined criteria for both treatment failure and subsequent therapy choices following treatment failure with a minimum of 5 years of follow-up.

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This is the first CTAF review of DMTs for MS.

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APPENDICES

Appendix A. Search Strategies and Results

Table A1. PRISMA 2009 Checklist

	#	Checklist item
TITLE		
Title	1	Identify the report as a systematic review, meta-analysis, or both.
ABSTRACT		
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.
INTRODUCTION		
Rationale	3	Describe the rationale for the review in the context of what is already known.
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).
METHODS		
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.

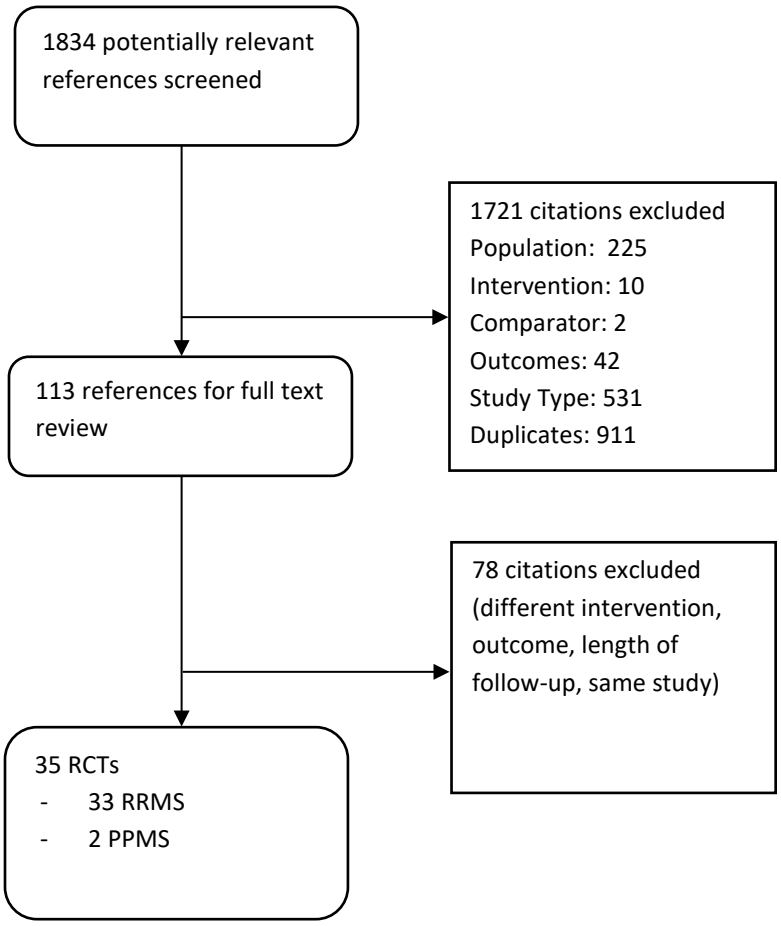
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.
RESULTS		
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).
DISCUSSION		
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.
FUNDING		
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.

From: Moher D, Liberati A, Tetzlaff J, Altman DG. The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

Table A2. Search Strategies for DMTs for RRMS

Search	Query	Items found
#20	"Search (#18 and #19) "	772
#19	"Search ((((clinical study) OR clinical trial) OR ""controlled clinical trial""[Publication Type]) OR ""randomized controlled trial""[Publication Type]) OR ""pragmatic clinical trial""[Publication Type] "	1052710
#18	"Search (#17) NOT #16"	2176
#17	"Search (#14 AND #15) "	2840
#16	"Search (guideline[Publication Type] OR practice guideline[Publication Type] OR letter[Publication Type] OR editorial[Publication Type] OR review[Publication Type] OR news[Publication Type] OR case report[Publication Type]) "	3677718
#15	"Search English[Language] "	21876235
#14	"Search (#1 AND #13) "	3066
#13	"Search (#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12)"	85479
#12	"Search ocrelizumab OR ocrevus "	113
#11	"Search zinbryta OR daclizumab "	995
#10	"Search rituxan OR rituximab "	16398
#9	"Search lemtrada OR alemtuzumab "	2368
#8	"Search tysabri OR natalizumab "	1835
#7	"Search tecfidera OR dimethyl fumarate "	734
#6	"Search aubagio OR teriflunomide "	267
#5	"Search gilenya OR fingolimod "	1931
#4	"Search (plegridy OR peginterferon) "	5916
#3	"Search (glatiramer OR copaxone OR copolymer) "	29103
#2	"Search (interferon beta OR avonex OR betaseron OR extavia OR rebif) "	29165
#1	"Search (relapsing remitting OR remitting relapsing OR relapsing-remitting OR remitting-relapsing OR RR-MS) "	9232

Figure A1. PRISMA flow Chart Showing Results of Literature Search for Multiple Sclerosis DMTs



Appendix B. Ongoing Studies

Table B1. Ongoing Studies of Injectable DMTs for MS

Title/ Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Est. Completion Date
Glatiramer acetate					
A Study in Subjects With Relapsing-Remitting Multiple Sclerosis (RRMS) to Assess the Efficacy, Safety and Tolerability of Glatiramer Acetate (GA) Injection 40 mg Administered Three Times a Week Compared to Placebo (GALA) **NCT01067521**	RCT	Glatiramer acetate 40mg Placebo	N = 1404, ages 18-55, both sexes Must have documented RRMs at screening Ambulatory with EDSS score 0-5.5 Relapse-free, stable condition, and free of corticosteroid and acthar treatment for 30 days prior to tx, between screening and baseline Must have one relapse in previous year, two relapses in previous two years, or one relapse with T1-Gd enhancing lesion in previous 12-24 months Women of child-bearing potential must use contraceptives No progressive MS No use of experimental/investigational drugs within 6 months No use of immunosuppressive or cytotoxic agents within 6 months No use of natalizumab or other monoclonal antibodies within 2 years No use of cladibrine within 2 years No previous tx with immunomodulators within 2 months No previous use of glatiramer acetate or other glatiramoid No chronic corticosteroid use within 6 months No previous total body or total lymphoid irradiation No previous stem-cell tx, autologous or allogenic bone marrow transplant No pregnant/lactating women No clinically significant or unstable medical/surgical condition No history of gadolinium sensitivity No inability to undergo MRI No drug hypersensitivity to Mannitol	Total number of confirmed relapses during placebo-controlled phase	Dec. 2016

Title/ Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Est. Completion Date
Copaxone Study to Follow Patients From the First Original Study for Safety and Effectiveness **NCT00203021**	Non-RCT	Glatiramer acetate	N = 102, ages 18+, both sexes Must have participated in original trial Women of childbearing potential must use contraceptives No pregnant/lactating women No inability to self-administer medication, or absence of other individual who can administer medication No use of interferons, experimental MS tx, previous immunosuppressive tx with cytotoxic chemotherapy, or totally lymphoid irradiation within 30 days of study entry	EDSS every 6 months AEs every 3 months	Sept. 2019

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

Table B2. Ongoing Trials of Oral DMTs for MS

Title/ Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Est. Completion Date
Dimethyl fumarate					
BG00012 Monotherapy Safety and Efficacy Extension Study in Multiple Sclerosis (MS) (ENDORSE) **NCT00835770**	RCT	Dimethyl fumarate 240 mg BID, placebo daily Dimethyl fumarate 240 mg TID (this arm was closed partway through study due to approval of 240 mg BID dosage	N = 1738, ages 19-58, both sexes Subjects must have participated in NCT00420212 or NCT00451451 to completion No significant change in medical history that would have precluded participation in above trials No participants who discontinued participation in above trials due to AE or reasons other than relapse or disability progression No participants in above trials who discontinued participation due to disability progression or relapse who did not follow modified visit schedule until week 96	Number of participants with AEs Secondary outcomes: ARR through 12 years EDSS change through 12 years Change in SF-36, EQ-5D, visual function through 12 years	Feb. 2023

Title/ Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Est. Completion Date
Fingolimod					
MS Study Evaluating Safety and Efficacy of Two Doses of Fingolimod Versus Copaxone **NCT01633112**	RCT	Fingolimod 0.5 mg daily Fingolimod 0.25 mg daily Glatiramer acetate 20 mg daily	N = 1960, ages 18-65, both sexes Diagnosis of RRMS EDSS score 0-6.0 Neurologically stable with no relapse/steroid use within 30 days 1 relapse within previous year or 2 relapses within previous 2 years Patients treated with IFN-β or glatiramer can continue tx until randomization No history of malignancy other than basal cell carcinoma No active chronic disease of the immune system other than MS No previous tx with high-dose immunoglobulin, immunosuppressive/chemotherapeutic medication, monoclonal antibodies, rituximab, alemtuzumab, ofatumumab, ocrelizumab, mitoxantrone, cladibrine, corticosteroids, adrenocorticotropic hormones at varying timeframes before randomization No uncontrolled diabetes mellitus No macular edema No hepatitis A, B, C, or E (acute or chronic) No patients who are negative for varicella zoster IgG antibodies No live or attenuated vaccination within 1 month No total lymphoid irradiation, bone marrow transplantation No unstable medical/psychiatric condition	ARR reduction through 12 months	Mar. 2022

Title/ Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Est. Completion Date
Efficacy of Fingolimod in de Novo Patients Versus Fingolimod in Patients Previously Treated With a First Line Disease Modifying Therapy (EARLiMS) **NCT01498887**	Open-label RCT	Fingolimod	N = 434, ages 18-50, both sexes Diagnosis of MS with at least 9 T2 lesions, disease duration ≥ 1 year, ≤ 5 years Patients who have had at least 2 relapses in previous 2 years and who have EDSS score 0-3.5 Patients who are DMT-naïve, patients who have been treated with a "first-line" DMT No prior tx with fingolimod, immunosuppressant drugs, monoclonal antibodies at any time No tx with immunoglobulins in previous 6 months	ARR difference between groups at 12 months Secondary outcomes: Time to first relapse Disability progression by EDSS at 12 months	July 2016

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

Table B2. Ongoing Trials of Infused DMTs for MS

Title/ Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Est. Completion Date
Alemtuzumab					
Phase IIIB-IV Long-Term Follow-up Study for Patients Who Participated in CAMMS03409 (TOPAZ) **NCT02255656**	Non-RCT	alemtuzumab	N = 812, ages 18+, both sexes Participants must complete at least 48 months of extension study CAMMS03409 No simultaneous participation in other investigational trials	AEs, SAEs through 5.5 years Secondary outcomes: ARR, change in EDSS through 5.5 years Change in self-reported QoL, EQ-5D	Mar. 2020

Title/ Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Est. Completion Date
Ocrelizumab					
A Study of Ocrelizumab in Comparison With Interferon Beta-1a (Rebif) in Participants With Relapsing Multiple Sclerosis **NCT01412333**	RCT	Ocrelizumab 600 mg IFN B-1a (Rebif) 44 mcg	N = 835, ages 18-55, both sexes Diagnosis of MS EDSS score 0-5.5 2+ documented attacks within previous 2 years, or one clinical attack in previous year but not within 30 days of screening Neurological stability in at least the month before screening/baseline No PPMS No disease duration of 10+ years with EDSS score ≤ 2.0 No contraindication for MRI No neurological disorders that may be similar to MS No pregnant/lactating women No requirement for chronic tx with systemic corticosteroids or immunosuppresives No primary or secondary immunodeficiency No history of allergic/anaphylactic reactions to monoclonal antibodies No chronic infection No history of PML No contraindication/intolerance to oral/IV corticosteroids No contraindication to Rebif	ARR at 96 weeks Secondary outcomes: 12- and 24- week confirmed disability progression by EDSS score SF-36 at week 96 NEDA at week 96	Jan. 2020

Title/ Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Est. Completion Date
A Study of Ocrelizumab in Comparison With Interferon Beta-1a (Rebif) in Participants With Relapsing Multiple Sclerosis **NCT01247324**	RCT	Ocrelizumab 600 mg IFN B-1a (Rebif) 44 mcg	N = 821, ages 18-55, both sexes Diagnosis of MS EDSS score 0-5.5 2+ documented attacks within previous 2 years, or one clinical attack in previous year but not within 30 days of screening Neurological stability in at least the month before screening/baseline No PPMS No disease duration of 10+ years with EDSS score ≤ 2.0 No contraindication for MRI No neurological disorders that may be similar to MS No pregnant/lactating women No requirement for chronic tx with systemic corticosteroids or immunosuppressives No primary or secondary immunodeficiency No history of allergic/anaphylactic reactions to monoclonal antibodies No chronic infection No history of PML No contraindication/intolerance to oral/IV corticosteroids No contraindication to Rebif	ARR at 96 weeks Secondary outcomes: 12- and 24- week confirmed disability progression by EDSS score SF-36 at week 96 NEDA at week 96	Nov. 2019

Title/ Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Est. Completion Date
A Study of Ocrelizumab in Patients With Primary Progressive Multiple Sclerosis **NCT01194570**	RCT	Ocrelizumab 600 mg Placebo	N = 736, ages 18-55, both sexes Diagnosis of PPMS EDSS score 3-6.5 Disease duration of < 15 years if EDSS > 5, < 10 years if EDSS ≥ 5 Must use contraceptives during trial and 48 weeks after last dose No RRMS, SPMS, or PRMS No contraindication to MRI No presence of other neurological disorders No active infection or chronic/recurrent infection Know history of cancer No previous use of B-cell targeted therapies No previous treatment with lymphocyte trafficking blockers No concomitant disease that may require chronic use of systemic corticosteroids or immunosuppressants	12-week confirmed disability progression by EDSS score Secondary outcomes: 24-week confirmed disability progression by EDSS score	April 2021

Title/ Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Est. Completion Date
A Study of Ocrelizumab in Participants with Relapsing Remitting Multiple Sclerosis (RRMS) Who Have Had A Suboptimal Response to an Adequate Course of Disease-Modifying Treatment (DMT) **NCT02637856**	Open-label	Ocrelizumab 600 mg	N = 600, ages 18-55, both sexes Diagnosis of RRMS under 2010 McDonald criteria Disease duration of 10 years or less Prior treatment with up to 2 DMTs for longer than 6 months, discontinuation of most recent DMT due to lack of suboptimal treatment response (ie, 1+ relapses, 1+ T1 lesions, 2+ T2 lesions) No PPMS No contraindication to MRI No known presence of conditions that may mimic MS No pregnant/lactating women No chronic treatment with systemic corticosteroids or immunosuppressants during study No history of or active primary or secondary immunodeficiency No lack of peripheral venous access No history of allergic/anaphylactic reactions to monoclonal antibodies No active or past infection with hepatitis B, C, HIV, syphilis, or tuberculosis No history of PML No contraindication or intolerance to oral or IV corticosteroids	Percentage or participants free of relapse, T1 lesions, new or enlarging T2 Lesion, Confirmed disability progression	December 2019

Title/ Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Est. Completion Date
A Study of Ocrelizumab in Participants With Relapsing Remitting Multiple Sclerosis (RRMS) Who Have Had a Suboptimal Response to an Adequate Course of Disease-Modifying Treatment (DMT) **NCT02861014**	Open label	Ocrelizumab 600 mg	N = 600, ages 18-55, both sexes Diagnosis of RRMS under 2010 McDonald criteria Disease duration of less than 10 years Prior treatment with up to 2 DMTs for longer than 6 months, discontinuation of most recent DMT due to lack of suboptimal treatment response EDSS from 0.0 – 4.0 at screening No SPMS, PPMS, or PRMS No contraindication to MRI No other neurological disorders No concomitant disease that requires treatment with systemic corticosteroids or immunosuppressants No history of or active primary or secondary immunodeficiency No history of allergic/anaphylactic reactions to monoclonal antibodies No history of opportunistic infections No recurrent or chronic infection No history of malignancy No congestive heart failure No active bacterial, viral, fungal, mycobacterial infection or other infection	Percent of patients with No Evidence of Disease Activity (NEDA) Secondary Outcomes Percent of participants free of confirmed disability progression Annual relapse rate	December 2020

Title/ Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Est. Completion Date
Rituximab					
Rituximab Versus Fumarate in Newly Diagnosed Multiple Sclerosis. (RIFUND-MS) **NCT02746744**	RCT	Rituximab every 6 months Dimethyl fumarate Placebo	N = 200, ages 18-40, both sexes Diagnosis of RRMS or one demyelinating episode with ≥ 2 asymptomatic high-intensity lesions compatible with MS diagnosis No previous MS tx other than with interferon or glatiramer acetate <5 years disease duration ≥ 1 relapse, ≥ 2 T2 lesions, or ≥ Gd+ lesions in previous year EDSS score 0-5.5 Women of childbearing potential must use contraceptives No pregnant/lactating women No progressive MS No contraindication to MRI No simultaneous tx with other immunosuppressive drugs No active or severe infections No severe cardiac disorder No vaccination within 4 weeks No allergy or intolerance to study drugs No severe psychiatric condition	Relative risk of relapse during study period	Aug. 2021

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

Appendix C. Comparative Clinical Effectiveness Supplemental Information

We performed screening at both the abstract and full-text level. A single investigator 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 FDA documents related to MS. These included the manufacturer's submission to the agency, internal FDA review documents, and the transcript of Advisory Committee deliberations and discussions. All literature that did not undergo a formal peer review process is described separately.

We used criteria published by the US Preventive Services Task Force (USPSTF) to assess the quality of RCTs and comparative cohort studies, using the categories "good," "fair," or "poor" (see Appendix Table F2)[78] Guidance for quality ratings using these criteria is presented below, as is a description of any modifications we made to these ratings specific to the purposes of this review.

Good: *Meets all criteria: Comparable groups are assembled initially and maintained throughout the study; reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention is paid to confounders in analysis. In addition, intention to treat analysis is used for RCTs.*

Fair: *Studies were graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are addressed. Intention to treat analysis is done for RCTs.*

Poor: *Studies were graded "poor" if any of the following fatal flaws exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For RCTs, intention to treat analysis is lacking.*

Table C1. Summary of Randomized Trials of DMTs for RRMS

Reference	Study	Group*	N	F/U (weeks)	MS Definition	Prior Treatment
Interferon β-1a 30 mcg (Avonex)						
Jacobs 1996[80]	-	IFN β-1a 30 mcg IM Q week Placebo IM Q week	158 143	104	Poser	No
Calabrese 2012[124]	-	IFN β-1a 30 mcg IM Q week IFN β-1a 44 mcg SC TIW Glatiramer 20 mg SC QD	55 55 55	104	McDonald	Mixed
Lublin 2013[45]	CombiRx	IFN β-1a 30 mcg IM Q week Glatiramer 20 mg SC QD	250 259	156	McDonald	No
Vollmer 2014[101]	BRAVO	IFNβ-1a 30 mcg IM Q week Placebo IM Q week	447 450	104	McDonald	Mixed
Interferon β-1b 250 mcg (Betaseron)						
IFNβ Multiple Sclerosis Study Group 1993[92]	-	IFN β-1b 250 SC mcg QOD Placebo	124 123	104	Poser	No
Durelli 2002[149]	INCOMIN	IFN β-1b 250 SC mcg QOD IFN β-1a 30 mcg IM Q week	96 92	104	Poser	No
Etemadifar 2006[150]	-	IFN β-1b 250 SC mcg QOD IFN β-1a 30 mcg IM Q week IFN β-1a 44 mcg SC TIW	30 30 30	104	Poser	No
Cadavid 2009[151]	BECOME	IFN β-1b 250 SC mcg QOD Glatiramer 20 mg SC QD	36 39	104	McDonald	No
O'Connor 2009[152]	BEYOND	IFN β-1b 250 SC mcg QOD Glatiramer 20 mg SC QD	897 448	104+	McDonald	No
Glatiramer Acetate (Copaxone)						
Bornstein 1987[13]	-	Glatiramer 20 mg SC QD Placebo SC QD	25 23	104	Poser	No
Johnson 1995[93]	-	Glatiramer 20 mg SC QD Placebo SC QD	125 126	104	Poser	Mixed
Khan 2013[16]	GALA	Glatiramer 40 mg SC TIW Placebo SC QD	943 461	52	McDonald	Mixed

Reference	Study	Group*	N	F/U (weeks)	MS Definition	Prior Treatment
Interferon β-1a 22/44 mcg (Rebif)						
PRISMS 1998[94]	PRISMS	IFN β-1a 22 mcg SC TIW IFN β-1a 44 mcg SC TIW Placebo SC TIW	189 184 187	104	Poser	Mixed
Panitch 2002[153]	EVIDENCE	IFN β-1a 44 mcg SC TIW IFN β-1a 30 mcg IM Q week	339 338	48 (primary endpoint assessed at 24 weeks)	Poser	Mixed
Mikol 2008[154]	REGARD	IFN β-1a 44 mcg SC TIW Glatiramer 20 mg SC QD	386 378	96	McDonald	No
Peginterferon β-1a (Plegridy)						
Calabresi 2014[155]	ADVANCE	PEG β-1a 125 mcg SC Q 14 d Placebo SC Q 14 d	512 500	48	McDonald	Mixed
Fingolimod (Gilenya)						
Cohen 2010[85]	TRANSFORMS	Fingolimod 0.5 mg PO QD IFN β-1a 30 mcg IM Q week	429 431	52	McDonald	Mixed
Kappos 2010[81]	FREEDOMS	Fingolimod 0.5 mg PO QD Placebo PO QD	425 418	104	McDonald	Mixed
Calabresi 2014[96]	FREEDOMS II	Fingolimod 0.5 mg PO QD Placebo PO QD	358 355	104	McDonald	Mixed
Teriflunomide (Aubagio)						
O'Connor 2011[100]	TEMSO	Teriflunomide 7 mg PO QD Teriflunomide 14 mg PO QD Placebo PO QD	365 358 363	108	McDonald	Mixed
Confavreux 2014[97]	TOWER	Teriflunomide 7 mg PO QD Teriflunomide 14 mg PO QD Placebo PO QD	407 370 388	48+	McDonald	Mixed

Reference	Study	Group*	N	F/U (weeks)	MS Definition	Prior Treatment
Vermersch 2014[86]	TENERE	Teriflunomide 7 mg PO QD Teriflunomide 14 mg PO QD IFN β-1a 44 mcg SC TIW	109 111 104	48+	McDonald	Mixed
Dimethyl fumarate (Tecfidera)						
Fox 2012[87]	CONFIRM	Dimethyl fumarate 240 mg PO BID Glatiramer 20 mg SC QD Placebo	359 350 363	96	McDonald	Mixed
Gold 2012[99]	DEFINE	Dimethyl fumarate 240 mg PO BID Placebo PO BID	410 408	96	McDonald	Mixed
Natalizumab (Tysabri)						
Polman 2006[32]	AFFIRM	Natalizumab 300 mg IV Q 4 weeks Placebo IV Q 4 weeks	627 315	104	McDonald	Mixed
Alemtuzumab (Lemtrada)						
Coles 2008[89]	CAMMS223	Alemtuzumab 12 mg IV Q year IFN β-1a 44 mcg SC TIW	112 111	156	McDonald	No
Cohen 2012[88]	CARE-MS I	Alemtuzumab 12 mg IV Q year IFN β-1a 44 mcg SC TIW	376 187	104	McDonald	No
Coles 2012[90]	CARE-MS II	Alemtuzumab 12 mg IV Q year IFN β-1a 44 mcg SC TIW	426 202	104	McDonald	Yes
Daclizumab (Zinbryta)						
Gold 2013[82]	SELECT	Daclizumab 150 mg SC Q 4 weeks Placebo SC Q 4 weeks	201 196	52	McDonald	Mixed
Kappos 2015[83]	DECIDE	Daclizumab 150 mg SC Q 4 weeks IFN β-1a 30 mcg IM Q week	919 922	144	McDonald	Mixed
Ocrelizumab (Ocrevus)						
Hauser 2017[14]	OPERA I	Ocrelizumab 600 mg IV Q 24 weeks IFN β-1a 44 mcg SC TIW	410 411	96	McDonald	Mixed
Hauser 2017[14]	OPERA II	Ocrelizumab 600 mg IV Q 24 weeks IFN β-1a 44 mcg SC TIW	417 418	96	McDonald	Mixed

Reference	Study	Group*	N	F/U (weeks)	MS Definition	Prior Treatment
Rituximab (Rituxan)						
Hauser 2008[84]	HERMES	Rituximab 1000 mg IV on days 1&15 Placebo IV	69 35	48	McDonald	Mixed

Table C2. Baseline Characteristics of Patients in RCTs of DMTs for RRMS

Reference	Group	Age	% Female	% White	MS Duration	EDSS baseline	Relapses prior year	MRI GdE lesions
Interferon β-1a 30 mcg (Avonex)								
Jacobs 1996[80]	IFN β-1a 30 mcg IM Q week Placebo IM Q week	37	73	92	6.5	2.4	1.2	NR
Calabrese 2012[124]	IFN β-1a 30 mcg IM Q week IFN β-1a 44 mcg SC TIW Glatiramer 20 mg SC QD	37	70	NR	5.6	2.0	1.2	NR
Lublin 2013[45] **CombiRx**	IFN β-1a 30 mcg IM Q week Glatiramer 20 mg SC QD	38	72	88	1.2	2.0	1.7	4.3
Vollmer 2014[101] **BRAVO**	IFN β-1a 30 mcg IM Q week Placebo IM Q week	38	70	NR	5.0	2.5	1.0	65% with 0
Interferon β-1b 250 mcg (Betaseron)								
IFNβ Multiple Sclerosis Study Group 1993[92]	IFN β-1b 250 SC mcg QOD Placebo	35	70	94	NR	2.4	2 years: 2.6	4.3
Durelli 2002[149] **INCOMIN**	IFN β-1b 250 SC mcg QOD IFN β-1a 30 mcg IM Q week	37	65	NR	6.3	2.0	1.5	NR
Etemadifar 2006[150]	IFN β-1b 250 SC mcg QOD IFN β-1a 30 mcg IM Q week IFN β-1a 44 mcg SC TIW	29	76	NR	3.2	2.0	2.2	NR
Cadavid 2009[151] **BECOME**	IFN β-1b 250 SC mcg QOD Glatiramer 20 mg SC QD	36	69	52	1.1	2	1.9	NR
O'Connor 2009[152] **BEYOND**	IFN β-1b 250 SC mcg QOD Glatiramer 20 mg SC QD	36	69	91	5.3	2.3	1.3	2.1

Reference	Group	Age	% Female	% White	MS Duration	EDSS baseline	Relapses prior year	MRI GdE lesions
Glatiramer Acetate (Copaxone)								
Bornstein 1987[13]	Glatiramer 20 mg SC QD Placebo SC QD	31	56	96	5.6	3.0	2 years: 3.8	NR
Johnson 1995[93]	Glatiramer 20 mg SC QD Placebo SC QD	34	73	94	6.9	2.6	2 years: 2.9	NR
Khan 2013[16] **GALA**	Glatiramer 40 mg SC TIW Placebo SC QD	37	68	98	7.7	2.8	1.3	1.6
Interferon β-1a 22/44 mcg (Rebif)								
PRISMS 1998[94] **PRISMS**	IFNβ-1a 22 mg SC TIW IFNβ-1a 44 mcg SC TIW Placebo SC TIW	35	69	NR	5.3	2.5	2 years: 3.0	NR
Panitch 2002[153] **EVIDENCE**	IFNβ-1a 44 mcg SC TIW IFNβ-1a 30 mcg IM Q week	38	75	91	6.6	2.3	2 years: 2.6	NR
Mikol 2008[154] **REGARD**	IFNβ-1a 44 mcg SC TIW Glatiramer 20 mg SC QD	37	71	94	6.2	2.3	NR	1.6
Peginterferon β-1a (Plegridy)								
Calabresi 2014[155] **ADVANCE**	PegIFN β-1a 125 mcg SC Q 14 d Placebo SC Q 14 d	37	71	NR	6.6	NR, 84% <4	1.6	1.4
Fingolimod (Gilenya)								
Cohen 2010[85] **TRANSFORMS**	Fingolimod 0.5 mg PO QD IFNβ-1a 30 mcg IM Q week	38	72	88	1.2	2.0	1.7	4.3
Kappos 2010[81] **FREEDOMS**	Fingolimod 0.5 mg PO QD Placebo PO QD	37	70	94	NR	2.9	2 years: 3.4	NR
Calabresi 2014[96] **FREEDOMS II**	Fingolimod 0.5 mg PO QD Placebo PO QD	40	79	NR	10.5	2.4	1.4	1.3
Teriflunomide (Aubagio)								
O'Connor 2011[100] **TEMSO**	Teriflunomide 7 mg PO QD Teriflunomide 14 mg PO QD Placebo PO QD	38	72	97	8.7	2.7	1.4	1.7

Reference	Group	Age	% Female	% White	MS Duration	EDSS baseline	Relapses prior year	MRI GdE lesions
Confavreux 2014[97] **TOWER**	Teriflunomide 7 mg PO QD Teriflunomide 14 mg PO QD Placebo PO QD	38	71	82	8.0	2.7	1.4	NR
Vermersch 2014[86] **TENERE**	Teriflunomide 7 mg PO QD Teriflunomide 14 mg PO QD IFNβ-1a 44 mcg SC TIW	37	68	100	7.1	2.1	1.3	NR
Dimethyl fumarate (Tecfidera)								
Fox 2012[87] **CONFIRM**	Dimethyl fumarate 240 mg PO BID Glatiramer 20 mg SC QD Placebo	37	70	84	4.7	2.6	1.4	NR
Gold 2012[99] **DEFINE**	Dimethyl fumarate 240 mg PO BID Placebo PO BID	38	74	78	5.7	2.4	1.3	1.3
Natalizumab (Tysabri)								
Polman 2006[32] **AFFIRM**	Natalizumab 300 mg IV Q 4 weeks Placebo IV Q 4 weeks	36	70	95	5	2.3	1.5	2.2
Alemtuzumab (Lemtrada)								
Coles 2008[89] **CAMMS223**	Alemtuzumab 12 mg IV Q year IFNβ-1a 44 mcg SC TIW	32	64	90	NR	2.0	2 year: 2.7	NR
Cohen 2012[88] **CARE-MS I**	Alemtuzumab 12 mg IV Q year IFNβ-1a 44 mcg SC TIW	33	65	95	2.1	2.0	1.8	2.3
Coles 2012[90] **CARE-MS II**	Alemtuzumab 12 mg IV Q year IFNβ-1a 44 mcg SC TIW	35	67	89	4.5	2.7	1.6	2.4
Daclizumab (Zinbryta)								
Gold 2013[82] **SELECT**	Daclizumab 150 mg SC Q 4 weeks Placebo SC Q 4 weeks	36	65	97	2.5	2.7	1.3	2.0
Kappos 2015[83] **DECIDE**	Daclizumab 150 mg SC Q 4 weeks IFNβ-1a 30 mcg IM Q week	36	68	90	6.9	2.5	1.6	2.2
Ocrelizumab (Ocrevus)								
Hauser 2017[14] **OPERA I**	Ocrelizumab 600 mg IV Q 24 weeks IFNβ-1a 44 mcg SC TIW	37	66	91	6.5	2.8	1.3	1.8

Reference	Group	Age	% Female	% White	MS Duration	EDSS baseline	Relapses prior year	MRI GdE lesions
Hauser 2017[14] **OPERA II**	Ocrelizumab 600 mg IV Q 24 weeks IFNβ-1a 44 mcg SC TIW	37	66	90	6.7	2.8	1.3	1.9
Rituximab (Rituxan)								
Hauser 2008[84] **HERMES**	Rituximab 1000 mg IV on days 1 and 15 Placebo IV	41	78	NR	9.6	2.5	1.0	1.5

Table C3. Quality Assessment of Included RCTs of DMTs for RRMS

Reference	Comparable Groups	Maintain Comparability	Double-Blind	Measurements Equal and Valid	Clearly-defined Intervention	Key Outcomes Assessed	Analysis Appropriate	Quality
Interferon β-1a 30 mcg (Avonex)								
Jacobs 1996[80]	Yes	Yes – 8%	Yes	Yes	Yes	Yes	Yes	Good
Calabrese 2012[124]	Yes	Yes – 15%	No	Yes	Yes	No	No	Poor
Lublin 2013[45] **CombiRx**	Yes	Yes – 19%	No	No	Yes	Yes	Yes	Fair
Vollmer 2014[101] **BRAVO**	Yes	Yes – 18%	No	No	Yes	Yes	Yes	Fair
Interferon β-1b 250 mcg (Betaseron)								
IFNβ Multiple Sclerosis Study Group 1993[92]	Unclear	No – 33%	Yes	Yes	Yes	Yes	Yes	Poor
Durelli 2002[149] **INCOMIN**	Yes	Yes – 16%	No	No	Yes	Yes	Yes	Fair
Etemadifar 2006[150]	No	Yes – 0%	No	No	Yes	No	Yes	Poor
Cadavid 2009[151] **BECOME**	Unclear	Yes – 15%	No	No	Yes	No	Yes	Fair
O'Connor 2009[152] **BEYOND**	Yes	Yes – 15%	No	No	Yes	No	Unclear	Fair
Glatiramer Acetate (Copaxone)								
Bornstein 1987[13]	Yes	Yes – 14%	No	No	Yes	No	Yes	Fair
Johnson 1995[93]	Unclear	Yes – 14%	Yes	Yes	Yes	No	Yes	Fair

Reference	Comparable Groups	Maintain Comparability	Double-Blind	Measurements Equal and Valid	Clearly-defined Intervention	Key Outcomes Assessed	Analysis Appropriate	Quality
Khan 2013[16] GALA	Yes	Yes – 8%	Yes	Yes	Yes	No	Yes	Fair
Interferon β-1a 22/44 mcg (Rebif)								
PRISMS 1998[94] PRISMS	Yes	Yes- 10%	Yes	Yes	Yes	No	Yes	Fair
Panitch 2002[153] EVIDENCE	Yes	Yes – 4%	No	No	Yes	Yes	Yes	Fair
Mikol 2008[154] REGARD	Yes	Yes – 18%	No	No	Yes	Yes	Yes	Fair
Peginterferon β-1a (Plegridy)								
Calabresi 2014[155] ADVANCE	Yes	Yes – 12%	Yes	Yes	Yes	No	Yes	Fair
Fingolimod (Gilenya)								
Cohen 2010[85] TRANSFORMS	Yes	Yes – 11%	Yes	Yes	Yes	No	Yes	Fair
Kappos 2010[81] FREEDOMS	Yes	Yes – 19%	Yes	Yes	Yes	Yes	Yes	Good
Calabresi 2014[96] FREEDOMS II	Yes	No - 26%	Yes	Yes	Yes	Yes	Yes	Poor
Teriflunomide (Aubagio)								
O'Connor 2011[100] TEMSO	Yes	No – 27%	Yes	Yes	Yes	No	Yes	Poor
Confavreux 2014[97] TOWER	Yes	No – 33%	Yes	Yes	Yes	No	Yes	Poor
Vermersch 2014[86] TENERE	Unclear	No – 23%	No	No	Yes	No	Yes	Poor
Dimethyl fumarate (Tecfidera)								
Fox 2012[87] CONFIRM	Yes	No – 21%	No	No	Yes	No	Yes	Poor

Reference	Comparable Groups	Maintain Comparability	Double-Blind	Measurements Equal and Valid	Clearly-defined Intervention	Key Outcomes Assessed	Analysis Appropriate	Quality
Gold 2012[99] **DEFINE**	Yes	No – 23%	Yes	Yes	Yes	No	Yes	Poor
Natalizumab (Tysabri)								
Polman 2006[32] **AFFIRM**	Yes	Yes – 9%	Yes	Yes	Yes	Yes	Yes	Good
Alemtuzumab (Lemtrada)								
Coles 2008[89] **CAMMS223**	Unclear	No – 25%	Yes	Yes	Yes	Yes	Yes	Poor
Cohen 2012[88] **CARE-MS I**	Yes	Yes – 9%	No	No	Yes	Yes	Yes	Fair
Coles 2012[90] **CARE-MS II**	Yes	Yes – 15%	No	No	Yes	Yes	Yes	Fair
Daclizumab (Zinbryta)								
Gold 2013[82] **SELECT**	Yes	Yes – 9%	Yes	Yes	Yes	No	Yes	Fair
Kappos 2015[83] **DECIDE**	Yes	No – 23%	Yes	Yes	Yes	No	Yes	Poor
Ocrelizumab (Ocrevus)								
Hauser 2017[14] **OPERA I**	Yes	Yes – 14%	Yes	Yes	Yes	Yes	Yes	Good
Hauser 2017[14] **OPERA II**	Yes	Yes – 18%	Yes	Yes	Yes	Yes	Yes	Good
Rituximab (Rituxan)								
Hauser 2008[84] **HERMES**	Unclear	Unclear	Yes	Yes	Yes	No	Yes	Fair

GdE: gadolinium-enhancing

Table C4. Annual Relapse Rate by Study

Reference	Study	Group*	N	Person-years	Relapses	ARR	95% CI
Interferon β-1a 30 mcg							
Jacobs 1996[80]	-	IFN β-1a 30 mcg IM Q week	158	293	196	0.67	NR
		Placebo IM Q week	143	274	225	0.82	NR
Calabrese 2012[124]	-	IFN β-1a 30 mcg IM Q week	47	94	47	0.5	NR
		IFN β-1a 44 mcg SC TIW	46	92	37	0.4	NR
		Glatiramer 20 mg SC QD	48	96	48	0.5	NR
Lublin 2013[45]	CombiRx	IFN β-1a 30 mcg IM Q week	250	604.4	97	0.16	NR
		Glatiramer 20 mg SC QD	259	650.7	70	0.11	NR
Vollmer 2014[101]	BRAVO	IFN β-1a 30 mcg IM Q week	447	825	215	0.26	0.22-0.30
		Placebo IM Q week	450	809	275	0.34	0.28-0.40
Interferon β-1b 250 mcg							
IFNβ Multiple Sclerosis Study Group 1993[92]	-	IFN β-1b 250 SC mcg QOD	124	207	173	0.84	0.70-0.88
		Placebo	123	209.2	266	1.27	1.02-1.23
Durelli 2002[149]	INCOMIN	IFN β-1b 250 SC mcg QOD	96	190	95	0.5	NR
		IFN β-1a 30 mcg IM Q week	92	180	126	0.7	NR
Etemadifar 2006[150]	-	IFN β-1b 250 SC mcg QOD	30	60	21	0.35	NR
		IFN β-1a 30 mcg IM Q week	30	60	36	0.6	NR
		IFN β-1a 44 mcg SC TIW	30	60	18	0.3	NR
Cadavid 2009[151]	BECOME	IFN β-1b 250 SC mcg QOD	36	68.04	25	0.37	0.24-0.53
		Glatiramer 20 mcg SC QD	39	70.59	23	0.33	0.21-0.48
O'Connor 2009[152]	BEYOND	IFN β-1b 250 SC mcg QOD	897	2260	814	0.36	0.27-0.45
		Glatiramer 20 mg SC QD	448	1099.5	374	0.34	0.22-0.46
Glatiramer Acetate							
Bornstein 1987[13]	-	Glatiramer 20 mg SC QD	25	47.5	16	0.34	NR
		Placebo SC QD	23	45.1	62	1.38	NR
Johnson 1995[93]	-	Glatiramer 20 mg SC QD	125	273	161	0.59	0.5-0.7
		Placebo SC QD	126	250	210	0.84	0.73-0.97

Reference	Study	Group*	N	Person-years	Relapses	ARR	95% CI
Khan 2013[16]	GALA	Glatiramer 40 mg SC TIW	943	884.4	293	0.331	0.28-0.39
		Placebo SC QD	461	442.5	223	0.505	0.42-0.61
Interferon β-1a 22/44 mcg							
PRISMS 1998[94]	PRISMS	IFN β-1a 22 mcg SC TIW	189	378.02	344	0.91	0.82-1.01
		IFN β-1a 44 mcg SC TIW	184	365.52	318	0.87	0.78-0.97
		Placebo SC TIW	187	374.22	479	1.28	1.17-1.4
Panitch 2002[153]	EVIDENCE	IFN β-1a 44 mcg SC TIW	339	304.71	165	0.54	NR
		IFN β-1a 30 mcg IM Q week	338	304.2	195	0.64	NR
Mikol 2008[154]	REGARD	IFN β-1a 44 mcg SC TIW	386	669.5	201	0.3	NR
		Glatiramer 20 mg SC QD	378	669.5	194	0.29	NR
Peginterferon β-1a							
Calabresi 2014[155]	ADVANCE	PEG β-1a 125 mcg SC Q 14 d	512	404.3	103	0.256	0.21-0.32
		Placebo SC Q 14 d	500	420.9	167	0.397	0.33-0.48
Fingolimod							
Cohen 2010[85]	TRANSFORMS	Fingolimod 0.5 mg PO QD	429	424.6	68	0.16	0.12-0.21
		IFN β-1a 30 mcg IM Q week	431	415.7	137	0.33	0.26-0.42
Kappos 2010[81]	FREEDOMS	Fingolimod 0.5 mg PO QD	425	810.3	146	0.18	0.15-0.22
		Placebo PO QD	418	766.3	307	0.40	0.34-0.47
Calabresi 2014[96]	FREEDOMS II	Fingolimod 0.5 mg PO QD	358	623.8	131	0.21	0.17-0.25
		Placebo PO QD	355	615	246	0.40	0.34-0.48
Teriflunomide							
O'Connor 2011[100]	TEMSO	Teriflunomide 7 mg PO QD	365	633.7	233	0.37	0.32-0.43
		Teriflunomide 14 mg PO QD	358	615.0	227	0.37	0.31-0.44
		Placebo PO QD	363	627.7	335	0.54	0.47-0.62
Confavreux 2014[97]	TOWER	Teriflunomide 7 mg PO QD	407	614	235	0.39	0.33-0.46
		Teriflunomide 14 mg PO QD	370	573.6	177	0.32	0.27-0.38
		Placebo PO QD	388	608.4	296	0.50	0.43-0.58

Reference	Study	Group*	N	Person-years	Relapses	ARR	95% CI
Vermersch 2014[86]	TENERE	Teriflunomide 7 mg PO QD	109	136.2	58	0.41	0.27-0.64
		Teriflunomide 14 mg PO QD	111	132.2	35	0.26	0.15-0.44
		IFN β-1a 44 mcg SC TIW	104	112.1	25	0.22	0.11-0.42
Dimethyl fumarate							
Fox 2012[87]	CONFIRM	Dimethyl fumarate 240 mg PO BID	359	552.99	124	0.22	NR
		Glatiramer 20 mg SC QD	350	569.62	163	0.29	NR
Supplemental data from European Medicines Agency Filing[156]		Placebo	363	561.43	212	0.40	NR
Gold 2012[99]	DEFINE	Dimethyl fumarate 240 mg PO BID	410	628.61	128	0.17	NR
		Placebo PO BID	408	612.35	246	0.36	NR
Supplemental data from European Medicines Agency Filing[156]							
Natalizumab							
Polman 2006[32]	AFFIRM	Natalizumab 300 mg IV Q 4 weeks	627	1200	276	0.23	0.19-0.28
		Placebo IV Q 4 weeks	315	578	422	0.73	0.62-0.87
Alemtuzumab							
Coles 2008[89]	CAMMS223	Alemtuzumab 12 mg IV Q year	112	309.09	34	0.11	0.08-0.16
		IFN β-1a 44 mcg SC TIW	111	247.22	89	0.36	0.29-0.44
Cohen 2012[88]	CARE-MS I	Alemtuzumab 12 mg IV Q year	376	661.11	119	0.18	0.13-0.23
		IFN β-1a 44 mcg SC TIW	187	312.82	122	0.39	0.29-0.53
Coles 2012[90]	CARE-MS II	Alemtuzumab 12 mg IV Q year	426	907.69	236	0.26	0.21-0.33
		IFN β-1a 44 mcg SC TIW	202	386.54	201	0.52	0.41-0.66
Rituximab							
Hauser 2008[84]	HERMES	Rituximab 1000 mg IV on days 1&15	69	59.227.2	2119	0.40.7	NR
		Placebo IV	35				NR

Reference	Study	Group*	N	Person-years	Relapses	ARR	95% CI
Daclizumab							
Gold 2013[82]	SELECT	Daclizumab 150 mg SC Q 4 weeks Placebo SC Q 4 weeks	201 196	217.75 212.33	46 98	0.21 0.46	0.16-0.29 0.37-0.57
Kappos 2015[83]	DECIDE	Daclizumab 150 mg SC Q 4 weeks IFN β-1a 30 mg IM Q week	919 922	1692.5 1698	372 662	0.22 0.39	0.19-0.24 0.35-0.44
Ocrelizumab							
Hauser 2017[14]	OPERA I	Ocrelizumab 600 mg IV Q 24 weeks IFN β-1a 44 mcg SC TIW	410 411	754.3 756.2	121 219	0.16 0.29	0.12-0.20 0.24-0.36
Hauser 2017[14]	OPERA II	Ocrelizumab 600 mg IV Q 24 weeks IFN β-1a 44 mcg SC TIW	417 418	767.2 769.1	123 223	0.16 0.29	0.12-0.20 0.23-0.36

Table C5. 24-week Confirmed Disability Progression Outcomes by Study

Reference	Study	Group	N	EDSS Prog24	HR	95% CI	Included in Base Case NMA?
Interferon β-1a 30 mcg (Avonex)							
Jacobs 1996[80]	-	IFN β-1a 30 mcg IM Q week Placebo IM Q week	158 143	35 50	NR	P=0.02	Y
Calabrese 2012[124]	-	IFN β-1a 30 mcg IM Q week IFN β-1a 44 mcg SC TIW Glatiramer 20 mg SC QD	55 55 55	NR NR NR			N
Lublin 2013[45]	CombiRx	IFN β-1a 30 mcg IM Q week Glatiramer 20 mg SC QD	241 246	52 61	NR	NS	Y
Vollmer 2014[101]	BRAVO	IFN β-1a 30 mcg IM Q week Placebo IM Q week	447 450	35 46	0.73	0.47-1.14	Y
Interferon β-1b 250 mcg (Betaseron)							
IFNβ Multiple Sclerosis Study Group 1993[92]	-	IFN β-1b 250 SC mcg QOD Placebo	122 122	43 56	NR	NS	Y

Reference	Study	Group	N	EDSS Prog24	HR	95% CI	Included in Base Case NMA?
Durelli 2002[149]	INCOMIN	IFN β-1b 250 SC mcg QOD IFN β-1a 30 mcg IM Q week	96 92	13 28	0.44	0.25-0.80	Y
Etemadifar 2006[150]	-	IFN β-1b 250 SC mcg QOD IFN β-1a 30 mcg IM Q week IFN β-1a 44 mcg SC TIW	30 30 30	NR NR NR			N
Cadavid 2009[151]	BECOME	IFNβ-1b 250 SC mcg QOD Glatiramer 20 mg SC QD	36 39	NR NR			N
O'Connor 2009[152]	BEYOND	IFNβ-1b 250 SC mcg QOD Glatiramer 20 mg SC QD	897 448	NR NR			N
Glatiramer Acetate (Copaxone)							
Bornstein 1987[13]	-	Glatiramer 20 mg SC QD Placebo SC QD	25 23	NR NR			N
Johnson 1995[93]	-	Glatiramer 20 mg SC QD Placebo SC QD	125 126	NR NR			N
Khan 2013[16]	GALA	Glatiramer 40 mg SC TIW Placebo SC QD	943 461	NR NR			N
Interferon β-1a 22/44 mcg (Rebif)							
PRISMS 1998[94]	PRISMS	IFN β-1a 22 mcg SC TIW IFN β-1a 44 mcg SC TIW Placebo SC TIW	189 184 187	NR NR NR			N
Panitch 2002[153]	EVIDENCE	IFN β-1a 44 mcg SC TIW IFN β-1a 30 mcg IM Q week	339 338	20 28	0.70	0.39-1.25	Y
Mikol 2008[154]	REGARD	IFN β-1a 44 mcg SC TIW Glatiramer 20 mg SC QD	386 378	45 33	NR	P=0.12	Y
Peginterferon β-1a (Plegridy)							
Calabresi 2014[155]	ADVANCE	PEG β-1a 125 mcg SC Q 14 d Placebo SC Q 14 d	512 500	NR NR			N

Reference	Study	Group	N	EDSS Prog24	HR	95% CI	Included in Base Case NMA?
Fingolimod (Gilenya)							
Cohen 2010[85]	TRANSFORMS	Fingolimod 0.5 mg PO QD IFN β-1a 30 mcg IM Q week	429 431	NR NR			N
Kappos 2010[81]	FREEDOMS	Fingolimod 0.5 mg PO QD Placebo PO QD	425 418	53 79	0.63	0.44-0.90	Y
Calabresi 2014[96]	FREEDOMS II	Fingolimod 0.5 mg PO QD Placebo PO QD	358 355	49 63	0.72	0.48-1.07	Y
Teriflunomide (Aubagio)							
O'Connor 2011[100]	TEMSO	Teriflunomide 7 mg PO QD Teriflunomide 14 mg PO QD Placebo PO QD	365 358 363	NR NR NR			N
Confavreux 2014[97]	TOWER	Teriflunomide 7 mg PO QD Teriflunomide 14 mg PO QD Placebo PO QD	407 370 388	NR NR NR			N
Vermersch 2014[86]	TENERE	Teriflunomide 7 mg PO QD Teriflunomide 14 mg PO QD IFN β-1a 44 mcg SC TIW	109 111 104	NR NR NR			N
Dimethyl fumarate (Tecfidera)							
Fox 2012[87]	CONFIRM	Dimethyl fumarate 240 mg PO BID Glatiramer 20 mg SC QD Placebo	359 350 363	NR NR NR	0.62 0.87	0.37-1.03 0.55-1.38	N
Gold 2012[99]	DEFINE	Dimethyl fumarate 240 mg PO BID Placebo PO BID	409 408	NR NR			N

Reference	Study	Group	N	EDSS Prog24	HR	95% CI	Included in Base Case NMA?
Natalizumab (Tysabri)							
Polman 2006[32]	AFFIRM	Natalizumab 300 mg IV Q 4 weeks Placebo IV Q 4 weeks	627 315	NR NR	0.46	0.33-0.64	N
Alemtuzumab (Lemtrada)							
Coles 2008[89]	CAMMS223	Alemtuzumab 12 mg IV Q year IFN β-1a 44 mcg SC TIW	112 111	8 24	0.25	0.11-0.57	Y
Cohen 2012[88]	CARE-MS I	Alemtuzumab 12 mg IV Q year IFN β-1a 44 mcg SC TIW	376 187	30 20	0.70	0.40-1.23	Y
Coles 2012[90]	CARE-MS II	Alemtuzumab 12 mg IV Q year IFN β-1a 44 mcg SC TIW	426 202	54 40	0.58	0.38-0.87	Y
Rituximab (Rituxan)							
Hauser 2008[84]	HERMES	Rituximab 1000 mg IV Placebo IV	69 35	NR NR			N
Daclizumab (Zinbryta)							
Gold 2013[82]	SELECT	Daclizumab 150 mg SC Q 4 weeks Placebo SC Q 4 weeks	201 196	NR NR			N
Kappos 2015[83]	DECIDE	Daclizumab 150 mg SC Q 4 weeks IFN β-1a 30 mcg IM Q week	919 922	120 167	0.79	0.59-1.06	N
Ocrelizumab (Ocrevus)							
Hauser 2017[14]	OPERA I	Ocrelizumab 600 mg IV Q 24 weeks IFN β-1a 44 mcg SC TIW	410 411	27 43	0.57	0.34-0.95	Y
Hauser 2017[14]	OPERA II	Ocrelizumab 600 mg IV Q 24 weeks IFN β-1a 44 mcg SC TIW	417 418	36 56	0.63	0.40-0.98	Y

Table C6. 12-week Confirmed EDSS Progression by Study

Reference	Study	Group	N	EDSS Prog12	HR	95% CI	Included in Base Case NMA?
Interferon β-1a 30 mcg (Avonex)							
Jacobs 1996[80]	-	IFN β-1a 30 mcg IM Q week Placebo IM Q week	158 143	NR NR			N
Calabrese 2012[124]	-	IFN β-1a 30 mcg IM Q week IFN β-1a 44 mcg SC TIW Glatiramer 20 mg SC QD	55 55 55	NR NR NR			N
Lublin 2013[45]	CombiRx	IFN β-1a 30 mcg IM Q week Glatiramer 20 mg SC QD	241 246	NR NR			N
Vollmer 2014[101]	BRAVO	IFN β-1a 30 mcg IM Q week Placebo IM Q week	447 450	47 60	0.74	0.51-1.09	N
Interferon β-1b 250 mcg (Betaseron)							
IFNβ Multiple Sclerosis Study Group 1993[92]	-	IFN β-1b 250 SC mcg QOD Placebo	122 122	NR NR			N
Durelli 2002[149]	INCOMIN	IFN β-1b 250 SC mcg QOD IFN β-1a 30 mg IM Q week	96 92	NR NR			N
Etemadifar 2006[150]	-	IFN β-1b 250 SC mcg QOD IFN β-1a 30 mg IM Q week IFN β-1a 44 mg SC TIW	30 30 30	NR NR NR			N
Cadavid 2009[151]	BECOME	IFN β-1b 250 SC mcg QOD Glatiramer 20 mg SC QD	36 39	NR NR			N
O'Connor 2009[152]	BEYOND	IFN β-1b 250 SC mcg QOD Glatiramer 20 mg SC QD	897 448	188 90	NR	P=0.68	Y
Glatiramer Acetate (Copaxone)							
Bornstein 1987[13]	-	Glatiramer 20 mg SC QD Placebo SC QD	25 23	NR NR			N
Johnson 1995[93]	-	Glatiramer 20 mg SC QD Placebo SC QD	125 126	27 31	NR	NS	Y

Reference	Study	Group	N	EDSS Prog12	HR	95% CI	Included in Base Case NMA?
Khan 2013[16]	GALA	Glatiramer 40 mg SC TIW Placebo SC QD	943 461	42 17			Y
Interferon β-1a 22/44 mcg (Rebif)							
PRISMS 1998[94]	PRISMS	IFN β-1a 22 mcg SC TIW IFN β-1a 44 mcg SC TIW Placebo SC TIW	189 184 187	64 54 77	0.68 0.62	0.48-0.98 0.43-0.91	Y
Panitch 2002[153]	EVIDENCE	IFN β-1a 44 mcg SC TIW IFN β-1a 30 mg IM Q week	339 338	43 49	0.87	0.58-1.31	N
Mikol 2008[154]	REGARD	IFN β-1a 44 mcg SC TIW Glatiramer 20 mg SC QD	386 378	NR NR			N
Peginterferon β-1a (Plegridy)							
Calabresi 2014[155]	ADVANCE	PEG β-1a 125 mcg SC Q 14 d Placebo SC Q 14 d	512 500	31 50	.62	0.40-0.97	Y
Fingolimod (Gilenya)							
Cohen 2010[85]	TRANSFORMS	Fingolimod 0.5 mg PO QD IFN β-1a 30 mg IM Q week	429 431	25 34		NS	Y
Kappos 2010[81]	FREEDOMS	Fingolimod 0.5 mg PO QD Placebo PO QD	425 418	75 101	0.70	0.52-0.96	N
Calabresi 2014[96]	FREEDOMS II	Fingolimod 0.5 mg PO QD Placebo PO QD	358 355	91 103	0.83	0.61-1.12	N
Teriflunomide (Aubagio)							
O'Connor 2011[100]	TEMSO	Teriflunomide 7 mg PO QD Teriflunomide 14 mg PO QD Placebo PO QD	365 358 363	68 62 86	0.76 0.70	0.56-1.05 0.51-0.97	Y

Reference	Study	Group	N	EDSS Prog12	HR	95% CI	Included in Base Case NMA?
Confavreux 2014[97]	TOWER	Teriflunomide 7 mg PO QD Teriflunomide 14 mg PO QD Placebo PO QD	407 370 388	65 44 65	0.95 0.68	0.68-1.35 0.47-1.00	Y
Vermersch 2014[86]	TENERE	Teriflunomide 7 mg PO QD Teriflunomide 14 mg PO QD IFN β-1a 44 mg SC TIW	109 111 104	NR NR NR			N
Dimethyl fumarate (Tecfidera)							
Fox 2012[87]	CONFIRM	Dimethyl fumarate 240 mg PO BID Glatiramer 20 mg SC QD Placebo	359 350 363	47 56 62	0.79 0.93	0.52-1.19 0.63-1.37	Y
Gold 2012[99]	DEFINE	Dimethyl fumarate 240 mg PO BID Placebo PO BID	409 408	65 110	0.62	0.44-0.87	Y
Natalizumab (Tysabri)							
Polman 2006[32]	AFFIRM	Natalizumab 300 mg IV Q 4 weeks Placebo IV Q 4 weeks	627 315	107 91	0.58	0.43-0.77	Y
Alemtuzumab (Lemtrada)							
Coles 2008[89]	CAMMS223	Alemtuzumab 12 mg IV Q year IFN β-1a 44 mcg SC TIW	112 111	16 30	0.42	0.23-0.77	N
Cohen 2012[88]	CARE-MS I	Alemtuzumab 12 mg IV Q year IFN β-1a 44 mcg SC TIW	376 187	NR NR			N
Coles 2012[90]	CARE-MS II	Alemtuzumab 12 mg IV Q year IFN β-1a 44 mcg SC TIW	426 202	NR NR			N
Rituximab (Rituxan)							
Hauser 2008[84]	HERMES	Rituximab 1000 mg IV Placebo IV	69 35	NR NR			N
Daclizumab (Zinbryta)							
Gold 2013[82]	SELECT	Daclizumab 150 mg SC Q 4 weeks Placebo SC Q 4 weeks	201 196	11 25	0.43	0.21-0.88	Y

Reference	Study	Group	N	EDSS Prog12	HR	95% CI	Included in Base Case NMA?
Kappos 2015[83]	DECIDE	Daclizumab 150 mg SC Q 4 weeks IFN β-1a 30 mg IM Q week	919 922	147 184	0.84	0.66-1.07	Y
Ocrelizumab (Ocrevus)							
Hauser 2017[14]	OPERA I	Ocrelizumab 600 mg IV Q 24 weeks IFN β-1a 44 mcg SC TIW	410 411	34 53	0.57	0.37-0.90	N
Hauser 2017[14]	OPERA II	Ocrelizumab 600 mg IV Q 24 weeks IFN β-1a 44 mcg SC TIW	417 418	47 73	0.63	0.42-0.92	N

Appendix D. Network Meta-Analysis Methods and Results

Network Meta-Analysis Methods

We used WinBUGS version 1.4.3 to perform a Bayesian NMA using Markov Chain Monte Carlo methods to combine direct and indirect evidence for annualized relapse rates and the risk for confirmed disability progression sustained for 24 weeks.

Uninformative priors were used for both analyses to allow the study results to inform the estimated pooled relative risks. For our primary results, we used a random-effects model. We expected *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. The deviance information criteria (DIC) and residual deviance (resdev) statistics were similar for the fixed and random effects models for both analyses. 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. In general, the trials that reported ARRs adjusted for baseline characteristics of the participants rather than crude ARRs. In order 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 number of relapses reported in the trial. If the number of relapses was not reported, then we estimated the person-years of follow-up from Kaplan-Meier curves, if reported, or by the treatment duration multiplied by the number of participants completing 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 disability progression, the primary inputs to the model were the number of patients with confirmed disability progression and the number randomized to each treatment group analyzed as a binomial outcome. We used a dichotomous model as our primary analysis due to the limited number of studies that reported disability progression as a continuous measure. For our primary analysis, we preferentially used sustained disability progression that was confirmed at 24 weeks (or 6 months) and used confirmed disability progression sustained at 12 weeks (or 3 months) when the preferred 24-week outcome was not available. We chose to combine the two outcomes in order to maximize the data available for direct and indirect comparisons in the network. We assessed the effect of this approach to imputation by comparing our primary results to those obtained when

restricting the network to trials reporting 24-week sustained disability progression and to the results using 12-week sustained disability progression. Finally, we compared our results to prior published NMA results for sustained disability progression. The relative ordering of drug effectiveness and the magnitude of the relative risk were similar in all analyses with a few exceptions, which are discussed in detail in the results section in the full report.

Methods Used to Assess Heterogeneity

We performed several analyses to assess the impact of heterogeneity on our results. As noted above, for disability progression, we analyzed the results using solely a 24-week or 12-week definition for sustained disability. For both analyses, we assessed the impact of excluding poor quality trials, smaller trials (<100 participants in any arm, which also excludes phase II trials), trials of treatment-naïve patients, trials including treatment-experienced patients, trials with a study duration less than 18 months, trials using the Poser criteria, trials using the McDonald criteria, and open-label trials. We report both the fixed- and random-effects model results of the base-case analysis. We also performed meta-regression to assess the impact of disease duration, mean number of relapses in the prior year, and baseline EDSS score on the NMA estimates. We acknowledge the limitations of using trial level data for the meta-regression analyses, but individual patient level data, which would allow for a more detailed meta-analysis, were not available.

WinBUGS Code

Base-case Model: Annual Relapse Rate

```
model{
for(i in 1:ns){
   w[i,1] <- 0
   delta[i,1] <- 0
   mu[i] ~ dnorm(0,.0001)
   for (k in 1:na[i]) {
      r[i,k] ~ dpois(theta[i,k])
      theta[i,k] <- lambda[i,k]*E[i,k] # failure rate * exposure
      log(lambda[i,k]) <- mu[i] + delta[i,k]  # model for linear predictor

      dev[i,k] <- 2*((theta[i,k]-r[i,k]) + r[i,k]*log(r[i,k]/theta[i,k]))          }

   resdev[i] <- sum(dev[i,1:na[i]])
   for (k in 2:na[i]) {
      delta[i,k] ~ dnorm(md[i,k],taud[i,k])
      md[i,k] <-  d[t[i,k]] - d[t[i,1]] + sw[i,k]
      taud[i,k] <- tau *2*(k-1)/k
      w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])
      sw[i,k] <- sum(w[i,1:k-1])/(k-1)
```

```
    }
  }
totresdev <- sum(resdev[])
d[1]<-0
for (k in 2:nt){  d[k] ~ dnorm(0,.0001)
}
for (c in 1:(nt-1))
        {
        for (k in (c+1):nt)
                {
                RR[k,c] <- exp(d[k] - d[c] )
                RR[c,k] <- 1/RR[k,c]
                }
        }
sd ~ dunif(0,5)
tau <- pow(sd,-2)
tau2<- 1/tau
for (i in 1:ns) {
                mu1[i] <- mu[i] * equals(t[i,1],1)
                count1[i] <- equals(t[i,1],1)
                }

for (k in 1:nt) { log(T[k]) <- sum(mu1[])/sum(count1[]) + d[k]  }
}
```

Base-case Model: Disability Progression

```
model
{
for(i in 1:NS)
{
  w[i,1] <-0
  delta[i,1]<-0
  mu[i] ~ dnorm(0,.0001)
    for (k in 1:na[i]){
      r[i,k] ~ dbin(p[i,k],n[i,k])
      logit(p[i,k]) <- mu[i] + delta[i,k]
      rhat[i,k] <- p[i,k] * n[i,k]
      dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))   +  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-
rhat[i,k])))
      }
  resdev[i] <- sum(dev[i,1:na[i]])
  for (k in 2:na[i]){
    delta[i,k] ~ dnorm(md[i,k],taud[i,k])
    md[i,k] <-  d[t[i,k]] - d[t[i,1]] + sw[i,k]
```

```
    taud[i,k] <- tau *2*(k-1)/k
    w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])
    sw[i,k] <- sum(w[i,1:k-1])/(k-1)
    }
}

totresdev <- sum(resdev[])
d[1]<-0
for (k in 2:NT){
  d[k] ~ dnorm(0,.0001) #  vague priors for basic parameters
  }
sd~dunif(0,2)
tau<-1/pow(sd,2)
# ranking
for (k in 1:NT){
  rk[k]<-NT+1-rank(d[],k)
  best[k]<-equals(rk[k],1)
  for (h in 1:NT){
    prob[k,h]<-equals(rk[k],h)
    }
  }
for (k in 1:NT){
  for (h in 1:NT){
    cumeffectiveness[k,h]<-sum(prob[k,1:h])
    }
  }
for(i in 1:NT){
  SUCRA[i]<-sum(cumeffectiveness[i,1:(NT-1)])/(NT-1)
  }
# pairwise ORs
for (c in 1:(NT-1)){
  for (k in (c+1):NT){
    OR[c,k] <- exp(d[k] - d[c] )
    lOR[c,k]<-d[k]-d[c]
    }
  }
for (i in 1:NS){
  mu1[i] <- mu[i] * equals(t[i,1],1)
  count1[i] <- equals(t[i,1],1)
  }
L<-sum(mu1[])/sum(count1[])
#RR
for (k in 1:NT) {
  logit(T[k]) <- d[k] +L
  }
```

```
for (c in 1:(NT-1)){
  for (k in (c+1):NT){
    RR[k,c] <- T[c]/T[k]
    RR[c,k] <- T[k]/T[c]
    }
  }
}
```

Fixed-Effects Model: Annualized Relapse Rate

```
model{
for(i in 1:ns){
   mu[i] ~ dnorm(0,.0001)
   for (k in 1:na[i]) {
      r[i,k] ~ dpois(theta[i,k])
      theta[i,k] <- lambda[i,k]*E[i,k] # failure rate * exposure
      log(lambda[i,k]) <- mu[i] + d[t[i,k]]-d[t[i,1]]
      dev[i,k] <- 2*((theta[i,k]-r[i,k]) + r[i,k]*log(r[i,k]/theta[i,k]))}
   resdev[i] <- sum(dev[i,1:na[i]])
  }
totresdev <- sum(resdev[])
d[1]<-0
for (k in 2:nt){  d[k] ~ dnorm(0,.0001)
}
for (c in 1:(nt-1))
          {
          for (k in (c+1):nt)
                    {
                    RR[k,c] <- exp(d[k] - d[c] )
                    RR[c,k] <- 1/RR[k,c]
                    }
          }

for (i in 1:ns) {
                    mu1[i] <- mu[i] * equals(t[i,1],1)
                    count1[i] <- equals(t[i,1],1)
                    }

for (k in 1:nt) { log(T[k]) <- sum(mu1[])/sum(count1[]) + d[k]  }
}
```

Fixed Effects Model: Disability Progression

```
model
{
for(i in 1:NS){
```

```
  mu[i] ~ dnorm(0,.0001)
  for (k in 1:na[i]){
    r[i,k] ~ dbin(p[i,k],n[i,k])
    logit(p[i,k]) <- mu[i] + d[t[i,k]]-d[t[i,1]]
    rhat[i,k] <- p[i,k] * n[i,k]
    dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))   +  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-
rhat[i,k])))
    }
  resdev[i] <- sum(dev[i,1:na[i]])

  }
totresdev <- sum(resdev[])
d[1]<-0
for (k in 2:NT){
  d[k] ~ dnorm(0,.0001)
  }
# ranking
  for (k in 1:NT){
    rk[k]<-NT+1-rank(d[],k)
    best[k]<-equals(rk[k],1)
    for (h in 1:NT){
      prob[k,h]<-equals(rk[k],h)
      }
    }
  for (k in 1:NT){
    for (h in 1:NT){
      cumeffectiveness[k,h]<-sum(prob[k,1:h])
      }
    }
  for(i in 1:NT){
    SUCRA[i]<-sum(cumeffectiveness[i,1:(NT-1)])/(NT-1)

    }
# pairwise ORs
  for (c in 1:(NT-1)){
    for (k in (c+1):NT){
      OR[c,k] <- exp(d[k] - d[c] )
      lOR[c,k]<-d[k]-d[c]
      }
     }
  for (i in 1:NS){
    mu1[i] <- mu[i] * equals(t[i,1],1)
    count1[i] <- equals(t[i,1],1)
    }
L<-sum(mu1[])/sum(count1[])
```

```
#RR
  for (k in 1:NT){
    logit(T[k]) <- d[k] +L
    }
  for (c in 1:(NT-1)){
    for (k in (c+1):NT){
      RR[k,c] <- T[c]/T[k]
      RR[c,k] <- T[k]/T[c]
      }
    }
}
```

Disability Progression Adjusted for Continuous Covariate

```
model{
  for(i in 1:NS){
    w[i,1] <-0
    delta[i,1]<-0
    mu[i] ~ dnorm(0,.0001)
    for (k in 1:na[i]){
      r[i,k] ~ dbin(p[i,k],n[i,k])
      logit(p[i,k]) <- mu[i] + delta[i,k]  + (beta[t[i,k]]-beta[t[i,1]])*(x[i]-mx)

      rhat[i,k] <- p[i,k] * n[i,k]
      dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))   +  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-
rhat[i,k])))
      }
    resdev[i] <- sum(dev[i,1:na[i]])
    for (k in 2:na[i]){
      delta[i,k] ~ dnorm(md[i,k],taud[i,k])
      md[i,k] <-  d[t[i,k]] - d[t[i,1]] + sw[i,k]
      taud[i,k] <- tau *2*(k-1)/k
      w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])
      sw[i,k] <- sum(w[i,1:k-1])/(k-1)
      }
    }
totresdev <- sum(resdev[])
d[1]<-0
beta[1]<-0
for (k in 2:NT){
  d[k] ~ dnorm(0,.0001)
  beta[k]<- B
  }
B ~ dnorm(0, .0001)
sd~dunif(0,2)
```

```
tau<-1/pow(sd,2)
# ranking
 for (k in 1:NT){
  rk[k]<-NT+1-rank(d[],k)
  best[k]<-equals(rk[k],1)
  for (h in 1:NT){
   prob[k,h]<-equals(rk[k],h)
   }
  }
 for (k in 1:NT){
  for (h in 1:NT){
   cumeffectiveness[k,h]<-sum(prob[k,1:h])
   }
  }
 for(i in 1:NT){
  SUCRA[i]<-sum(cumeffectiveness[i,1:(NT-1)])/(NT-1)

  }
# pairwise ORs
 for (c in 1:(NT-1)){
  for (k in (c+1):NT){
   OR[c,k] <- exp(d[k] - d[c] )
   lOR[c,k]<-d[k]-d[c]
   }
  }
 for (i in 1:NS) {
  mu1[i] <- mu[i] * equals(t[i,1],1)
  count1[i] <- equals(t[i,1],1)
  }
 L<-sum(mu1[])/sum(count1[])
#RR
 for (k in 1:NT){
  logit(T[k]) <- d[k] +L
  }
 for (c in 1:(NT-1)){
  for (k in (c+1):NT){
   RR[k,c] <- T[c]/T[k]
   RR[c,k] <- T[k]/T[c]
   }
  }
}
```

Annualized Relapse Rate Adjusted for Continuous Covariate

```
model{
```

```
for(i in 1:ns){
   w[i,1] <- 0
   delta[i,1] <- 0
   mu[i] ~ dnorm(0,.0001)
   for (k in 1:na[i]) {
      r[i,k] ~ dpois(theta[i,k])
      theta[i,k] <- lambda[i,k]*E[i,k] # failure rate * exposure
      log(lambda[i,k]) <- mu[i] + delta[i,k] + (beta[t[i,k]]-beta[t[i,1]])*(x[i]-mx)
      dev[i,k] <- 2*((theta[i,k]-r[i,k]) + r[i,k]*log(r[i,k]/theta[i,k]))          }
   resdev[i] <- sum(dev[i,1:na[i]])
   for (k in 2:na[i]) {
      delta[i,k] ~ dnorm(md[i,k],taud[i,k])
      md[i,k] <-  d[t[i,k]] - d[t[i,1]] + sw[i,k]
      taud[i,k] <- tau *2*(k-1)/k
      w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])
      sw[i,k] <- sum(w[i,1:k-1])/(k-1)
    }
 }
totresdev <- sum(resdev[])
d[1]<-0
beta[1]<-0
for (k in 2:nt){  d[k] ~ dnorm(0,.0001)
beta[k]<-B
}
for (c in 1:(nt-1))
        {
        for (k in (c+1):nt)
                {
                RR[k,c] <- exp(d[k] - d[c] )
                RR[c,k] <- 1/RR[k,c]
                }
        }

B ~ dnorm(0, .0001)
sd ~ dunif(0,5)

tau <- pow(sd,-2)
tau2<- 1/tau
for (i in 1:ns) {
                mu1[i] <- mu[i] * equals(t[i,1],1)
                count1[i] <- equals(t[i,1],1)
                }

for (k in 1:nt) { log(T[k]) <- sum(mu1[])/sum(count1[]) + d[k]  }
}
```

Figure D1. Network Diagram for Base-case ARR Analysis.

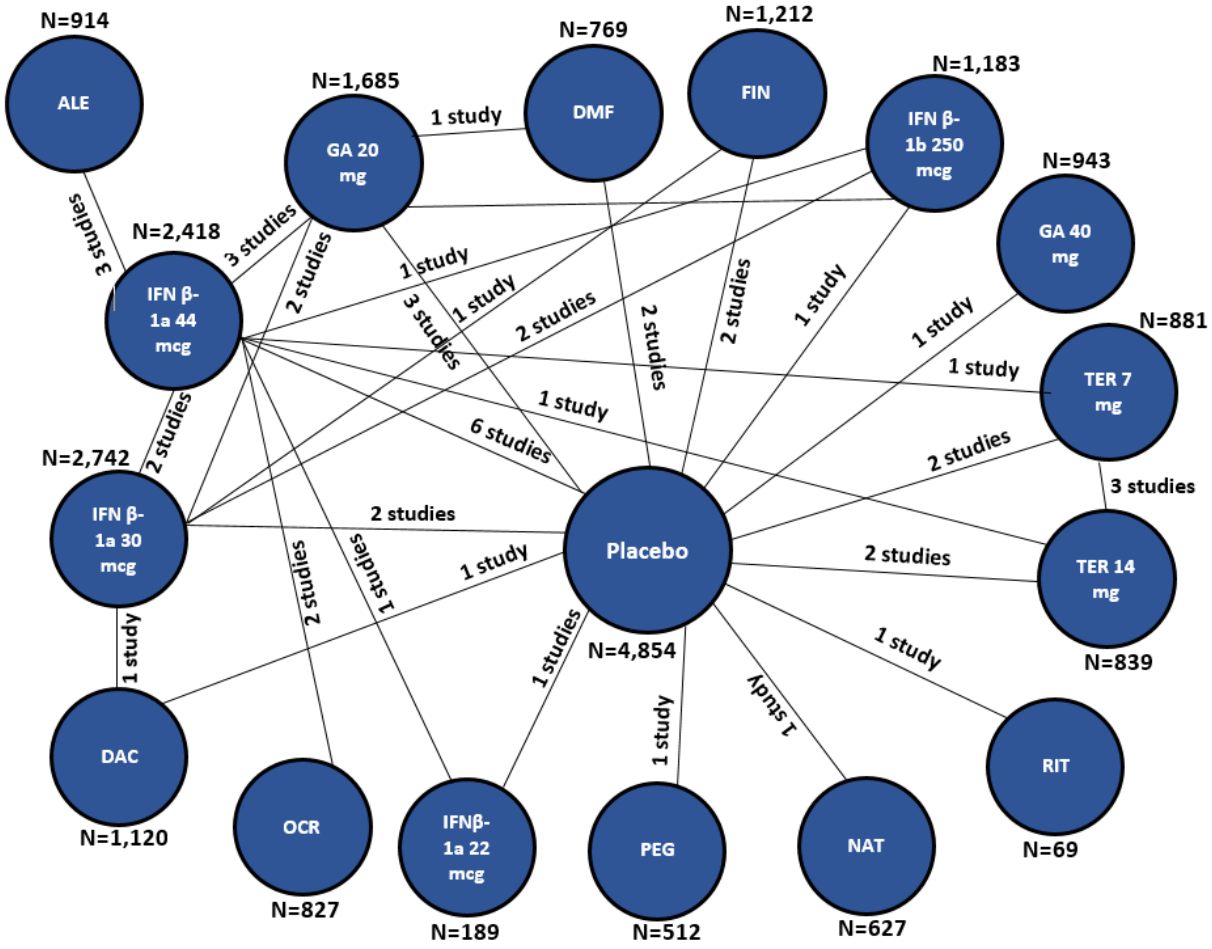


Table D1. NMA Sensitivity Analyses for ARR

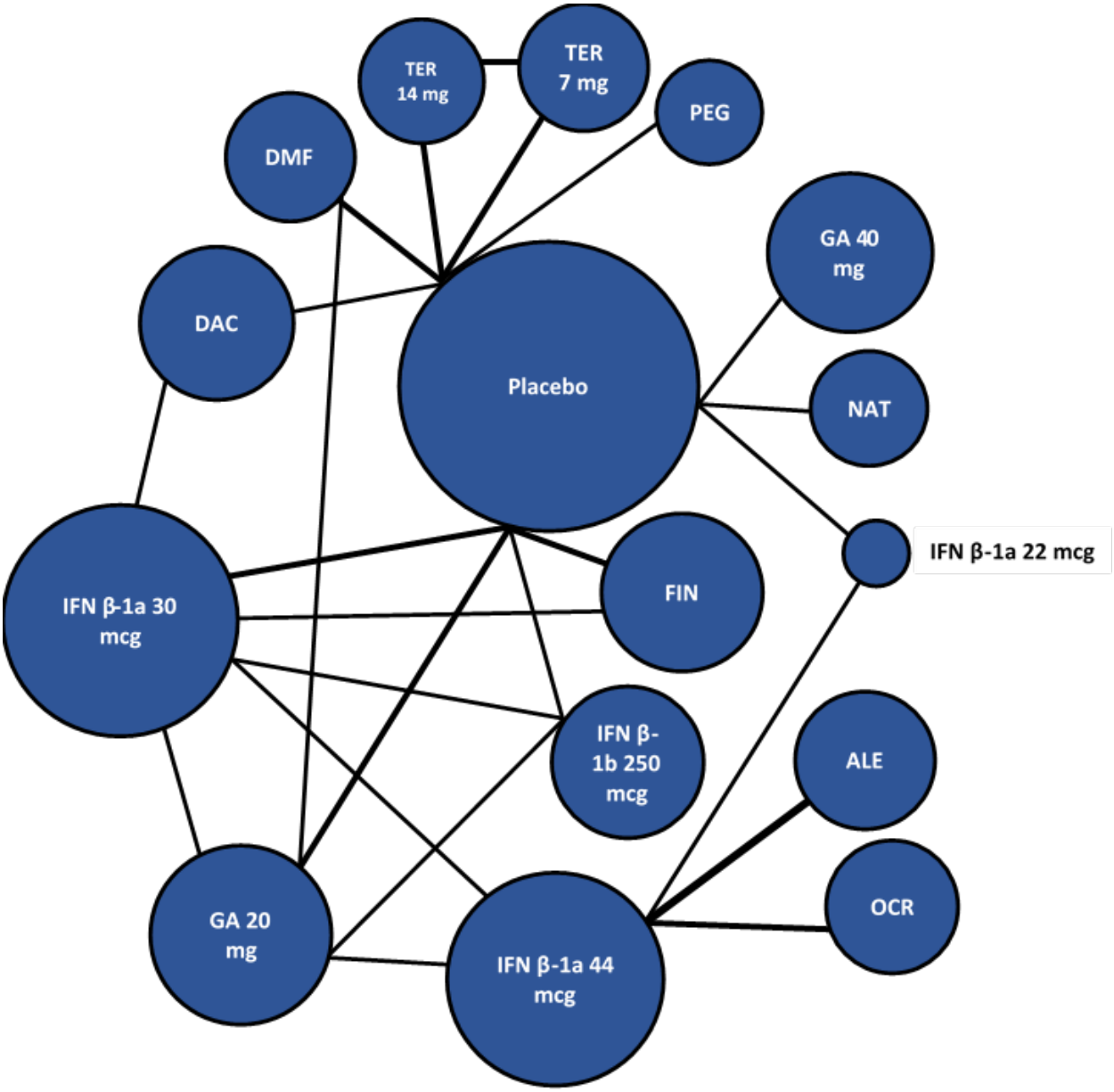
Treatment	Base Case ARR	Direct Meta-Analysis	Fixed Effects Results	Covariate: Disease Duration	Covariate: Mean # Relapses in Prior Year	Covariate: Baseline EDSS State
ALE	0.28 (0.22-0.35)	N/A	0.30 (0.25-0.35)	0.31 (0.23-0.39)	0.27 (0.19-0.35)	0.30 (0.23-0.39)
NAT	0.31 (0.25-0.40)	0.32 (0.27-0.37)	0.31 (0.27-0.37)	0.32 (0.24-0.41)	0.31 (0.23-0.42)	0.30 (0.23-0.38)
OCR	0.35 (0.27-0.44)	N/A	0.36 (0.30-0.43)	0.35 (0.26-0.45)	0.33 (0.24-0.44)	0.38 (0.29-0.50)
FIN	0.46 (0.39-0.55)	0.48 (0.42-0.56)	0.47 (0.41-0.53)	0.47 (0.33-0.62)	0.46 (0.37-0.56)	0.52 (0.42-0.66)
DAC	0.46 (0.38-0.58)	0.46 (0.32-0.65)	0.47 (0.40-0.54)	0.46 (0.37-0.59)	0.44 (0.33-0.57)	0.50 (0.40-0.66)
RIT	0.51 (0.27-0.93)	0.51 (0.27-0.95)	0.51 (0.27-0.95)	0.49 (0.26-0.99)	0.42 (0.21-0.89)	0.56 (0.28-1.09)
DMF	0.53 (0.43-0.63)	0.55 (0.47-0.64)	0.53 (0.46-0.62)	0.52 (0.42-0.64)	0.51 (0.39-0.63)	0.55 (0.45-0.68)
GA 20 mg	0.63 (0.55-0.71)	0.56 (0.37-0.85)	0.64 (0.58-0.70)	0.63 (0.53-0.71)	0.61 (0.50-0.71)	0.68 (0.58-0.81)
PEG	0.63 (0.47-0.86)	0.64 (0.50-0.82)	0.64 (0.50-0.82)	0.63 (0.46-0.88)	0.66 (0.47-0.94)	N/A
IFN β-1a 44 mcg	0.64 (0.54-0.73)	0.68 (0.59-0.78)	0.65 (0.59-0.72)	0.64 (0.52-0.73)	0.61 (0.48-0.73)	0.68 (0.57-0.81)
IFN β-1b 250 mcg	0.65 (0.55-0.77)	0.66 (0.54-0.80)	0.66 (0.59-0.74)	0.64 (0.50-0.77)	0.62 (0.48-0.74)	0.68 (0.57-0.82)
TER 14 mg	0.67 (0.56-0.79)	0.67 (0.59-0.75)	0.67 (0.59-0.75)	0.67 (0.50-0.84)	0.65 (0.52-0.79)	0.76 (0.62-1.00)
GA 40mg	0.67 (0.52-0.86)	0.66 (0.55-0.78)	0.67 (0.56-0.80)	0.66 (0.48-0.89)	0.64 (0.45-0.86)	0.81 (0.59-1.21)
IFN β-1a 22 mcg	0.70 (0.55-0.85)	0.71 (0.62-0.82)	0.70 (0.61-0.80)	0.69 (0.54-0.86)	0.68 (0.51-0.87)	0.74 (0.58-0.93)
TER 7 mg	0.77 (0.67-0.93)	0.74 (0.65-0.84)	0.76 (0.68-0.86)	0.77 (0.59-0.99)	0.76 (0.63-0.94)	0.89 (0.72-1.18)
IFN β-1a 30 mcg	0.83 (0.74-0.94)	0.78 (0.69-0.90)	0.83 (0.76-0.91)	0.83 (0.72-0.95)	0.79 (0.64-0.93)	0.88 (0.77-1.04)

Table D2. NMA Subgroup Analyses for ARR

Treatment	Base Case ARR	Tx-naïve Population	Tx-naïve + Experienced Population	Exclude Trials with n<100	Trials Using Poser Criteria	Trials Using McDonald Criteria	Exclude Poor-quality Trials	Exclude Trials w/ Duration <18 months	Exclude Open-label Trials
ALE	**0.28 (0.22-0.35)**	**0.18 (0.07-0.33)**	**0.32 (0.24-0.42)**	**0.31 (0.26-0.38)**	N/A	**0.29 (0.20-0.40)**	**0.32 (0.24-0.41)**	**0.28 (0.21-0.36)**	**0.21 (0.13-0.33)**
NAT	**0.31 (0.25-0.40)**	N/A	**0.31 (0.26-0.39)**	**0.31 (0.26-0.38)**	N/A	**0.31 (0.24-0.41)**	**0.32 (0.24-0.41)**	**0.32 (0.24-0.41)**	**0.31 (0.25-0.40)**
OCR	**0.35 (0.27-0.44)**	N/A	**0.36 (0.28-0.45)**	**0.39 (0.31-0.48)**	N/A	**0.36 (0.24-0.50)**	**0.36 (0.27-0.47)**	**0.35 (0.26-0.46)**	**0.38 (0.28-0.52)**
FIN	**0.46 (0.39-0.55)**	N/A	**0.46 (0.39-0.54)**	**0.47 (0.40-0.54)**	N/A	**0.46 (0.38-0.56)**	**0.43 (0.34-0.54)**	**0.48 (0.39-0.60)**	**0.47 (0.39-0.56)**
DAC	**0.46 (0.38-0.58)**	N/A	**0.45 (0.37-0.55)**	**0.47 (0.40-0.56)**	N/A	**0.47 (0.37-0.59)**	**0.45 (0.30-0.68)**	**0.47 (0.35-0.64)**	**0.48 (0.37-0.60)**
RIT	**0.51 (0.27-0.93)**	N/A	**0.51 (0.27-0.98)**	N/A	N/A	**0.51 (0.27-0.96)**	N/A	N/A	0.51 (0.27-1.02)
DMF	**0.53 (0.43-0.63)**	N/A	**0.55 (0.46-0.65)**	**0.60 (0.51-0.71)**	N/A	**0.53 (0.43-0.65)**	N/A	**0.53 (0.43-0.65)**	**0.51 (0.38-0.67)**
GA 20 mg	**0.63 (0.55-0.71)**	**0.46 (0.27-0.65)**	**0.74 (0.63-0.85)**	**0.68 (0.60-0.76)**	**0.47 (0.20-0.92)**	**0.65 (0.53-0.78)**	**0.58 (0.46-0.68)**	**0.63 (0.53-0.72)**	**0.70 (0.54-0.92)**
PEG	**0.63 (0.47-0.86)**	N/A	**0.64 (0.48-0.84)**	**0.64 (0.49-0.83)**	N/A	**0.64 (0.47-0.88)**	**0.64 (0.46-0.88)**	N/A	**0.64 (0.47-0.86)**
IFN β-1a 44 mcg	**0.64 (0.54-0.73)**	**0.46 (0.23-0.74)**	**0.65 (0.55-0.74)**	**0.69 (0.61-0.79)**	0.65 (0.31-1.30)	**0.65 (0.47-0.85)**	**0.66 (0.54-0.78)**	**0.64 (0.51-0.75)**	**0.68 (0.54-0.86)**
IFN β-1b 250 mcg	**0.65 (0.55-0.77)**	**0.54 (0.34-0.76)**	N/A	**0.70 (0.60-0.81)**	0.63 (0.31-1.32)	**0.69 (0.51-0.92)**	**0.61 (0.47-0.76)**	**0.65 (0.53-0.76)**	**0.65 (0.50-0.85)**
TER 14 mg	**0.67 (0.56-0.79)**	N/A	**0.66 (0.57-0.78)**	**0.65 (0.56-0.75)**	N/A	**0.67 (0.56-0.80)**	N/A	**0.69 (0.52-0.93)**	**0.67 (0.55-0.79)**
GA 40 mg	**0.67 (0.52-0.86)**	N/A	**0.67 (0.53-0.84)**	**0.67 (0.54-0.82)**	N/A	**0.67 (0.51-0.88)**	**0.67 (0.51-0.89)**	N/A	**0.67 (0.52-0.86)**
IFN β-1a 22 mcg	**0.70 (0.55-0.85)**	N/A	**0.69 (0.57-0.83)**	**0.71 (0.60-0.84)**	N/A	N/A	**0.70 (0.54-0.89)**	**0.69 (0.53-0.88)**	**0.71 (0.56-0.90)**

Treatment	Base Case ARR	Tx-naïve Population	Tx-naïve + Experienced Population	Exclude Trials with n<100	Trials Using Poser Criteria	Trials Using McDonald Criteria	Exclude Poor-quality Trials	Exclude Trials w/ Duration <18 months	Exclude Open-label Trials
TER 7mg	**0.77 (0.67-0.93)**	N/A	**0.77 (0.67-0.91)**	**0.75 (0.65-0.86)**	N/A	**0.78 (0.66-0.95)**	N/A	**0.69 (0.52-0.92)**	**0.74 (0.62-0.88)**
IFN β-1a 30 mcg	**0.83 (0.74-0.94)**	0.78 (0.50-1.12)	**0.80 (0.69-0.92)**	**0.84 (0.75-0.95)**	0.88 (0.46-1.81)	**0.83 (0.70-0.99)**	**0.81 (0.69-0.94)**	**0.83 (0.72-0.98)**	0.86 (0.71-1.04)

Figure D2. Network Diagram for Base-case Disability Progression Analysis



Legend: The width of the connecting lines are related to the number of trials available for each pair of treatments, and the size of each node is related to the number of study participants.[157]

Table D3. League Table for NMA Subgroup Analysis of Trials Reporting 12-week Disability Progression

ALE															
0.72 (0.34-1.47)	OCR														
0.55 (0.24-1.24)	0.77 (0.41-1.37)	NAT													
0.52 (0.23-1.13)	0.73 (0.42-1.21)	0.93 (0.57-1.59)	DAC												
0.49 (0.20-1.17)	0.7 (0.35-1.28)	0.88 (0.50-1.64)	0.95 (0.53-1.71)	PEG											
0.49 (0.21-1.03)	0.69 (0.37-1.11)	0.87 (0.54-1.35)	0.94 (0.57-1.42)	0.98 (0.57-1.74)	DMF										
0.47 (0.24-0.86)	**0.64 (0.46-0.86)**	0.83 (0.51-1.40)	0.88 (0.58-1.36)	0.94 (0.54-1.66)	0.96 (0.64-1.53)	IFN β-1a 44 mcg									
0.43 (0.19-0.96)	0.62 (0.33-1.00)	0.78 (0.50-1.24)	0.84 (0.53-1.31)	0.88 (0.51-1.50)	0.90 (0.61-1.35)	0.95 (0.59-1.42)	TER 14 mg								
0.41 (0.19-0.90)	**0.59 (0.33-0.96)**	0.74 (0.49-1.19)	0.81 (0.53-1.18)	0.86 (0.49-1.45)	0.86 (0.61-1.23)	0.90 (0.59-1.34)	0.96 (0.66-1.39)	FIN							
0.40 (0.18-0.83)	**0.56 (0.31-0.91)**	0.72 (0.42-1.22)	0.77 (0.46-1.26)	0.82 (0.43-1.47)	0.83 (0.52-1.35)	0.86 (0.57-1.29)	0.91 (0.57-1.49)	0.96 (0.61-1.49)	IFN β-1a 22 mcg						
0.40 (0.18-0.80)	**0.55 (0.33-0.84)**	0.71 (0.45-1.10)	0.76 (0.56-0.97)	0.80 (0.46-1.36)	0.8 (0.55-1.20)	0.85 (0.59-1.16)	0.90 (0.61-1.32)	0.93 (0.69-1.28)	0.98 (0.63-1.52)	IFN β-1a 30 mcg					
0.36 (0.16-0.80)	**0.52 (0.28-0.84)**	0.65 (0.42-1.01)	0.71 (0.45-1.08)	0.74 (0.43-1.27)	0.74 (0.53-1.10)	0.79 (0.5-1.19)	0.83 (0.63-1.12)	0.87 (0.61-1.22)	0.90 (0.57-1.46)	0.93 (0.64-1.38)	TER 7 mg				
0.35 (0.16-0.78)	**0.49 (0.28-0.85)**	0.64 (0.40-1.00)	0.68 (0.42-1.07)	0.72 (0.42-1.30)	0.73 (0.50-1.05)	0.76 (0.49-1.19)	0.81 (0.55-1.21)	0.84 (0.60-1.25)	0.87 (0.55-1.44)	0.91 (0.59-1.36)	0.97 (0.68-1.43)	GA 20 mg			
0.34 (0.14-0.79)	**0.47 (0.25-0.89)**	0.61 (0.35-1.09)	0.65 (0.37-1.14)	0.69 (0.37-1.29)	0.70 (0.44-1.15)	0.73 (0.42-1.25)	0.78 (0.45-1.30)	0.81 (0.51-1.35)	0.84 (0.48-1.53)	0.87 (0.49-1.46)	0.93 (0.59-1.55)	0.95 (0.72-1.31)	IFN β-1b 250		
0.27 (0.11-0.64)	**0.37 (0.19-0.73)**	**0.49 (0.26-0.87)**	**0.51 (0.29-0.93)**	0.54 (0.27-1.06)	**0.56 (0.32-0.95)**	0.58 (0.32-1.04)	0.61 (0.35-1.09)	0.64 (0.38-1.11)	0.67 (0.37-1.23)	0.68 (0.41-1.19)	0.73 (0.43-1.29)	0.76 (0.43-1.32)	0.81 (0.42-1.47)	GA 40 mg	
0.31 (0.15-0.64)	**0.45 (0.26-0.66)**	**0.56 (0.39-0.80)**	**0.60 (0.41-0.85)**	0.63 (0.39-1.03)	**0.65 (0.49-0.84)**	**0.68 (0.46-0.91)**	**0.71 (0.54-0.95)**	**0.75 (0.59-0.93)**	0.78 (0.53-1.15)	0.80 (0.60-1.03)	0.86 (0.66-1.10)	0.88 (0.65-1.15)	0.92 (0.58-1.42)	1.17 (0.71-1.87)	Placebo

Legend: The DMTs are arranged from most effective (top left) to least effective (bottom right) Each box represents the estimated rate ratio and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in bold signify that the 95% credible interval does not contain 1.

Table D4. League Table for NMA Subgroup Analysis of Trials Reporting 24-week Disability Progression

ALE								
0.89 (0.39 – 1.84)	**OCR**							
0.88 (0.31 – 1.90)	0.99 (0.36 – 2.09)	**IFN β-1b 250 mcg**						
0.79 (0.23 – 2.07)	0.89 (0.26 – 2.40)	0.90 (0.31 – 2.13)	**DAC**					
0.61 (0.18 – 1.71)	0.70 (0.19 – 2.00)	0.71 (0.29 – 1.54)	0.79 (0.27 – 2.07)	**FIN**				
0.60 (0.24 – 1.28)	0.67 (0.27 – 1.52)	0.69 (0.26 – 1.60)	0.75 (0.28 – 1.86)	0.96 (0.37 – 2.28)	**GA 20 mg**			
0.56 (0.33 – 0.91)	0.64 (0.36 – 1.11)	0.65 (0.23 – 1.63)	0.72 (0.26 – 1.90)	0.92 (0.33 – 2.38)	0.97 (0.49 – 1.81)	**IFN β-1a 44 mcg**		
0.56 (0.23 – 1.20)	0.64 (0.24 – 1.41)	0.65 (0.32 – 1.19)	0.72 (0.34 – 1.41)	0.91 (0.42 – 1.77)	0.95 (0.48 – 1.66)	0.99 (0.48 – 1.74)	**IFNβ 1-a 30 mcg**	
0.44 (0.15 – 1.06)	0.50 (0.16 – 1.27)	**0.51 (0.25 – 0.92)**	0.57 (0.23 – 1.28)	0.72 (0.41 – 1.18)	0.74 (0.32 – 1.51)	0.77 (0.32 – 1.57)	0.78 (0.47 – 1.26)	**Placebo**

Legend: The DMTs are arranged from most effective (top left) to least effective (bottom right) Each box represents the estimated rate ratio and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in bold signify that the 95% credible interval does not contain 1.

Table D5. NMA Sensitivity Analyses for Disability Progression

Treatment	Base Case RR for EDSS Progression	Direct Meta-analysis	Results using Fixed Effects	Results using Continuous Measures (Random Effects)	Covariate: Disease Duration	Covariate: Baseline EDSS State	Covariate: Mean # Relapses in Prior Year
ALE	**0.42 (0.25-0.68)**	N/A	**0.43 (0.28-0.64)**	**0.31 (0.18-0.52)**	**0.45 (0.22-0.86)**	**0.39 (0.17-0.84)**	**0.37 (0.21-0.62)**
OCR	**0.47 (0.28-0.76)**	N/A	**0.47 (0.31-0.69)**	**0.35 (0.20-0.61)**	**0.43 (0.21-0.81)**	**0.43 (0.19-0.95)**	0.40 (0.23-0.69)
DAC	**0.54 (0.36-0.78)**	**0.43 (0.22 - 0.85)**	**0.55 (0.41-0.72)**	**0.54 (0.34-0.85)**	**0.51 (0.29-0.82)**	0.49 (0.22-1.06)	**0.58 (0.37-0.88)**
NAT	**0.56 (0.37-0.84)**	**0.59 (0.46 - 0.75)**	**0.56 (0.42-0.74)**	**0.46 (0.30-0.70)**	**0.53 (0.29-0.90)**	**0.54 (0.30-0.94)**	**0.56 (0.37-0.84)**
DMF	**0.62 (0.46-0.84)**	**0.66 (0.51 – 0.85)**	**0.62 (0.49-0.77)**	**0.62 (0.45-0.87)**	**0.58 (0.35-0.91)**	0.58 (0.30-1.10)	**0.67 (0.48-0.94)**
PEG	0.63 (0.37-1.02)	**0.60 (0.39 - 0.93)**	**0.63 (0.41-0.93)**	0.62 (0.37-1.02)	0.57 (0.25-1.13)	N/A	**0.61 (0.36-0.99)**
IFN β-1b 250 mcg	**0.66 (0.46-0.89)**	0.77 (0.56 - 1.05)	**0.69 (0.54-0.88)**	**0.32 (0.15-0.66)**	**0.58 (0.28-0.99)**	0.61 (0.30-1.13)	0.73 (0.49-1.03)
FIN	**0.68 (0.51-0.90)**	**0.71 (0.56 - 0.90)**	**0.68 (0.55-0.85)**	**0.67 (0.49-0.93)**	0.61 (0.24-1.27)	0.62 (0.27-1.32)	**0.68 (0.52-0.90)**
TER 14 mg	**0.72 (0.52-0.97)**	**0.72 (0.58 - 0.91)**	**0.72 (0.57-0.90)**	0.69 (0.51-0.94)	0.63 (0.26-1.27)	0.64 (0.26-1.48)	0.74 (0.53-1.02)
IFN β-1a 44 mcg	**0.73 (0.52-0.99)**	0.96 (0.52 - 1.77)	**0.73 (0.56-0.93)**	**0.58 (0.39-0.85)**	0.67 (0.40-1.08)	0.67 (0.34-1.28)	**0.63 (0.42-0.93)**
GA 20 mg	**0.74 (0.58-0.94)**	0.92 (0.67 - 1.20)	**0.74 0.61-0.89)**	0.87 (0.52-1.48)	0.68 (0.41-1.04)	0.69 (0.35-1.29)	0.83 (0.62-1.11)
IFN β-1a 30 mcg	0.79 (0.63-1.00)	**0.69 (0.52 - 0.91)**	**0.78 (0.65-0.94)**	0.72 (0.49-1.05)	0.74 (0.45-1.13)	0.73 (0.37-1.37)	0.85 (0.62-1.15)
IFN β-1a 22 mcg	0.81 (0.52-1.23)	0.82 (0.63 - 1.07)	0.81 (0.58-1.12)	0.68 (0.44-1.04)	0.76 (0.41-1.31)	0.76 (0.36-1.50)	0.76 (0.49-1.16)
TER 7 mg	0.86 (0.63-1.14)	0.86 (0.70 - 1.06)	0.86 (0.69-1.06)	0.85 (0.63-1.13)	0.76 (0.33-1.49)	0.77 (0.31-1.72)	0.89 (0.65-1.19)
GA 40 mg	1.17 (0.69-1.92)	1.21 (0.70 – 2.10)	1.18 (0.75-1.82)	N/A	1.07 (0.44-2.16)	1.05 (0.35-2.50)	1.25 (0.71-2.10)

Table D6. NMA Subgroup Analyses for Disability Progression

Treatment	Base Case RR for EDSS Progression	Tx-naïve Population	Tx-naïve and -experienced Population	Excluding Trials with n<100	Trials Using Poser Criteria	Trials Using MacDonald Criteria	Exclude Poor-quality Trials	Exclude trials with duration <18 months	Excluding Open-label Trials
ALE	**0.42 (0.25-0.68)**	0.43 (0.52 -2.15)	**0.46 (0.26-0.83)**	**0.42 (0.27-0.67)**	N/A	0.69 (0.36-1.31)	**0.46 (0.23-0.91)**	**0.46 (0.24-0.83)**	**0.19 (0.07-0.51)**
OCR	**0.47 (0.28-0.76)**	N/A	**0.47 (0.29-0.76)**	**0.46 (0.29-0.73)**	N/A	0.75 (0.39-1.47)	**0.42 (0.21-0.85)**	**0.51 (0.26-0.94)**	0.41 (0.22-0.75)
DAC	**0.54 (0.36-0.84)**	N/A	**0.56 (0.37-0.81)**	**0.51 (0.36-0.72)**	N/A	**0.53 (0.36-0.76)**	0.43 (0.18-1.00)	0.60 (0.31-1.10)	**0.49 (0.31-0.75)**
NAT	**0.56 (0.37-0.84)**	N/A	**0.56 (0.37-0.81)**	**0.56 (0.39-0.80)**	N/A	**0.56 (0.38-0.80)**	0.56 (0.30-1.01)	**0.58 (0.33-0.97)**	**0.56 (0.37-0.85)**
DMF	**0.62 (0.46-0.84)**	N/A	**0.63 (0.46-0.83)**	**0.63 (0.48-0.82)**	N/A	**0.64 (0.49-0.85)**	N/A	**0.63 (0.43-0.91)**	**0.57 (0.37-0.86)**
PEG	0.63 (0.37-1.02)	N/A	0.64 (0.37-1.00)	**0.62 (0.39-0.97)**	N/A	**0.61 (0.36-0.98)**	0.61 (0.31-1.18)	N/A	0.63 (0.37-1.02)
IFN β-1b 250 mcg	**0.66 (0.46-0.89)**	0.62 (0.14-1.53)	N/A	0.77 (0.56-1.05)	0.57 (0.14-1.49)	0.92 (0.58-1.43)	**0.55 (0.28-0.94)**	**0.65 (0.41-0.91)**	0.69 (0.40-1.14)
FIN	**0.68 (0.51-0.90)**	N/A	**0.69 (0.52-0.90)**	**0.67 (0.52-0.86)**	N/A	**0.68 (0.52-0.88)**	0.61 (0.37-1.01)	0.73 (0.49-1.05)	**0.67 (0.49-0.87)**
TER 14mg	**0.72 (0.52-0.97)**	N/A	**0.71 (0.52-0.95)**	**0.72 (0.54-0.94)**	N/A	**0.71 (0.53-0.95)**	N/A	0.74 (0.42-1.21)	**0.72 (0.53-0.97)**
IFN β-1a 44 mcg	**0.73 (0.52-0.99)**	0.89 (0.07-2.27)	0.74 (0.54-1.01)	**0.72 (0.54-0.97)**	0.68 (0.18-1.68)	1.15 (0.67-1.93)	0.68 (0.42-1.07)	0.78 (0.50-1.18)	0.64 (0.39-1.02)
GA 20 mg	**0.74 (0.58-0.94)**	0.71 (0.13-1.90)	0.76 (0.57-1.02)	**0.76 (0.61-0.96)**	0.89 (0.16-2.15)	0.89 (0.65-1.20)	0.64 (0.41-1.00)	**0.72 (0.52-0.98)**	0.86 (0.48-1.45)
IFN β-1a 30 mcg	0.79 (0.63-1.00)	0.67 (0.21-1.76)	0.83 (0.62-1.11)	**0.74 (0.59-0.92)**	0.85 (0.28-1.80)	0.77 (0.58-1.06)	0.76 (0.54-1.08)	0.83 (0.57-1.17)	**0.70 (0.48-0.98)**
IFN β-1a 22 mcg	0.81 (0.52-1.23)	N/A	0.82 (0.54-1.23)	0.81 (0.55-1.18)	0.80 (0.16-1.99)	N/A	0.78 (0.42-1.39)	0.85 (0.49-1.37)	0.77 (0.48-1.18)
TER 7 mg	0.86 (0.63-1.14)	N/A	0.86 (0.65-1.13)	0.86 (0.66-1.11)	N/A	0.86 (0.64-1.11)	N/A	0.79 (0.45-1.28)	0.86 (0.64-1.14)
GA 40mg	1.17 (0.69-1.92)	N/A	N/A	1.17 (0.72-1.88)	N/A	1.16 (0.60-1.91)	1.18 (0.59-2.18)	N/A	1.17 (0.68-1.91)

Appendix E. Comparative Value Supplemental Information

Table E1. DMT administration costs

Product Name	Administration instructions	Annual administration cost*	
		Year 1	Subsequent years
Alemtuzumab	Infusion over 4 hours; 5 infusions year 1, 3 infusions subsequent years	$634	$380
Ocrelizumab (PPMS)	Infusion of 300 mg given over 150 minutes (4.35 infusions per year)	$427	$427
Ocrelizumab (RRMS)	Dose 1: infusion of 300 mg given over 150 minutes (2 infusions year 1) Dose 2+: For each cycle, it is necessary to prepare two infusion bags. Infusions of bag 1 and bag 2 given over 240 minutes (2 infusions year 1, 2.17 infusions subsequent years)	$450	$275
Natalizumab	Infusion over 1 hour, 13.04 infusions per year	$910	$910

Table E2. Lab and utilization costs and sources

Category	Cost*	Variable Name	Source
Infusion cost (1st hour), CPT 96365	$70		Source: physician fee schedule 2016[158]
Infusion cost/hr (2+ hours), CPT 96366	$19		Source: physician fee schedule 2016[158]
Complete blood count, CPT 85025	$14	c_blood	Source: lab fee schedule 2016[159]
Serum Creatinine, CPT 80053	$19	c_creatinine	Source: lab fee schedule 2016[159]
Urinalysis, CPT 81000	$6	c_urine	Source: lab fee schedule 2016[159]
Thyroid, CPT 84436+84479	$25	c_thyroid	Source: lab fee schedule 2016[159]
Liver, CPT 80076	$15	c_liver	Source: lab fee schedule 2016[159]
MRI, CPT 70543	$495	c_MRI	Source: physician fee schedule 2016[158]
ECG, CPT 93000	$17	c_ecg	Source: physician fee schedule 2016[158]
ALT, CPT 84460	$10	c_ALT	Source: lab fee schedule 2016[159]
CD4 lymphocyte, CPT 86360	$87	c_cd4	Source: lab fee schedule 2016[159]
PML, ICD diagnosis code 046.3	$23,445		HCUP costs, 2012 data, accessed on July 6, 2015 by AbbVie, adjusted to 2016 USD using multiplier 1.0363629 [160]
Hospital stay for disorders of the biliary without complications, DRG 446	$4,477		Source: physician fee schedule 2016[158]
Inpatient stay for depression, DRG 881	$3,884		Source: physician fee schedule 2016[158]
Hospital stay for influenza/pneumonia, DRG 194	$5,687		Source: physician fee schedule 2016[158]
Serious infection, DRG 177	$11,177		Source: physician fee schedule 2016[158]
Cranial nerve disorder, DRG 073	$7,829		Source: physician fee schedule 2016[158]
Specialist visit, CPT 99215	$112	c_office	Source: physician fee schedule 2016[158]

*Varied ± 20% in sensitivity analysis

Table E3. DMT Monitoring Costs

Product Name	Monitoring instructions	Implemented as (annual)	Annual monitoring cost†		
			Year 1	Subsequent years	After discontinuation
Alemtuzumab	blood, urine, CD4 lymphocyte, and serum cr, (prior to treatment initiation and at monthly intervals thereafter), A test of thyroid function, such as thyroid stimulating hormone (TSH) level (prior to treatment initiation and every 3 months thereafter); must continue for 4 years after your last infusion	N/A	$0*	$0*	$0*
Daclizumab	Test transaminase levels and total bilirubin monthly, follow monthly for 6 months after the last dose	12*c_liver annual 6*c_liver after discontinuation	$180	$180	$90
Fingolimod	First Dose Monitoring: Observe all patients for bradycardia for at least 6 hours; monitor pulse and blood pressure hourly. Electrocardiograms (ECGs) prior to dosing and at end of observation period required. LFT every 6 months, CBC test every 2 months	2*c_liver +6*c_blood +2*c_ecg +c_office year 1 2*c_liver +6*c_blood subsequent	$262	$116	N/A
Glatiramer aAcetate 20 mg (Copaxone)	None	N/A	$0	$0	N/A
Glatiramer Acetate 20 mg (Glatopa)	None	N/A	$0	$0	N/A
Interferon β-1a 30 mcg (Avonex)	Blood cell counts and liver function tests are recommended at regular intervals (1, 3, and 6 months) and then periodically (2x/yr) thereafter	3*(c_blood+c_liver) year 1 2*(c_blood+c_liver) subsequent	$88	$59	N/A
Interferon β-1a 22/44 mcg (Rebif)	blood cell counts and liver function tests are recommended at regular	3*(c_blood+c_liver) year 1	$88	$59	N/A

Product Name	Monitoring instructions	Implemented as (annual)	Annual monitoring cost†		
			Year 1	Subsequent years	After discontinuation
	intervals (1, 3, and 6 months) and then periodically (2x/yr) thereafter	2*(c_blood+c_liver) subsequent			
Interferon β-1b 250 mcg (Betaseron)	Blood cell counts and liver function tests are recommended at regular intervals (1, 3, and 6 months) and then periodically (2x/yr) thereafter	3*(c_blood+c_liver) year 1 2*(c_blood+c_liver) subsequent	$88	$59	N/A
Interferon β-1b 250 mcg (Extavia)	Blood cell counts and liver function tests are recommended at regular intervals (1, 3, and 6 months) and then periodically (2x/yr) thereafter	3*(c_blood+c_liver) year 1 2*(c_blood+c_liver) subsequent	$88	$59	N/A
Dimethyl Fumarate	Obtain a complete blood cell count (CBC) including lymphocyte count before initiation of therapy; CBC every 6 months Obtain serum aminotransferase, alkaline phosphatase, and total bilirubin levels before initiating	6*c_blood c_liver	$44	$29	N/A
Natalizumab	MRI every 6 months CBC+ LFT every month	2*c_MRI +12*c_liver	$1,171	$1,171	N/A
Ocrelizumab (RRMS)	None	N/A	$0	$0	N/A
Ocrelizumab (PPMS)	None	N/A	$0	$0	N/A
Peginterferon β-1a	CBC and liver function every 6 months	2*(c_blood+c_liver)	$59	$59	N/A
Teriflunomide	CBC and LFTs within 6 months prior to starting teriflunomide. ALT level (not a full LFT panel) monthly for 6 months after starting therapy.	c_blood +c_liver +6* c_ALT year 1	$88	$0	N/A

Table E4. Rates of SAEs and Total Weighted Costs and Utilities per DMT.

Rate of severe AEs																
Severe AE	IFN β-1a 30mcg	IFN β-1b 250mcg (Betaseron)	IFN β-1b 250mcg (Betaseron)	GA 20 mg (Copaxone)	GA 20 mg (Glatopa)	IFN β-1a 22 mcg	IFN β-1a 44 mcg‡	PEG	FIN	TER 7 mg	TER 14 mg‡	DMF	NAT	ALE	DAC	OCR
Lymphopenia*						0.01	0.01									
ALT increased*										0.01	0.01					
Cholelithiasis*						0.01	0.01									
Influenza*						0.01	0.01									
Serious infection*												0.01				
Trigeminal neuralgia*						0.01	0.01									
Depression*						0.01	0.01									
PML†													0.0003			
Total Cost	$0	$0	$0	$0	$0	$154	$154	$0	$0	$4	$4	$3	$0	$0	$0	$0
Total Disutility	0	0	0	0	0	0.01075	0.01075	0	0	0	0	0.00007	0.00012	0	0	0

Table E5. Treatment Effect Parameters

Treatment	Relative Risk Disability Progression (Increasing EDSS and RRMS to SPMS)		Rate Ratio for Relapse Rate (for RRMS/SPMS)	
	Base Case	Range for SA	Base Case	Range for SA
Alemtuzumab (Lemtrada)	0.42	0.25-0.68	0.28	0.22-0.35
Daclizumab (Zinbryta)	0.54	0.36-0.78	0.46	0.38-0.58
Dimethyl Fumarate (Tecfidera)	0.62	0.46-0.84	0.53	0.43-0.63
Fingolimod (Gilenya)	0.68	0.51-0.9	0.46	0.39-0.55
Glatiramer acetate 20 mg (Glatopa)	0.74	0.58-0.94	0.63	0.55-0.71
Glatiramer acetate 20 mg (Copaxone)	0.74	0.58-0.94	0.63	0.55-0.71
Interferon β-1a 30 mcg (Avonex)	0.79	0.63-1	0.83	0.74-0.94
Interferon β-1a 22 mcg (Rebif)	0.81	0.52-1.23	0.7	0.55-0.85
Interferon β-1a 44 mcg (Rebif)	0.73	0.52-0.99	0.64	0.54-0.73
Interferon β-1b 250 mcg (Betaseron)	0.66	0.46-0.89	0.65	0.55-0.77
Interferon β-1b 250 mcg (Extavia)	0.66	0.46-0.89	0.65	0.55-0.77
Natalizumab (Tysabri)	0.56	0.37-0.84	0.31	0.25-0.4
Ocrelizumab (Ocrevus) (RRMS)	0.47	0.28-0.76	0.35	0.27-0.44
Ocrelizumab (Ocrevus) (PPMS)[91]	0.75	0.58-0.98	N/A	
Peginterferon β-1a (Plegridy)	0.63	0.37-1.02	0.63	0.47-0.86
Teriflunomide 7 mg (Aubagio)	0.86	0.63-1.14	0.77	0.67-0.93
Teriflunomide 14mg (Aubagio)	0.72	0.52-0.97	0.67	0.56-0.79

Table E6. EDSS Distribution of Populations of RRMS and PPMS Patients Entering the Model

EDSS State	RRMS												PPMS
	CONFIRM[87] (n)				DEFINE[99] (n)			OPERA I & II[118] (n)	TOWER & TEMSO[119] (% of n)	CARE II[120] (% of n)	TOTAL		ORATORIO[118] trial
0	13	15	15	18	21	29	24	51	5%	3%	280	4.4%	0.1%
1	78	85	84	77	105	109	104	312	20%	21%	1385	21.8%	0.3%
2	11	94	94	96	112	116	146	504	30%	28%	1805	28.4%	26.5%
3	98	105	99	99	97	82	85	389	21%	25%	1540	24.3%	27.3%
4	50	47	42	46	56	56	42	244	17%	16%	940	14.8%	15.7%
5	13	12	11	14	16	16	14	145	7%	7%	396	6.2%	29.9%
6								10			10	0.2%	0.1%
7												0%	0.0%
8												0%	0.0%
9												0%	0.1%
Total n	263	358	345	350	407	408	415	1655	1493	666	6355		

Table E7. Natural History ARR by EDSS States, Base Case and Sensitivity Analysis Values

EDSS State	Relapse Rate, RRMS		Relapse Rate, SPMS		Relapse Rate, PPMS	Scenario SA[117]*		Scenario SA[139]	
	Base case[117,125]**	Range for One-Way SA	Base case[117,125]†	Range for One-Way SA		Relapse Rate, RRMS	Relapse Rate, SPMS	Relapse Rate, RRMS	Relapse Rate, SPMS
0	0.71	0.57-0.85				1.26		0.261	
1	0.73	0.58-0.88	0.00	0.00-0.10	0	1.32	0	0.237	0
2	0.68	0.54-0.82	0.47	0.38-0.56	0	1.32	0.91	0.46	0.315
3	0.72	0.58-0.86	0.88	0.70-1.06	0	1.35	1.64	0.495	0.602
4	0.71	0.57-0.85	0.55	0.44-0.66	0	1.36	1.05	0.67	0.515
5	0.59	0.47-0.71	0.52	0.42-0.62	0	1.43	1.27	0.181	0.16
6	0.49	0.39-0.59	0.45	0.36-0.54	0	1.18	1.1	0.15	0.139
7	0.51	0.41-0.61	0.34	0.27-0.41	0	1.23	0.82	0.156	0.104
8	0.51	0.41-0.61	0.34	0.27-0.41	0	1.23	0.82	0.156	0.104
9	0.51	0.41-0.61	0.34	0.27-0.41	0	1.23	0.82	0.156	0.104

* Rates based on observational data

† Rates based on trial data

Table E8. Annual Probability of Moving Between EDSS States for Patients with Relapsing-Remitting Multiple Sclerosis

		EDSS State at End of Year[39,87,99,117]									
		0	1	2	3	4	5	6	7	8	9
EDSS State at Start of Year	0	0.311	0.289	0.312	0.07	0.016	0.001	0	0	0	0
	1	0.178	0.231	0.419	0.127	0.039	0.004	0.001	0	0	0
	2	0.06	0.13	0.493	0.215	0.088	0.011	0.002	0	0	0
	3	0.019	0.055	0.299	0.322	0.241	0.044	0.013	0.003	0.004	0
	4	0.005	0.017	0.127	0.251	0.411	0.121	0.048	0.014	0.007	0
	5	0.001	0.004	0.033	0.096	0.252	0.295	0.211	0.085	0.023	0
	6	0	0.001	0.009	0.034	0.123	0.257	0.329	0.19	0.056	0.001
	7	0	0	0.003	0.013	0.057	0.169	0.309	0.257	0.189	0.004
	8	0	0	0	0	0	0	0	0	0.995	0.005
	9	0	0	0	0	0	0	0	0	0	1

Table E9. Annual Probability of Conversion from Relapsing-Remitting Multiple Sclerosis to Secondary Progressive Multiple Sclerosis, by EDSS State

Initial RRMS EDSS State	Probability of transitioning to SPMS[39,117]	Range for SA
0	0	0-0.003
1	0.003	0.002-0.004
2	0.032	0.026-0.038
3	0.117	0.094-0.140
4	0.210	0.168-0.252
5	0.299	0.239-0.359
6	0.237	0.190-0.284
7	0.254	0.203-0.305
8	0.153	0.122-0.184
9*	1.000	0.900-1.000

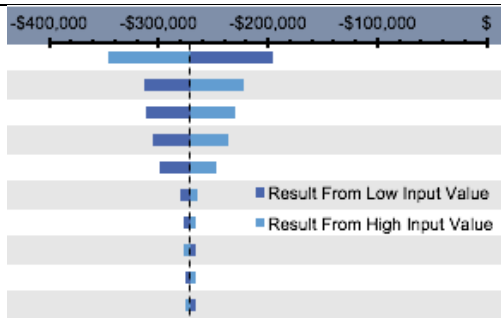
*In a cycle when a transition from RRMS to SPMS occurs we assumed a 1 level increase in EDSS, except in the case of RRMS EDSS 9, where transition was directly to SPMS 9.

Table E10. Annual Probability of Moving Between EDSS States for Patients with Primary Progressive or Secondary Progressive Multiple Sclerosis

		EDSS State at End of Year[39,117]								
		1	2	3	4	5	6	7	8	9
EDSS State at Start of Year	1	0.769	0.154	0.077	0	0	0	0	0	0
	2	0	0.636	0.271	0.062	0.023	0.008	0	0	0
	3	0	0	0.629	0.253	0.077	0.033	0.003	0.005	0
	4	0	0	0	0.485	0.35	0.139	0.007	0.018	0
	5	0	0	0	0	0.633	0.317	0.022	0.026	0.002
	6	0	0	0	0	0	0.763	0.19	0.045	0.002
	7	0	0	0	0	0	0	0.805	0.189	0.006
	8	0	0	0	0	0	0	0	0.926	0.074
	9	0	0	0	0	0	0	0	0	1

Table E11. Results of One-way Sensitivity Analyses

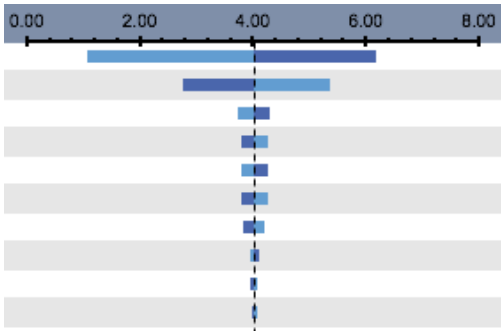
Incremental Cost



Parameter	Low Value	High Value
WAC, GA 20 mg (Glatopa)	$4,155	$6,233
Relative Risk, Progression, GA 20 mg (Glatopa)	0.58	0.94
Discount, GA 20 mg (Glatopa)	0.28	0.42
WAC, ALE	$16,600	$24,900
Discontinuation Rate, ALE	0.02	0.03
Relative Risk, Progression, ALE	0.25	0.68
Discontinuation Rate, GA 20 mg (Glatopa)	0.04	0.06
Direct Costs, EDSS 9	$16,882	$25,323
Age at beginning treatment, RRMS	23	35
Direct Costs, EDSS 8	$15,257	$22,886

Incremental QALYs

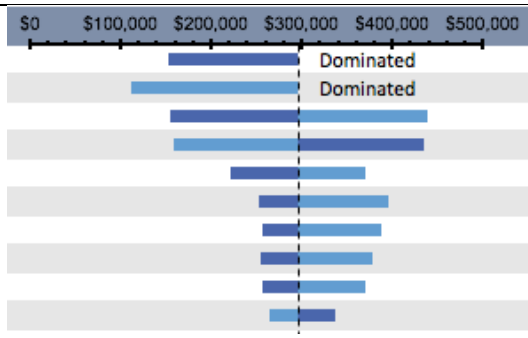
RRMS
ALE vs. GA 20 mg (Glatopa)



Parameter	Low Value	High Value
Relative Risk, Progression, ALE	0.25	0.68
Relative Risk, Progression, GA 20 mg (Glatopa)	0.58	0.94
Age at beginning treatment, RRMS	23	35
Annual Utility, RRMS, EDSS 0	0.70	1.00
Discontinuation Rate, ALE	0.02	0.03
Annual Utility, RRMS, EDSS 2	0.62	0.94
Annual Utility, RRMS, EDSS 1	0.67	1.00
Rate Ratio, Relapse, ALE	0.22	0.35
Rate Ratio, Relapse, GA 20 mg (Glatopa)	0.55	0.71
Annual Utility, SPMS, EDSS 9	0.17	0.26

Cost per additional QALY

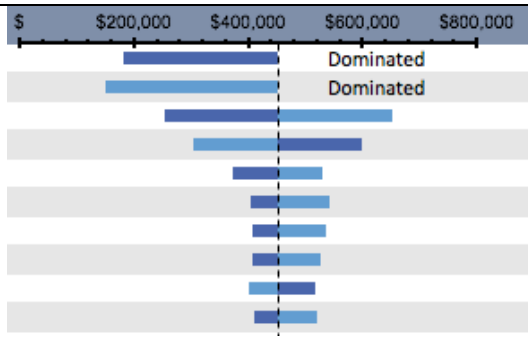
RRMS
DMF vs. GA 20 mg (Glatopa)



Parameter	Low Value	High Value
Relative Risk, Progression, DMF	0.46	0.84
Relative Risk, Progression, GA 20 mg (Glatopa)	0.58	0.94
WAC, DMF	$5,456	$8,184
WAC, GA 20 mg (Glatopa)	$4,155	$6,233
Discount, GA 20 mg (Glatopa)	0.28	0.42
Relative Risk, Progression, NAT	0.37	0.84
Relative Risk, Progression, ALE	0.25	0.68
Relative Risk, Progression, DAC	0.36	0.78
Relative Risk, Progression, FIN	0.51	0.90
Rate Ratio, Relapse, GA 20 mg (Glatopa)	0.55	0.71

Cost per Additional QALY

RRMS
FIN vs. GA 20 mg (Glatopa)



Parameter	Low Value	High Value
Relative Risk, Progression, FIN	0.51	0.90
Relative Risk, Progression, GA 20 mg (Glatopa)	0.58	0.94
WAC, FIN	$5,395	$8,092
WAC, GA 20 mg (Glatopa)	$4,155	$6,233
Discount, GA 20 mg (Glatopa)	0.28	0.42
Relative Risk, Progression, NAT	0.37	0.84
Relative Risk, Progression, ALE	0.25	0.68
Relative Risk, Progression, DAC	0.36	0.78
Rate Ratio, Relapse, GA 20 mg (Glatopa)	0.55	0.71
Relative Risk, Progression, DMF	0.46	0.84

Incremental costs

RRMS
GA 20 mg (Copaxone) vs. GA 20 mg (Glatopa)

Parameter	Low Value	High Value
WAC, GA 20 mg (Copaxone)	$5,691	$8,537
WAC, GA 20 mg (Glatopa)	$4,155	$6,233
Relative Risk, Progression, GA 20 mg (Copaxone)	0.58	0.94
Relative Risk, Progression, GA 20 mg (Glatopa)	0.58	0.94
Discount, GA 20 mg (Glatopa)	0.28	0.42
Discontinuation Rate, GA 20 mg (Copaxone)	0.04	0.06
Discount, GA 20 mg (Copaxone)	0.12	0.18
Discontinuation Rate, GA 20 mg (Glatopa)	0.04	0.06
Probability, PPMS 6 to 7	0.15	0.23
Probability: RRMS to SPMS, EDSS 4	0.17	0.25

Incremental costs

Parameter	Low Value	High Value
WAC, IFN β-1a 30 mcg	$5,030	$7,544
WAC, GA 20 mg (Glatopa)	$4,155	$6,233
Relative Risk, Progression, IFN β-1a 30 mcg	0.63	1.00
Relative Risk, Progression, GA 20 mg (Glatopa)	0.58	0.94
Discount, GA 20 mg (Glatopa)	0.28	0.42
Discount, IFN β-1a 30 mcg	0.16	0.24
Discontinuation Rate, IFN β-1a 30 mcg	0.04	0.06
Discontinuation Rate, GA 20 mg (Glatopa)	0.04	0.06
Probability, PPMS 6 to 7	0.15	0.23
Probability: RRMS to SPMS, EDSS 4	0.17	0.25

Incremental QALYs

RRMS
IFN β-1a 30 mcg vs. GA 20 mg (Glatopa)

Parameter	Low Value	High Value
Relative Risk, Progression, GA 20 mg (Glatopa)	0.58	0.94
Relative Risk, Progression, IFN β-1a 30 mcg	0.63	1.00
Rate Ratio, Relapse, IFN β-1a 30 mcg	0.74	0.94
Rate Ratio, Relapse, GA 20 mg (Glatopa)	0.55	0.71
Discontinuation Rate, IFN β-1a 30 mcg	0.04	0.06
AE Disutility, GA 20 mg (Glatopa)	0.00	0.05
AE Disutility, IFN β-1a 30 mcg	0.00	0.05
Annual Utiity, RRMS, EDSS 2	0.62	0.94
Age at beginning treatment, RRMS	23	35
Annual Utiity, RRMS, EDSS 1	0.67	1.00

Incremental costs

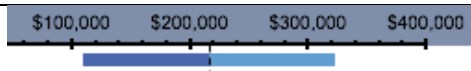
Parameter	Low Value	High Value
Relative Risk, Progression, IFN β-1a 22 mcg	0.52	1.23
WAC, IFN β-1a 22 mcg	$5,303	$7,955
WAC, GA 20 mg (Glatopa)	$4,155	$6,233
Relative Risk, Progression, GA 20 mg (Glatopa)	0.58	0.94
Discount, GA 20 mg (Glatopa)	0.28	0.42
Discontinuation Rate, IFN β-1a 22 mcg	0.04	0.07
Discount, IFN β-1a 22 mcg	0.12	0.18
Discontinuation Rate, GA 20 mg (Glatopa)	0.04	0.06
Probability, PPMS 6 to 7	0.15	0.23
Rate Ratio, Relapse, IFN β-1a 22 mcg	0.55	0.85

Incremental QALYs

RRMS
IFN β-1a 22 mcg vs. GA 20 mg (Glatopa)

Parameter	Low Value	High Value
Relative Risk, Progression, IFN β-1a 22 mcg	0.52	1.23
Relative Risk, Progression, GA 20 mg (Glatopa)	0.58	0.94
Rate Ratio, Relapse, IFN β-1a 22 mcg	0.55	0.85
Rate Ratio, Relapse, GA 20 mg (Glatopa)	0.55	0.71
Annual Utility, RRMS, EDSS 2	0.62	0.94
Discontinuation Rate, IFN β-1a 22 mcg	0.04	0.07
Age at beginning treatment, RRMS	23	35
AE Disutility, GA 20 mg (Glatopa)	0.00	0.05
AE Disutility, IFN β-1a 22 mcg	0.00	0.05
Annual Utility, RRMS, EDSS 1	0.67	1.00

Incremental costs



Parameter	Low Value	High Value
WAC, IFN β-1a 44 mcg	$5,303	$7,955
WAC, GA 20 mg (Glatopa)	$4,155	$6,233
Relative Risk, Progression, IFN β-1a 44 mcg	0.52	0.99
Relative Risk, Progression, GA 20 mg (Glatopa)	0.58	0.94
Discount, GA 20 mg (Glatopa)	0.28	0.42
Discontinuation Rate, IFN β-1a 44 mcg	0.07	0.10
Discount, IFN β-1a 44 mcg	0.12	0.18
Discontinuation Rate, Second Line, Year >X	0.08	0.12
Discontinuation Rate, GA 20 mg (Glatopa)	0.04	0.06
WAC, DAC	$5,467	$8,200

Incremental QALYs

RRMS
IFN β-1a 44 mcg vs. GA 20 mg (Glatopa)

Parameter	Low Value	High Value
Relative Risk, Progression, IFN β-1a 44 mcg	0.52	0.99
Relative Risk, Progression, GA 20 mg (Glatopa)	0.58	0.94
Rate Ratio, Relapse, GA 20 mg (Glatopa)	0.55	0.71
Rate Ratio, Relapse, IFN β-1a 44 mcg	0.54	0.73
Discontinuation Rate, Second Line, Year >X	0.08	0.12
Relative Risk, Progression, NAT	0.37	0.84
Relative Risk, Progression, ALE	0.25	0.68
Relative Risk, Progression, DAC	0.36	0.78
Relative Risk, Progression, FIN	0.51	0.90
Relative Risk, Progression, DMF	0.46	0.84

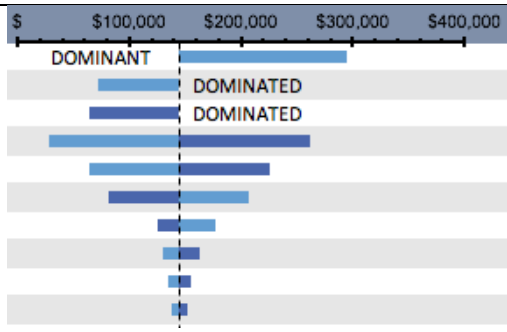
Cost per additional QALY

RRMS
IFN β-1b 250 mcg (Betaseron) vs. GA 20 mg (Glatopa)

Parameter	Low Value	High Value
DOMINATED Relative Risk, Progression, GA 20 mg (Glatopa)	0.58	0.94
DOMINATED Relative Risk, Progression, IFN β-1b 250 mcg (Betaseron)	0.46	0.89
WAC, IFN β-1b 250 mcg (Betaseron)	$5,318	$7,977
WAC, GA 20 mg (Glatopa)	$4,155	$6,233
Discount, IFN β-1b 250 mcg (Betaseron)	0.28	0.42
Discount, GA 20 mg (Glatopa)	0.28	0.42
Rate Ratio, Relapse, IFN β-1b 250 mcg (Betaseron)	0.55	0.77
Rate Ratio, Relapse, GA 20 mg (Glatopa)	0.55	0.71
Annual Utility, RRMS, EDSS 2	0.62	0.94
Age at beginning treatment, RRMS	23	35

Cost per additional QALY

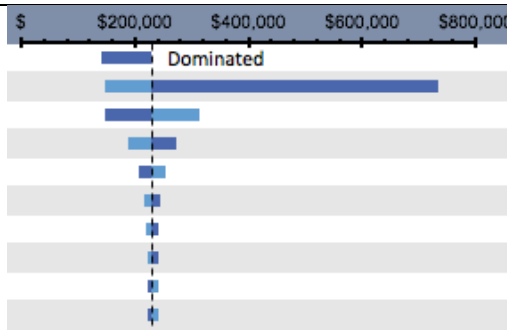
RRMS
IFN β-1b 250 mcg (Extavia) vs. GA 20 mg (Glatopa)



Parameter	Low Value	High Value
WAC, IFN β-1b 250 mcg (Extavia)	$4,758	$7,137
Relative Risk, Progression, GA 20 mg (Glatopa)	0.58	0.94
Relative Risk, Progression, IFN β-1b 250 mcg (Extavia)	0.46	0.89
WAC, GA 20 mg (Glatopa)	$4,155	$6,233
Discount, IFN β-1b 250 mcg (Extavia)	0.28	0.42
Discount, GA 20 mg (Glatopa)	0.28	0.42
Rate Ratio, Relapse, IFN β-1b 250 mcg (Extavia)	0.55	0.77
Rate Ratio, Relapse, GA 20 mg (Glatopa)	0.55	0.71
Annual Utility, RRMS, EDSS 2	0.62	0.94
Annual Utility, RRMS, EDSS 0	0.70	1.00

Cost per additional QALY

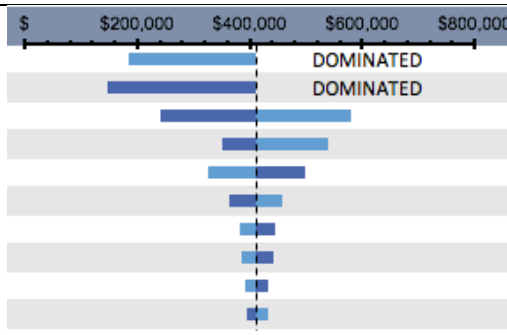
RRMS
NAT vs. GA 20 mg (Glatopa)



Parameter	Low Value	High Value
Relative Risk, Progression, NAT	0.37	0.84
Relative Risk, Progression, GA 20 mg (Glatopa)	0.58	0.94
WAC, NAT	$4,800	$7,200
WAC, GA 20 mg (Glatopa)	$4,155	$6,233
Discount, GA 20 mg (Glatopa)	0.28	0.42
Annual Utility, RRMS, EDSS 2	0.62	0.94
Annual Utility, RRMS, EDSS 0	0.70	1.00
Annual Utility, RRMS, EDSS 1	0.67	1.00
Age at beginning treatment, RRMS	23	35
Rate Ratio, Relapse, NAT	0.25	0.40

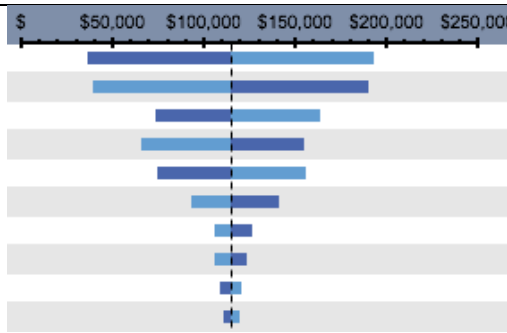
Cost per additional QALY

RRMS
PEG vs. GA 20 mg (Glatopa)



Parameter	Low Value	High Value
Relative Risk, Progression, GA 20 mg (Glatopa)	0.58	0.94
Relative Risk, Progression, PEG	0.37	1.02
WAC, PEG	$5,030	$7,544
Rate Ratio, Relapse, PEG	0.47	0.86
WAC, GA 20 mg (Glatopa)	$4,155	$6,233
Discount, GA 20 mg (Glatopa)	0.28	0.42
Rate Ratio, Relapse, GA 20 mg (Glatopa)	0.55	0.71
Annual Utility, RRMS, EDSS 2	0.62	0.94
Annual Utility, RRMS, EDSS 0	0.70	1.00
Age at beginning treatment, RRMS	23	35

Incremental costs



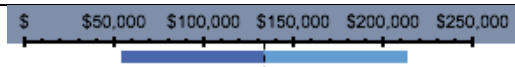
Parameter	Low Value	High Value
WAC, TER 7 mg	$4,702	$7,052
WAC, GA 20 mg (Glatopa)	$4,155	$6,233
Relative Risk, Progression, GA 20 mg (Glatopa)	0.58	0.94
Relative Risk, Progression, TER 7 mg	0.63	1.14
Discount, GA 20 mg (Glatopa)	0.28	0.42
Discontinuation Rate, TER 7 mg	0.10	0.15
Discontinuation Rate, Second Line, Year >X	0.08	0.12
Discount, TER 7 mg	0.08	0.12
Discontinuation Rate, GA 20 mg (Glatopa)	0.04	0.06
WAC, DAC	$5,467	$8,200

Incremental QALYs

RRMS TER 7 mg vs. GA 20 mg (Glatopa)

Parameter	Low Value	High Value
Relative Risk, Progression, GA 20 mg (Glatopa)	0.58	0.94
Relative Risk, Progression, TER 7 mg	0.63	1.14
Rate Ratio, Relapse, TER 7 mg	0.67	0.93
Rate Ratio, Relapse, GA 20 mg (Glatopa)	0.55	0.71
Discontinuation Rate, TER 7 mg	0.10	0.15
Discontinuation Rate, Second Line, Year >X	0.08	0.12
Relative Risk, Progression, NAT	0.37	0.84
Relative Risk, Progression, ALE	0.25	0.68
Relative Risk, Progression, DAC	0.36	0.78
Relative Risk, Progression, FIN	0.51	0.90

Incremental costs



Parameter	Low Value	High Value
WAC, TER 14 mg	$4,702	$7,052
WAC, GA 20 mg (Glatopa)	$4,155	$6,233
Relative Risk, Progression, GA 20 mg (Glatopa)	0.58	0.94
Discount, GA 20 mg (Glatopa)	0.28	0.42
Relative Risk, Progression, TER 14 mg	0.52	0.97
Discontinuation Rate, TER 14 mg	0.10	0.15
Discontinuation Rate, Second Line, Year >X	0.08	0.12
Discount, TER 14 mg	0.08	0.12
Discontinuation Rate, GA 20 mg (Glatopa)	$0	$0
WAC, DAC	$5,467	$8,200

Incremental QALYs

RRMS TER 14 mg vs. GA 20 mg (Glatopa)

Parameter	Low Value	High Value
Relative Risk, Progression, GA 20 mg (Glatopa)	0.58	0.94
Relative Risk, Progression, TER 14 mg	0.52	0.97
Discontinuation Rate, Second Line, Year >X	0.08	0.12
Relative Risk, Progression, NAT	0.37	0.84
Rate Ratio, Relapse, GA 20 mg (Glatopa)	0.55	0.71
Relative Risk, Progression, ALE	0.25	0.68
Relative Risk, Progression, DAC	0.36	0.78
Rate Ratio, Relapse, TER 14 mg	0.56	0.79
Relative Risk, Progression, FIN	0.51	0.90
Relative Risk, Progression, DMF	0.46	0.84

Incremental QALYs

RRMS OCR vs. GA 20 mg (Glatopa)

Parameter	Low Value	High Value
Relative Risk, Progression, OCR (RRMS)	0.28	0.76
Relative Risk, Progression, GA 20 mg (Glatopa)	0.58	0.94
Discontinuation Rate, OCR	0.04	0.06
Annual Utility, RRMS, EDSS 2	0.62	0.94
Annual Utility, RRMS, EDSS 0	0.70	1.00
Age at beginning treatment, RRMS	23	35
Annual Utility, RRMS, EDSS 1	0.67	1.00
Rate Ratio, Relapse, OCR	0.27	0.44
Rate Ratio, Relapse, GA 20 mg (Glatopa)	0.55	0.71
Annual Utility, SPMS, EDSS 9	0.17	0.26

Incremental QALYs PPMS OCR vs. Supportive care		Parameter	Low Value	High Value
		Relative Risk, Progression, OCR (PPMS)	0.58	0.98
		Age at beginning treatment, PPMS	33	50
		Annual Utility, PPMS, EDSS 6	0.33	0.49
		Discontinuation Rate, OCR	0.04	0.06
		Annual Utility, PPMS, EDSS 5	0.40	0.60
		AE Disutility, OCR	0.00	0.05
		Annual Utility, PPMS, EDSS 4	0.47	0.70
		Annual Utility, PPMS, EDSS 3	0.52	0.78
		PPMS EDSS 6 Entering the Model	0.24	0.36
		PPMS EDSS 5 Entering the Model	0.13	0.19

Table E12. Results of Probabilistic Sensitivity Analyses by DMT, RRMS

	Supportive Care				Alemtuzumab				Daclizumab			
	Mean	Credible Range			Mean	Credible Range			Mean	Credible Range		
Total Costs	**$341,064**	**$298,607**	-	**$382,986**	**$595,752**	**$534,832**	-	**$656,045**	**$1,144,393**	**$997,084**	-	**$1,296,928**
Drug Costs	$0	$0	-	$0	$343,868	$284,013	-	$402,379	$854,919	$703,670	-	$1,015,575
Healthcare Costs	$341,064	$298,607	-	$382,986	$251,883	$210,304	-	$301,953	$289,471	$252,018	-	$329,640
Adverse Event Costs	$0	$0	-	$0	$1	$0	-	$5	$3	$0	-	$20
Total QALYs	**5.4**	**4.63**	-	**6.08**	**12.6**	**9.28**	-	**15.35**	**9.6**	**7.90**	-	**11.26**
Relapses	16.3	14.46	-	18.30	11.3	9.46	-	13.35	14.1	12.16	-	16.15
Life-Years	21.6	20.01	-	23.10	23.3	21.66	-	24.79	22.5	21.02	-	23.90
	Dimethyl fumarate				**Fingolimod**				**Glatiramer acetate 20 mg (Glatopa)**			
	Mean	Credible Range			Mean	Credible Range			Mean	Credible Range		
Total Costs	**$1,027,335**	**$912,240**	-	**$1,152,391**	**$1,098,670**	**$960,890**	-	**$1,248,215**	**$863,923**	**$759,705**	-	**$979,203**
Drug Costs	$728,786	$616,405	-	$852,411	$799,958	$662,197	-	$955,189	$557,406	$452,283	-	$669,672
Healthcare Costs	$298,542	$262,228	-	$336,185	$298,709	$260,790	-	$337,784	$306,516	$268,755	-	$346,902
Adverse Event Costs	$7	$0	-	$41	$3	$0	-	$19	$2	$0	-	$9
Total QALYs	**8.9**	**7.55**	-	**10.19**	**8.8**	**7.29**	-	**10.45**	**8.3**	**6.69**	-	**9.94**
Relapses	14.4	12.46	-	16.41	13.7	11.84	-	15.76	14.5	12.51	-	16.58
Life-Years	22.4	20.82	-	23.72	22.3	20.78	-	23.74	22.2	20.68	-	23.68
	Glatiramer acetate 20 mg (Copaxone)				**Interferon β-1a 30 mcg (Avonex)**				**Interferon β-1a 22 mcg (Rebif)**			
	Mean	Credible Range			Mean	Credible Range			Mean	Credible Range		
Total Costs	**$1,157,630**	**$1,002,040**	-	**$1,333,716**	**$1,066,837**	**$927,814**	-	**$1,219,387**	**$1,119,155**	**$929,070**	-	**$1,326,070**
Drug Costs	$850,978	$692,340	-	$1,029,968	$753,170	$613,056	-	$904,571	$807,832	$601,262	-	$1,026,576
Healthcare Costs	$306,650	$267,760	-	$346,795	$313,665	$273,572	-	$353,313	$311,311	$267,796	-	$359,617
Adverse Event Costs	$2	$0	-	$9	$2	$0	-	$10	$12	$0	-	$46
Total QALYs	**8.3**	**6.72**	-	**9.84**	**7.8**	**6.22**	-	**9.32**	**7.9**	**5.32**	-	**10.28**
Relapses	14.5	12.49	-	16.57	15.7	13.52	-	17.92	14.8	12.45	-	17.24
Life-Years	22.2	20.71	-	23.67	22.2	20.58	-	23.60	22.2	20.54	-	23.64

Continued on next page

	Interferon β-1a 44 mcg (Rebif)				Interferon β-1b 250 mcg (Betaseron)				Interferon β-1b 250 mcg (Extavia)			
	Mean	Credible Range			Mean	Credible Range			Mean	Credible Range		
Total Costs	**$1,079,343**	**$941,261**	-	**$1,221,538**	**$1,051,767**	**$891,058**	-	**$1,226,553**	**$959,508**	**$826,384**	-	**$1,102,126**
Drug Costs	$773,406	$634,506	-	$916,374	$753,355	$588,418	-	$930,229	$661,360	$519,336	-	$813,067
Healthcare Costs	$305,924	$267,460	-	$345,530	$298,411	$258,301	-	$342,854	$298,147	$259,102	-	$340,810
Adverse Event Costs	$12	$0	-	$44	$1	$0	-	$8	$1	$0	-	$8
Total QALYs	**8.3**	**6.60**	-	**9.85**	**9.0**	**6.94**	-	**11.07**	**9.0**	**6.92**	-	**11.04**
Relapses	14.7	12.65	-	16.71	15.0	12.73	-	17.37	15.0	12.72	-	17.35
Life-Years	22.2	20.70	-	23.66	22.4	20.89	-	23.90	22.4	20.88	-	23.91
	Natalizumab				**Ocrelizumab**				**Peginterferon β-1a**			
	Mean	Credible Range			Mean	Credible Range			Mean	Credible Range		
Total Costs	**$1,265,250**	**$1,070,251**	-	**$1,459,458**	-	-	-	-	**$1,225,658**	**$1,015,039**	-	**$1,447,733**
Drug Costs	$982,994	$778,759	-	$1,190,520	-	-	-	-	$931,765	$693,180	-	$1,167,864
Healthcare Costs	$282,254	$242,722	-	$325,605	$271,654	$231,531	-	$318,449	$293,891	$249,886	-	$343,703
Adverse Event Costs	$2	$0	-	$10	$1	$0	-	$9	$1	$0	-	$9
Total QALYs	**10.1**	**7.66**	-	**12.40**	**11.0**	**8.33**	-	**13.28**	**9.3**	**6.47**	-	**11.99**
Relapses	12.5	10.58	-	14.51	13.1	11.05	-	15.17	15.0	12.40	-	18.16
Life-Years	22.7	21.08	-	24.06	22.9	21.36	-	24.31	22.5	20.94	-	23.99
	Teriflunomide 7 mg				**Teriflunomide 14 mg**							
	Mean	Credible Range			Mean	Credible Range						
Total Costs	**$979,028**	**$867,222**	-	**$1,089,996**	**$999,326**	**$890,279**	-	**$1,112,136**				
Drug Costs	$664,699	$556,980	-	$776,151	$693,114	$585,983	-	$804,237				
Healthcare Costs	$314,326	$275,493	-	$354,132	$306,207	$268,373	-	$345,048				
Adverse Event Costs	$4	$0	-	$23	$4	$0	-	$22				
Total QALYs	**7.6**	**6.14**	-	**9.01**	**8.3**	**6.84**	-	**9.65**				
Relapses	15.0	12.97	-	17.05	14.9	12.88	-	16.91				
Life-Years	22.1	20.54	-	23.49	22.2	20.71	-	23.64				

Table E13. Results of Probabilistic Sensitivity Analyses by DMT, PPMS

	Supportive Care				Ocrelizumab			
	Mean	Credible Range			Mean	Credible Range		
Total Costs	**$266,649**	**$246,836**	**-**	**$266,026**	-	-	-	-
Drug Costs	$0	$0	-	$0	-	-	-	-
Healthcare Costs	$266,649	$246,836	-	$266,026	-	-	-	-
Adverse Event Costs	$0	$0	-	$0	-	-	-	-
Total QALYs	**2.8**	**2.63**	**-**	**2.80**	**3.4**	**3.16**	**-**	**3.43**
Life-Years	15.7	14.88	-	15.71	16.3	15.37	-	16.23

Table E14. Results of Probabilistic Sensitivity Analyses, Pairwise Results Compared to Supportive Care, RRMS

	Alemtuzumab				Daclizumab				Dimethyl fumarate			
	Mean	Credible Range			Mean	Credible Range			Mean	Credible Range		
$ per QALY	**$35,333**	**$22,480**	**-**	**$65,937**	**$190,095**	**$143,533**	**-**	**$281,077**	**$196,804**	**$150,553**	**-**	**$267,719**
$ per Relapse	$50,513	$35,911	-	$73,839	$361,664	$235,044	-	$688,800	$351,900	$241,940	-	$610,223
$ per Life-Year	$149,428	$92,941	-	$312,973	$868,647	$612,859	-	$1,392,242	$919,906	$669,703	-	$1,373,662
Total Costs	**$254,655**	**$268,505**	**-**	**$312,251**	**$802,047**	**$666,124**	**-**	**$947,591**	**$687,437**	**$607,053**	**-**	**$807,694**
Drug Costs	$345,282	$283,782	-	$301,797	$854,015	$707,342	-	$958,950	$730,330	$621,537	-	$668,073
Healthcare Costs	-$90,627	-$129,418	-	-$128,369	-$51,971	-$73,029	-	-$62,454	-$42,900	-$59,419	-	-$43,758
Adverse Event Costs	$1	$0	-	$2	$3	$0	-	$9	$7	$0	-	$19
Total QALYs	**7.28**	**4.15**	**-**	**8.97**	**4.23**	**2.75**	**-**	**4.79**	**3.50**	**2.49**	**-**	**2.93**
Relapses	-5.03	-6.25	-	-4.99	-2.22	-3.15	-	-2.84	-1.95	-2.67	-	-2.21
Life-Years	1.72	0.87	-	2.19	0.93	0.55	-	1.18	0.75	0.49	-	0.83
	Fingolimod				**Glatiramer acetate 20 mg (Glatopa)**				**Glatiramer acetate 20 mg (Copaxone)**			
	Mean	Credible Range			Mean	Credible Range			Mean	Credible Range		
$ per QALY	**$218,622**	**$160,178**	**-**	**$336,658**	**$180,224**	**$124,309**	**-**	**$323,579**	**$282,283**	**$197,919**	**-**	**$492,379**
$ per Relapse	$292,552	$204,286	-	$462,289	$277,361	$168,731	-	$648,216	$436,201	$265,960	-	$1,061,246
$ per Life-Year	$1,025,952	$700,076	-	$1,748,279	$822,747	$530,390	-	$1,734,293	$1,286,089	$835,999	-	$2,608,260
Total Costs	**$759,252**	**$731,703**	**-**	**$910,437**	**$520,925**	**$483,070**	**-**	**$625,620**	**$818,053**	**$896,957**	**-**	**$982,394**
Drug Costs	$801,865	$665,657	-	$763,618	$555,370	$450,783	-	$487,130	$852,506	$696,519	-	$715,356
Healthcare Costs	-$42,616	-$61,726	-	-$34,816	-$34,447	-$54,603	-	-$49,167	-$34,455	-$53,946	-	-$41,477
Adverse Event Costs	$3	$0	-	$9	$2	$0	-	$5	$2	$0	-	$4
Total QALYs	**3.47**	**2.18**	**-**	**4.35**	**2.87**	**1.38**	**-**	**4.51**	**2.88**	**1.46**	**-**	**4.16**
Relapses	-2.60	-3.40	-	-2.87	-1.90	-2.80	-	-1.52	-1.89	-2.76	-	-1.35
Life-Years	0.74	0.42	-	0.75	0.63	0.24	-	0.60	0.63	0.28	-	0.79

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	Interferon β-1a 30 mcg (Avonex)				Interferon β-1a 22 mcg (Rebif)				Interferon β-1a 44 mcg (Rebif)			
	Mean	Credible Range			Mean	Credible Range			Mean	Credible Range		
$ per QALY	**$303,819**	**$202,958**	**-**	**$605,742**	**$312,939**	**$179,717**	**-**	**$6,292,671**	**$253,073**	**$176,225**	**-**	**$466,841**
$ per Relapse	$1,149,713	$380,749	-	Dominated	$504,943	$214,460	-	Dominated	$438,725	$255,469	-	$1,155,669
$ per Life-Year	$1,335,456	$834,610	-	$3,043,004	$1,419,068	$758,686	-	Dominated	$1,164,929	$751,820	-	$2,528,933
Total Costs	**$729,559**	**$636,444**	**-**	**$884,100**	**$778,708**	**$850,445**	**-**	**$977,351**	**$737,019**	**$676,688**	**-**	**$881,043**
Drug Costs	$757,461	$619,163	-	$736,776	$808,750	$609,712	-	$954,285	$772,379	$622,264	-	$753,284
Healthcare Costs	-$27,904	-$44,842	-	-$39,517	-$30,055	-$58,619	-	-$27,513	-$35,373	-$55,658	-	-$58,607
Adverse Event Costs	$2	$0	-	$5	$12	$1	-	$7	$13	$0	-	$9
Total QALYs	**2.42**	**1.17**	**-**	**2.50**	**2.50**	**0.18**	**-**	**2.74**	**2.92**	**1.43**	**-**	**2.48**
Relapses	-0.61	-1.64	-	-0.91	-1.51	-2.98	-	-0.89	-1.70	-2.61	-	-2.03
Life-Years	0.55	0.23	-	0.59	0.55	-0.02	-	1.52	0.63	0.27	-	0.80
	Interferon β-1b 250 mcg (Betaseron)				**Interferon β-1b 250 mcg (Extavia)**				**Natalizumab**			
	Mean	**Credible Range**			**Mean**	**Credible Range**			**Mean**	**Credible Range**		
$ per QALY	**$195,504**	**$130,292**	**-**	**$366,745**	**$169,225**	**$115,876**	**-**	**$324,051**	**$193,786**	**$137,994**	**-**	**$330,719**
$ per Relapse	$520,521	$229,427	-	Dominated	$454,717	$199,148	-	Dominated	$238,498	$168,164	-	$367,095
$ per Life-Year	$853,255	$546,462	-	$1,894,198	$738,577	$475,098	-	$1,681,745	$883,227	$595,345	-	$1,774,195
Total Costs	**$713,049**	**$768,142**	**-**	**$875,867**	**$617,580**	**$572,865**	**-**	**$762,750**	**$923,482**	**$839,747**	**-**	**$1,112,485**
Drug Costs	$756,203	$584,235	-	$661,973	$660,371	$519,198	-	$522,309	$982,508	$768,463	-	$831,132
Healthcare Costs	-$43,155	-$67,809	-	-$78,512	-$42,793	-$68,526	-	-$71,027	-$59,029	-$87,643	-	-$74,208
Adverse Event Costs	$1	$0	-	$3	$1	$0	-	$3	$2	$0	-	$5
Total QALYs	**3.65**	**1.64**	**-**	**3.15**	**3.62**	**1.72**	**-**	**3.64**	**4.76**	**2.43**	**-**	**4.45**
Relapses	-1.37	-2.74	-	-1.95	-1.38	-2.68	-	-0.81	-3.89	-4.81	-	-4.27
Life-Years	0.84	0.33	-	1.26	0.83	0.34	-	0.64	1.04	0.47	-	1.95

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	Ocrelizumab				Peginterferon β-1a				Teriflunomide 7 mg			
	Mean	Credible Range			Mean	Credible Range			Mean	Credible Range		
$ per QALY	-	-	-	-	**$222,416**	**$147,284**	-	**$649,002**	**$286,338**	**$195,125**	-	**$594,754**
$ per Relapse	-	-	-	-	$658,295	$225,158	-	Dominated	$461,855	$258,425	-	$1,447,830
$ per Life-Year	-	-	-	-	$964,845	$597,278	-	$3,847,398	$1,359,212	$860,693	-	$3,684,015
Total Costs	-	-	-	-	**$883,265**	**$1,050,933**	-	**$1,094,298**	**$638,186**	**$623,189**	-	**$739,666**
Drug Costs	-	-	-	-	$930,601	$691,933	-	$845,492	$665,249	$556,875	-	$665,726
Healthcare Costs	-$69,612	-$103,003	-	-$103,826	-$47,338	-$82,000	-	-$68,784	-$27,067	-$41,962	-	-$35,887
Adverse Event Costs	$2	$0	-	$4	$2	$0	-	$4	$4	$0	-	$12
Total QALYs	**5.63**	**3.10**	-	**4.07**	**3.96**	**1.11**	-	**3.34**	**2.24**	**1.03**	-	**2.29**
Relapses	-3.29	-4.37	-	-3.55	-1.38	-3.34	-	-0.83	-1.37	-2.27	-	-2.13
Life-Years	1.28	0.61	-	1.36	0.91	0.18	-	1.07	0.47	0.17	-	0.51

	Teriflunomide 14 mg			
	Mean	Credible Range		
$ per QALY	**$226,946**	**$167,517**	-	**$358,703**
$ per Relapse	$444,325	$267,912	-	$1,115,856
$ per Life-Year	$1,057,270	$740,525	-	$1,894,360
Total Costs	**$658,649**	**$660,232**	-	**$761,843**
Drug Costs	$693,987	$587,041	-	$618,080
Healthcare Costs	-$35,342	-$51,010	-	-$45,319
Adverse Event Costs	$4	$0	-	$10
Total QALYs	**2.93**	**1.79**	-	**3.08**
Relapses	-1.47	-2.26	-	-1.38
Life-Years	0.63	0.34	-	0.60

Table E15. Results of Probabilistic Sensitivity Analyses, Pairwise Results Compared to Supportive Care, PPMS

	Ocrelizumab			
	Mean	Credible Range		
Healthcare Costs	$1,984	-$700	-	$856
Adverse Event Costs	$0	$0	-	$0
Total QALYs	**0.64**	**0.11**	-	**0.61**
Life-Years	0.52	0.09	-	0.74

Table E16. Results of Probabilistic Sensitivity Analyses, Pairwise Results Compared to Glatiramer Acetate 20mg (Glatopa), RRMS

	Alemtuzumab				Daclizumab				Dimethyl fumarate			
	Mean	Credible Range			Mean	Credible Range			Mean	Credible Range		
Total Costs	**Dominant**	**Dominant**	**-**	**Dominant**	**$211,712**	**$85,537**	**-**	**Dominated**	**$278,902**	**$64,246**	**-**	**Dominated**
$ per Life-Year	Dominant	Dominant	-	Dominant	$834,523	$108,453	-	Dominated	$2,511,333	$48,427	-	Dominated
$ per Relapse	Dominant	Dominant	-	Dominant	$969,476	$364,116	-	Dominated	$1,478,588	$295,301	-	Dominated
Total Costs	**-$266,269**	**-$382,871**	**-**	**-$169,226**	**$281,122**	**$126,304**	**-**	**$451,417**	**$166,512**	**$29,503**	**-**	**$300,978**
Drug Costs	-$210,088	-$332,898	-	-$100,233	$298,645	$132,880	-	$478,867	$174,961	$29,969	-	$315,750
Healthcare Costs	-$56,181	-$92,957	-	-$17,064	-$17,525	-$39,640	-	$4,483	-$8,454	-$27,524	-	$11,105
Adverse Event Costs	-$1	-$4	-	$0	$2	$0	-	$11	$5	$0	-	$30
Total QALYs	**4.41**	**1.22**	**-**	**7.24**	**1.36**	**-0.45**	**-**	**3.19**	**0.62**	**-1.08**	**-**	**2.32**
Relapses	-3.13	-4.65	-	-1.63	-0.32	-1.49	-	0.95	-0.05	-1.14	-	1.00
Life-Years	1.10	0.25	-	1.82	0.30	-0.15	-	0.75	0.12	-0.31	-	0.56
	Fingolimod				**Glatiramer acetate 20 mg (Copaxone)**				**Interferon β-1a 30 mcg (Avonex)**			
	Mean	Credible Range			Mean	Credible Range			Mean	Credible Range		
Total Costs	**$416,064**	**$103,419**	**-**	**Dominated**	-	-	-	-	**Dominated**	**$177,146**	**-**	**Dominated**
$ per Life-Year	$333,200	$64,327	-	Dominated	-	-	-	-	Dominated	$1,514,627	-	Dominated
$ per Relapse	$2,280,476	$443,457	-	Dominated	-	-	-	-	Dominated	$614,844	-	Dominated
Total Costs	**$238,328**	**$89,832**	**-**	**$395,032**	**$297,128**	**$113,534**	**-**	**$483,348**	**$208,635**	**$53,422**	**-**	**$371,539**
Drug Costs	$246,496	$86,960	-	$414,186	$297,136	$101,131	-	$493,823	$202,091	$34,314	-	$373,953
Healthcare Costs	-$8,170	-$29,388	-	$11,742	-	-	-	-	$6,543	-$15,291	-	$27,200
Adverse Event Costs	$2	$0	-	$9	-	-	-	-	$0	-$1	-	$1
Total QALYs	**0.60**	**-1.13**	**-**	**2.39**	-	-	-	-	**-0.45**	**-2.27**	**-**	**1.50**
Relapses	-0.70	-1.87	-	0.42	-	-	-	-	1.29	-0.06	-	2.76
Life-Years	0.11	-0.32	-	0.57	-	-	-	-	-0.08	-0.53	-	0.41

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	Interferon β-1a 22 mcg (Rebif)				Interferon β-1a 44 mcg (Rebif)				Interferon β-1b 250 mcg (Betaseron)			
	Mean	Credible Range			Mean	Credible Range			Mean	Credible Range		
Total Costs	**Dominated**	**$147,242**	**-**	**Dominated**	**$13,391,374**	**$124,390**	**-**	**Dominated**	**$255,895**	**$46,042**	**-**	**Dominated**
$ per Life-Year	Dominated	$69,218	-	Dominated	Dominated	$106,902	-	Dominated	Dominated	$27,981	-	Dominated
$ per Relapse	Dominated	$566,984	-	Dominated	Dominated	$517,886	-	Dominated	$951,456	$178,072	-	Dominated
Total Costs	**$257,783**	**$64,737**	**-**	**$469,362**	**$216,094**	**$53,854**	**-**	**$371,058**	**$192,125**	**-$6,104**	**-**	**$386,974**
Drug Costs	$253,381	$42,906	-	$484,987	$217,010	$44,651	-	$382,018	$200,833	-$20,173	-	$409,284
Healthcare Costs	$4,392	-$26,216	-	$35,806	-$927	-$23,627	-	$20,665	-$8,708	-$35,121	-	$19,836
Adverse Event Costs	$11	$0	-	$45	$11	$0	-	$41	$0	-$2	-	$0
Total QALYs	**-0.37**	**-3.20**	**-**	**2.31**	**0.04**	**-1.94**	**-**	**1.98**	**0.78**	**-1.72**	**-**	**3.08**
Relapses	0.39	-1.38	-	2.50	0.20	-1.02	-	1.45	0.53	-1.14	-	2.28
Life-Years	-0.08	-0.78	-	0.60	0.01	-0.49	-	0.50	0.21	-0.44	-	0.84
	Interferon β-1b 250 mcg (Extavia)				**Natalizumab**				**Ocrelizumab**			
	Mean	**Credible Range**			**Mean**	**Credible Range**			**Mean**	**Credible Range**		
Total Costs	**$126,870**	**Dominant**	**-**	**Dominated**	**$214,849**	**$99,387**	**-**	**Dominated**	-	-	-	-
$ per Life-Year	Dominated	Dominant	-	Dominated	$201,681	$74,724	-	$677,049	-	-	-	-
$ per Relapse	$473,565	Dominant	-	Dominated	$976,774	$417,822	-	Dominated	-	-	-	-
Total Costs	**$96,655**	**-$70,975**	**-**	**$273,583**	**$402,557**	**$196,962**	**-**	**$604,027**	-	-	-	-
Drug Costs	$105,001	-$74,982	-	$293,028	$427,139	$196,269	-	$642,705	-	-	-	-
Healthcare Costs	-$8,346	-$33,820	-	$17,488	-$24,582	-$53,125	-	$5,368	-$35,166	-$67,630	-	-$1,829
Adverse Event Costs	$0	-$2	-	$0	$0	$0	-	$2	$0	-$1	-	$1
Total QALYs	**0.75**	**-1.50**	**-**	**3.07**	**1.89**	**-0.67**	**-**	**4.06**	**2.75**	**-0.01**	**-**	**5.34**
Relapses	0.52	-1.05	-	2.18	-1.99	-3.20	-	-0.66	-1.39	-2.91	-	0.09
Life-Years	0.20	-0.37	-	0.81	0.42	-0.25	-	1.01	0.65	-0.06	-	1.32

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	Peginterferon β-1a				Teriflunomide 7 mg				Teriflunomide 14 mg			
	Mean	Credible Range			Mean	Credible Range			Mean	Credible Range		
Total Costs	**$336,172**	**$106,502**	**-**	**Dominated**	**Dominated**	**$134,034**	**-**	**Dominated**	**Dominated**	**$81,181**	**-**	**Dominated**
$ per Life-Year	Dominated	$122,037	-	Dominated	Dominated	Dominant	-	Dominated	Dominated	$45,693	-	Dominated
$ per Relapse	$1,285,842	$411,813	-	Dominated	Dominated	$514,679	-	Dominated	Dominated	$324,541	-	Dominated
Total Costs	**$362,340**	**$119,204**	**-**	**$597,918**	**$117,261**	**-$27,301**	**-**	**$253,718**	**$137,724**	**$7,554**	**-**	**$265,385**
Drug Costs	$375,232	$100,987	-	$631,272	$109,879	-$46,510	-	$254,777	$138,617	$80	-	$277,347
Healthcare Costs	-$12,892	-$48,302	-	$22,934	$7,380	-$11,384	-	$28,469	-$895	-$21,718	-	$19,423
Adverse Event Costs	$0	-$1	-	$0	$2	$0	-	$14	$2	$0	-	$14
Total QALYs	**1.09**	**-2.12**	**-**	**4.09**	**-0.63**	**-2.44**	**-**	**1.07**	**0.05**	**-1.72**	**-**	**1.90**
Relapses	0.53	-1.60	-	3.34	0.53	-0.80	-	1.78	0.43	-0.81	-	1.53
Life-Years	0.29	-0.52	-	1.06	-0.15	-0.63	-	0.27	0.00	-0.45	-	0.47

Results of Scenario Analyses

For the first scenario, we used alternative untreated ARR rates by EDSS state that were higher than the base case rates (Table E17). Projected relapses were higher compared to the base case, as were total projected costs, while projected life-years did not change and projected QALYs decreased. Because of the decrease in QALYs, and because the costs of supportive care and generic glatiramer acetate 20 mg also increased, the costs per additional QALY, costs per additional life-year, and costs per relapse avoided compared to supportive care all decreased. Changes in pairwise results with generic glatiramer acetate 20 mg were mixed. The decreases in cost per relapse avoided were particularly large. For example, the cost per relapse avoided for natalizumab compared to supportive care and glatiramer acetate 20 mg went from $206,934 and $230,210 to $180,124 and $197,021, respectively. The exception to a decrease was the costs per additional QALY and costs per additional life-year for Peginterferon β-1a, interferon β-1b 250 mcg (Betaseron), and interferon β-1b 250 mcg (Extavia) compared to generic glatiramer acetate 20 mg, which slightly increased.

In the second scenario, we used alternative untreated ARR rates by EDSS state that were lower than the base case rates (Table E18). This had the opposite effect, decreasing projected relapses and costs and increasing QALYs compared to the base case, which in turn increased the costs per additional QALY, costs per additional life-year, and costs per relapse avoided compared to supportive care. However, changes versus generic glatiramer acetate 20 mg were more variable, with some increases and some decreases depending on DMT.

In scenario three, we used results from the NMA including only studies with 12-week progression results (Table E19). This resulted in many quantitative changes in results. Of note, when compared to generic glatiramer acetate, interferon β-1b 30 mg, teriflunomide 7/14 mg, and interferon β-1a 22/44 mcg went from less effective and more costly to increased costs, QALYS, and life-years, while interferon β-1b 250 mcg (Betaseron/Extavia) went from more QALYS and life-years to fewer compared to generic glatiramer acetate.

In scenario four, we used results from the NMA including only studies with 24-week progression results (Table E20). Those DMTs without results did not have any trials with 24-week results. Results varied by DMT. Projected costs, relapses, life-years, QALYs, and costs per relapse avoided increased and costs per QALY and life-year decreased compared to the supportive care for three DMTs (interferon β-1a 30 mcg, interferon β-1b 250 mcg [Betaseron, Extavia]). Results were opposite for five DMTs (dimethyl fumarate, interferon β-1a 44 mcg, glatiramer acetate 20 mg [branded and generic], fingolimod, natalizumab, ocrelizumab, and alemtuzumab). The cost per QALY compared to generic glatiramer acetate for interferon β-1b 250 mcg (Extavia and Betaseron) decreased to $71,897 and $124,722, respectively.

In scenario five, we included indirect costs (Table E21). This increased the projected costs for all DMTs and supportive care without changing health outcomes from the base case. This resulted in non-influential decreases from base case for pairwise results.

In scenario six, we removed the stopping rule for EDSS 7 and modeled all patients to continue DMTs beyond EDSS 7 (Table E21). This resulted in higher projected costs, fewer relapses, more life-years, and more QALYs compared to base case. The costs per QALY and life-year increased and cost per relapse-avoided decreased compared to supportive care. Pairwise changes compared to generic glatiramer acetate were more varied, but changes in costs per QALY were all non-influential.

In scenario seven, used higher AE rates and related costs and utility decrements for all DMTs to demonstrate the effects of higher AE risk on the base case results (Table E22). This resulted in minimal increases in projected costs and insubstantial changes to pairwise results from base case.

In scenario eight, we changed the aggregate second-line regimen to be evenly distributed among all DMTs except the first-line DMT (Table E23). This increased the projected relapses and decreased the projected life-years and QALYS compared to the base case. Changes in projected costs were varied. Pairwise results compared to supportive care all increased with the exception of alemtuzumab. Compared to generic glatiramer acetate, pairwise results non-influentially increased for dimethyl fumarate, fingolimod, peginterferon β-1a, and natalizumab, and decreased for interferon β-1b (Extavia and Betaseron) and daclizumab.

In scenario nine, we used a discontinuation rate of 10% for the first 2 years and 3% thereafter for all DMTs (Table E24). Changes to projected and pairwise results were varied. Most changes in results were non-influential, though pairwise results for costs per additional QALY and life-year for interferon β-1a 44 mcg and teriflunomide 14 mg compared to generic glatiramer acetate 20 mg changed from more costly and worse health outcomes to more costly but better health outcomes.

In scenario ten, we removed four studies from the calculation for discontinuation rates because they did not have a constant follow-up time (median time was used in the base case) (Table E25).[45,83,86,97] This resulted in an increase in costs and a decrease in relapses, with minimal changes to projected life-years and QALYs. Pairwise results compared to supportive care, while pairwise results compared to generic glatiramer acetate were mixed but non-influential.

Table E17. Scenario 1 Results: Higher Untreated ARR by EDSS States Data Source[117] (Based on Trial Data)

Drug	Cost	Relapses	Life-Years	QALYs	Compared to Supportive Care: Cost per Additional QALY	Compared to Supportive Care: Cost per Additional Life-Year	Compared to Supportive Care: Cost per Relapse Avoided	Compared to GA 20 mg (Glatopa): Cost per Additional QALY	Compared to GA 20 mg (Glatopa): Cost per Additional Life-Year	Compared to GA 20 mg (Glatopa): Cost per Relapse Avoided
	Results for RRMS				Pairwise Results for RRMS					
Supportive Care	$374,662	36.77	21.82	4.04	-	-	-	-	-	-
Teriflunomide 7mg	$1,014,789	33.18	22.25	6.38	$273,194	$1,499,175	$178,403	DOMINATED	DOMINATED	DOMINATED
Interferon β-1a 30 mcg (Avonex)	$1,108,663	34.54	22.32	6.48	$300,770	$1,471,844	$329,559	DOMINATED	DOMINATED	DOMINATED
Interferon β-1a 22mcg (Rebif)	$1,153,573	32.59	22.28	6.54	$312,115	$1,671,657	$186,232	DOMINATED	DOMINATED	DOMINATED
Teriflunomide 14mg	$1,032,801	32.82	22.39	7.08	$216,222	$1,152,120	$166,759	DOMINATED	DOMINATED	DOMINATED
Interferon β-1a 44mcg (Rebif)	$1,114,996	32.35	22.40	7.12	$240,529	$1,274,357	$167,455	DOMINATED	DOMINATED	DOMINATED
Glatiramer acetate 20mg (Copaxone)	$1,196,371	31.92	22.41	7.14	$265,395	$1,399,559	$169,584	Cost-Increasing	Cost-Increasing	Cost-Increasing
Glatiramer acetate 20mg (Glatopa)	$898,354	31.92	22.41	7.14	$169,142	$891,967	$108,080	--	--	--
Dimethyl fumarate	$1,058,924	31.75	22.50	7.72	$185,925	$999,348	$136,378	$274,888	$1,645,387	$933,847
Fingolimod	$1,128,964	30.42	22.49	7.75	$203,218	$1,115,671	$118,754	$374,602	$2,591,797	$153,091
Interferon β-1b 250 mcg (Betaseron)	$1,088,252	32.65	22.58	7.77	$191,538	$942,413	$173,354	$301,707	$1,116,561	DOMINATED
Interferon β-1b 250 mcg (Extavia)	$992,194	32.65	22.58	7.77	$165,754	$815,553	$150,018	$149,091	$551,759	DOMINATED
Peginterferon β-1a	$1,257,286	32.52	22.63	8.01	$222,437	$1,092,819	$207,843	$411,710	$1,627,533	DOMINATED
Daclizumab	$1,172,805	30.94	22.66	8.44	$181,390	$948,987	$136,863	$210,472	$1,080,825	$278,276
Natalizumab	$1,294,815	27.41	22.78	9.15	$180,124	$959,656	$98,314	$197,021	$1,066,569	$87,832
Ocrelizumab	--	28.30	22.98	9.89	--	--	--	--	--	--
Alemtuzumab	$618,880	24.22	23.38	11.60	$32,330	$156,037	$19,461	DOMINANT	DOMINANT	DOMINANT

Table E18. Scenario 2 Results: Lower Untreated ARR by EDSS States Data Source[139]

Drug	Cost	Relapses	Life-Years	QALYs	Compared to Supportive Care: Cost per Additional QALY	Compared to Supportive Care: Cost per Additional Life-Year	Compared to Supportive Care: Cost per Relapse Avoided	Compared to GA 20 mg (Glatopa): Cost per Additional QALY	Compared to GA 20 mg (Glatopa): Cost per Additional Life-Year	Compared to GA 20 mg (Glatopa): Cost per Relapse Avoided
	Results for RRMS				Pairwise Results for RRMS					
Supportive Care	$326,179	7.61	21.82	6.39	-	-	-	-	-	-
Teriflunomide 7 mg	$973,759	6.98	22.25	8.37	$327,094	$1,516,630	$1,028,495	DOMINATED	DOMINATED	DOMINATED
Interferon β-1a 22 mcg (Rebif)	$1,113,403	6.85	22.28	8.48	$376,549	$1,689,497	$1,030,712	DOMINATED	DOMINATED	DOMINATED
Interferon β-1a 30 mcg (Avonex)	$1,065,628	7.45	22.32	8.57	$340,095	$1,482,768	$4,424,176	DOMINATED	DOMINATED	DOMINATED
Teriflunomide 14 mg	$993,018	6.99	22.39	9.01	$254,513	$1,167,351	$1,078,607	DOMINATED	DOMINATED	DOMINATED
Glatiramer acetate 20 mg (Copaxone)	$1,157,659	6.76	22.41	9.01	$317,293	$1,416,200	$977,866	Cost-Increasing	Cost-Increasing	Cost-Increasing
Glatiramer acetate 20 mg (Glatopa™)	$859,642	6.76	22.41	9.01	$203,570	$908,609	$627,381	--	--	--
Interferon β-1a 44 mcg (Rebif)	$1,075,840	6.87	22.40	9.02	$285,709	$1,290,410	$1,010,551	$65,186,736	DOMINATED	DOMINATED
Fingolimod	$1,093,195	6.38	22.49	9.49	$247,941	$1,134,476	$623,725	$493,769	$2,624,874	$615,532
Dimethyl fumarate	$1,021,348	6.77	22.50	9.54	$220,714	$1,015,277	$822,645	$305,632	$1,657,026	DOMINATED
Interferon β-1b 250 mcg (Betaseron)	$1,049,032	7.12	22.58	9.67	$220,745	$954,646	$1,469,427	$289,558	$1,113,570	DOMINATED
Interferon β-1b 250 mcg (Extavia)	$952,973	7.12	22.58	9.67	$191,411	$827,785	$1,274,158	$142,694	$548,768	DOMINATED
Peginterferon β-1a	$1,218,487	7.12	22.63	9.89	$255,198	$1,104,810	$1,823,974	$409,647	$1,627,141	DOMINATED
Daclizumab	$1,136,892	6.67	22.66	10.18	$213,974	$963,933	$856,449	$237,311	$1,091,852	$2,879,108
Natalizumab	$1,263,948	5.77	22.78	10.65	$220,513	$978,028	$507,972	$247,718	$1,087,674	$406,010
Ocrelizumab	--	6.18	22.98	11.42	--	--	--	--	--	--
Alemtuzumab	$592,704	5.37	23.38	12.86	$41,189	$170,289	$118,658	DOMINANT	DOMINANT	DOMINANT

Table E19. Scenario 3 Results: NMA Inputs Using Only 12-week Disability Progression Results

					Compared to Supportive Care			Compared to GA 20 mg (Glatopa)		
Drug	Cost	Relapses	Life-Years	QALYs	Cost per Additional QALY	Cost per Additional Life-Year	Cost per Relapse Avoided	Cost per Additional QALY	Cost per Additional Life-Year	Cost per Relapse Avoided
	Results for RRMS				Pairwise Results for RRMS					
Interferon β-1b 250 mcg (Betaseron)	$967,025	14.16	22.09	7.12	$431,403	$2,296,749	$244,135	DOMINATED	DOMINATED	$3,258,484
Interferon β-1b 250 mcg (Extavia)	$885,076	14.16	22.09	7.12	$374,919	$1,996,036	$212,171	DOMINATED	DOMINATED	$1,208,315
Glatiramer acetate 20 mg (Copaxone)	$1,111,970	14.20	22.16	7.44	$434,011	$2,225,942	$305,433	Cost-Increasing	Cost-Increasing	Cost-Increasing
Glatiramer acetate 20 mg (Glatopa)	$836,777	14.20	22.16	7.44	$279,069	$1,431,282	$196,394	--	--	--
Teriflunomide 7 mg	$986,216	15.19	22.24	7.72	$314,214	$1,540,494	$419,266	$539,617	$2,062,462	DOMINATED
Interferon β-1a 30 mcg(Avonex)	$1,075,040	15.88	22.29	7.83	$339,438	$1,541,285	$870,110	$617,173	$1,834,608	DOMINATED
Interferon β-1a 22 mcg (Rebif)	$1,137,485	15.03	22.33	8.06	$333,238	$1,562,068	$471,363	$490,013	$1,839,058	DOMINATED
Teriflunomide 14 mg	$1,006,818	15.11	22.39	8.42	$241,854	$1,161,855	$412,758	$174,156	$750,208	DOMINATED
Fingolimod	$1,086,022	13.80	22.40	8.54	$259,230	$1,285,498	$254,579	$227,121	$1,068,974	$619,669
Interferon β-1a 44 mcg (Rebif)	$1,101,465	15.02	22.46	8.69	$251,952	$1,181,108	$445,395	$213,165	$889,848	DOMINATED
Dimethyl fumarate	$1,028,868	14.55	22.47	8.82	$218,015	$1,060,250	$316,668	$139,350	$635,299	DOMINATED
Peginterferon β-1a	$1,230,427	15.11	22.62	9.28	$246,275	$1,109,308	$550,220	$214,532	$864,454	DOMINATED
Daclizumab	$1,134,056	14.16	22.57	9.28	$219,316	$1,049,157	$309,257	$161,619	$725,989	$7,392,930
Natalizumab	$1,273,499	12.60	22.77	10.15	$208,245	$980,428	$225,891	$161,677	$722,226	$272,309
Ocrelizumab	--	13.24	23.02	11.10	--	--	--	--	--	--
Alemtuzumab	$594,763	11.63	23.76	13.85	$31,003	$130,462	$49,797	DOMINANT	DOMINANT	DOMINANT

Table E20. Scenario 4 Results: NMA Inputs Using Only 24-week Disability Progression Results

Drug	Cost	Relapses	Life-Years	QALYs	Compared to Supportive Care: Cost per Additional QALY	Compared to Supportive Care: Cost per Additional Life-Year	Compared to Supportive Care: Cost per Relapse Avoided	Compared to GA 20 mg (Glatopa): Cost per Additional QALY	Compared to GA 20 mg (Glatopa): Cost per Additional Life-Year	Compared to GA 20 mg (Glatopa): Cost per Relapse Avoided
	Results for RRMS				Pairwise Results for RRMS					
Interferon β-1a 30 mcg (Avonex)	$1,081,703	15.96	22.32	7.95	$324,541	$1,464,335	$970,294	DOMINATED	DOMINATED	DOMINATED
Interferon β-1a 44 mcg (Rebif)	$1,075,823	14.73	22.33	8.15	$296,487	$1,431,923	$368,361	DOMINATED	DOMINATED	DOMINATED
Glatiramer acetate 20 mg (Copaxone)	$1,168,721	14.65	22.40	8.39	$304,158	$1,434,721	$399,703	Cost-Increasing	Cost-Increasing	Cost-Increasing
Glatiramer acetate 20 mg (Glatopa)	$870,704	14.65	22.40	8.39	$194,631	$918,081	$255,771	--	--	--
Fingolimod	$1,092,575	13.83	22.43	8.67	$250,653	$1,234,562	$260,096	$800,875	$6,967,556	$271,035
Daclizumab	$1,139,791	14.20	22.60	9.41	$213,671	$1,017,813	$316,698	$264,617	$1,294,590	$596,207
Interferon β-1b 250 mcg (Betaseron)	$1,118,425	15.91	22.91	10.38	$165,133	$710,887	$958,993	$124,722	$479,530	DOMINATED
Interferon β-1b 250 mcg (Extavia)	$1,013,505	15.91	22.91	10.38	$142,843	$614,932	$829,549	$71,897	$276,430	DOMINATED
Ocrelizumab	--	13.07	22.90	10.62	--	--	--	--	--	--
Alemtuzumab	$600,842	11.33	23.31	12.17	$39,921	$174,618	$48,175	DOMINANT	DOMINANT	DOMINANT

Table E21. Scenario 5 Results: Inclusion of Indirect Costs

					Compared to Supportive Care			Compared to GA 20 mg (Glatopa)		
Drug	Cost	Relapses	Life-Years	QALYs	Cost per Additional QALY	Cost per Additional Life-Year	Cost per Relapse Avoided	Cost per Additional QALY	Cost per Additional Life-Year	Cost per Relapse Avoided
	Results for RRMS				Pairwise Results for RRMS					
Supportive Care	$1,021,192	16.72	21.82	5.67	-	-	-	-	-	-
Teriflunomide 7 mg	$1,603,489	15.21	22.25	7.76	$279,010	$1,363,738	$383,908	DOMINATED	DOMINATED	DOMINATED
Interferon β-1a 22mcg (Rebif)	$1,739,967	14.94	22.28	7.88	$325,250	$1,542,596	$402,514	DOMINATED	DOMINATED	DOMINATED
Interferon β-1a 30 mcg (Avonex)	$1,690,608	15.94	22.32	7.92	$297,249	$1,342,337	$854,659	DOMINATED	DOMINATED	DOMINATED
Teriflunomide 1 4mg	$1,600,579	15.11	22.39	8.41	$211,110	$1,014,260	$359,160	DOMINATED	DOMINATED	DOMINATED
Interferon β-1a 44 mcg (Rebif)	$1,683,674	14.88	22.40	8.43	$240,261	$1,140,349	$359,772	DOMINATED	DOMINATED	DOMINATED
Glatiramer acetate 20 mg (Copaxone)	$1,766,849	14.68	22.41	8.43	$270,123	$1,270,025	$364,901	Cost-Increasing	Cost-Increasing	Cost-Increasing
Glatiramer acetate 20mg (Glatopa)	$1,468,832	14.68	22.41	8.43	$162,163	$762,433	$219,061	--	--	--
Fingolimod	$1,684,730	13.96	22.49	8.94	$202,543	$981,425	$240,121	$418,730	$2,426,456	$299,900
Dimethyl fumarate	$1,609,778	14.63	22.50	8.97	$178,055	$859,616	$281,203	$258,517	$1,444,295	$2,838,811
Interferon β-1b 250 mcg (Betaseron)	$1,636,843	15.16	22.58	9.07	$180,760	$813,068	$393,215	$260,298	$987,866	DOMINATED
Interferon β-1b 250 mcg (Extavia)	$1,540,784	15.16	22.58	9.07	$152,557	$686,207	$331,863	$111,475	$423,064	DOMINATED
Peginterferon β-1a	$1,798,392	15.12	22.63	9.30	$213,897	$962,289	$485,716	$377,468	$1,494,348	DOMINATED
Daclizumab	$1,703,529	14.32	22.66	9.64	$171,953	$811,294	$283,866	$194,331	$924,269	$651,432
Natalizumab	$1,815,909	12.62	22.78	10.17	$176,350	$828,835	$193,578	$198,780	$933,714	$168,323
Alemtuzumab	$1,069,277	11.40	23.38	12.46	$7,081	$30,723	$9,025	DOMINANT	DOMINANT	DOMINANT
	Results for PPMS				Pairwise Results for PPMS					
Supportive Care	$860,057	--	15.61	2.75	--	--	--	--	--	--

Table E22. Scenario 6 Results: Continuation of DMT Use Beyond EDSS 7

					Compared to Supportive Care			Compared to GA 20 mg (Glatopa)		
Drug	Cost	Relapses	Life-Years	QALYs	Cost per Additional QALY	Cost per Additional Life-Year	Cost per Relapse Avoided	Cost per Additional QALY	Cost per Additional Life-Year	Cost per Relapse Avoided
	Results for RRMS				Pairwise Results for RRMS					
Teriflunomide 7 mg	$1,148,125	14.67	22.44	7.95	$349,584	$1,791,239	$370,650	DOMINATED	DOMINATED	DOMINATED
Interferon β-1a 22 mcg (Rebif)	$1,413,409	14.01	22.50	8.13	$430,515	$2,129,657	$378,145	DOMINATED	DOMINATED	DOMINATED
Interferon β-1a 30 mcg (Avonex)	$1,347,316	15.24	22.53	8.17	$398,496	$1,874,928	$626,898	DOMINATED	DOMINATED	DOMINATED
Teriflunomide 14 mg	$1,133,742	14.63	22.57	8.61	$267,021	$1,382,178	$358,482	DOMINATED	DOMINATED	DOMINATED
Interferon β-1a 44 mcg (Rebif)	$1,272,902	14.21	22.59	8.66	$308,609	$1,558,100	$353,057	DOMINATED	DOMINATED	DOMINATED
Glatiramer acetate 20 mg (Copaxone)	$1,440,471	13.70	22.62	8.71	$358,122	$1,766,262	$349,245	Cost-Increasing	Cost-Increasing	Cost-Increasing
Glatiramer acetate 20 mg (Glatopa)	$1,060,251	13.70	22.62	8.71	$233,857	$1,153,389	$228,061	--	--	--
Dimethyl fumarate	$1,133,675	14.19	22.66	9.16	$224,872	$1,184,909	$297,748	$163,609	$1,615,035	DOMINATED
Fingolimod	$1,269,660	13.20	22.68	9.19	$261,104	$1,348,819	$254,531	$433,809	$3,203,662	$421,820
Interferon β-1b 250 mcg (Betaseron)	$1,277,117	14.26	22.78	9.38	$250,205	$1,181,110	$361,982	$325,215	$1,282,843	DOMINATED
Interferon β-1b 250 mcg (Extavia)	$1,157,455	14.26	22.78	9.38	$218,095	$1,029,533	$315,527	$145,769	$575,001	DOMINATED
Peginterferon β-1a	$1,459,999	14.30	22.83	9.60	$282,734	$1,341,171	$439,287	$451,735	$1,892,784	DOMINATED
Daclizumab	$1,267,389	13.77	22.81	9.85	$219,721	$1,124,964	$301,098	$181,766	$1,036,705	DOMINATED
Natalizumab	$1,468,732	11.54	22.97	10.49	$232,429	$1,157,319	$212,291	$229,969	$1,164,269	$189,354
Ocrelizumab	--	12.39	23.15	11.22	--	--	--	--	--	--
Alemtuzumab	$646,583	10.24	23.57	12.81	$42,154	$191,343	$45,768	DOMINANT	DOMINANT	DOMINANT
	Results for PPMS				Pairwise Results for PPMS					
Ocrelizumab	--	--	17.16	3.45	--	--	--	--	--	--

Table E23. Scenario 7 Results: Higher AE Rates, Utility Decrements, and Associated Costs

					Compared to Supportive Care			Compared to GA 20 mg (Glatopa)		
Drug	Cost	Relapses	Life-Years	QALYs	Cost per Additional QALY	Cost per Additional Life-Year	Cost per Relapse Avoided	Cost per Additional QALY	Cost per Additional Life-Year	Cost per Relapse Avoided
	Results for RRMS				Pairwise Results for RRMS					
Teriflunomide 7 mg	$986,739	15.21	22.25	7.73	$313,552	$1,512,038	$425,656	DOMINATED	DOMINATED	DOMINATED
Interferon β-1a 22 mcg (Rebif)	$1,126,030	14.94	22.28	7.86	$357,702	$1,684,529	$439,549	DOMINATED	DOMINATED	DOMINATED
Interferon β-1a 30 mcg (Avonex)	$1,079,117	15.94	22.32	7.89	$331,570	$1,479,855	$942,216	DOMINATED	DOMINATED	DOMINATED
Teriflunomide 14 mg	$1,005,650	15.11	22.39	8.38	$244,634	$1,163,306	$411,939	DOMINATED	DOMINATED	DOMINATED
Glatiramer acetate 20 mg (Copaxone)	$1,169,865	14.68	22.41	8.40	$303,104	$1,411,541	$405,561	Cost-Increasing	Cost-Increasing	Cost-Increasing
Glatiramer acetate 20 mg (Glatopa)	$871,847	14.68	22.41	8.40	$194,108	$903,949	$259,721	--	--	--
Interferon β-1a 44 mcg (Rebif)	$1,088,216	14.88	22.40	8.41	$272,561	$1,285,994	$405,723	$31,667,742	DOMINATED	DOMINATED
Fingolimod	$1,104,566	13.96	22.49	8.92	$234,977	$1,129,195	$276,275	$452,027	$2,615,496	$323,265
Dimethyl fumarate	$1,033,333	14.63	22.50	8.95	$211,201	$1,010,960	$330,712	$297,218	$1,654,766	$3,252,500
Interferon β-1b 250 mcg (Betaseron)	$1,061,404	15.16	22.58	9.05	$213,112	$951,252	$460,044	$293,591	$1,114,548	DOMINATED
Interferon β-1b 250 mcg (Extavia)	$965,345	15.16	22.58	9.05	$184,691	$824,391	$398,691	$144,812	$549,746	DOMINATED
Peginterferon β-1a	$1,230,749	15.12	22.63	9.28	$246,616	$1,101,492	$555,979	$411,041	$1,627,394	DOMINATED
Daclizumab	$1,148,339	14.32	22.66	9.61	$204,828	$959,778	$335,819	$229,116	$1,088,864	$767,440
Natalizumab	$1,273,799	12.62	22.78	10.15	$208,168	$972,718	$227,182	$230,182	$1,081,337	$194,935
Ocrelizumab	--	13.19	22.98	10.91	--	--	--	--	--	--
Alemtuzumab	$601,152	11.40	23.38	12.43	$38,436	$166,140	$48,805	DOMINANT	DOMINANT	DOMINANT
	Results for PPMS				Pairwise Results for PPMS					
OCR	--	--	16.11	3.31	--	--	--	--	--	--

Table E24. Scenario 8 Results: Inclusion of all DMTs, Equally Distributed, in the Aggregate Second-line Calculation, Except for the DMT Being Modelled as First-line

					Compared to Supportive Care			Compared to GA 20 mg (Glatopa)		
Drug	Cost	Relapses	Life-Years	QALYs	Cost per Additional QALY	Cost per Additional Life-Year	Cost per Relapse Avoided	Cost per Additional QALY	Cost per Additional Life-Year	Cost per Relapse Avoided
	Results for RRMS				Pairwise Results for RRMS					
Teriflunomide 7 mg	$983,797	15.54	22.15	7.30	$392,961	$1,937,922	$540,967	DOMINATED	DOMINATED	DOMINATED
Interferon β-1a 22 mcg (Rebif)	$1,122,729	15.19	22.22	7.57	$409,881	$1,962,538	$508,366	DOMINATED	DOMINATED	DOMINATED
Interferon β-1a 30 mcg (Avonex)	$1,077,134	16.16	22.25	7.62	$376,332	$1,705,165	$1,313,403	DOMINATED	DOMINATED	DOMINATED
Teriflunomide 14 mg	$1,002,397	15.47	22.28	7.90	$296,318	$1,431,572	$526,889	DOMINATED	DOMINATED	DOMINATED
Interferon β-1a 44 mcg (Rebif)	$1,084,100	15.21	22.31	8.00	$318,330	$1,522,029	$489,462	DOMINATED	DOMINATED	DOMINATED
Glatiramer acetate 20 mg (Copaxone)	$1,166,489	14.94	22.34	8.12	$336,922	$1,597,371	$462,506	Cost-Increasing	Cost-Increasing	Cost-Increasing
Glatiramer acetate 20 mg (Glatopa)	$874,086	14.94	22.34	8.12	$217,561	$1,031,472	$298,654	--	--	--
Dimethyl fumarate	$1,040,837	15.13	22.37	8.34	$261,628	$1,269,626	$439,435	$741,941	$4,845,122	DOMINATED
Fingolimod	$1,108,500	14.31	22.38	8.41	$279,717	$1,377,237	$318,351	$798,166	$5,790,294	$374,509
Interferon β-1b 250 mcg (Betaseron)	$1,060,933	15.40	22.51	8.77	$231,849	$1,047,698	$545,385	$285,289	$1,096,919	DOMINATED
Interferon β-1b 250 mcg (Extavia)	$966,398	15.40	22.51	8.77	$201,399	$910,101	$473,758	$140,947	$541,933	DOMINATED
Peginterferon β-1a	$1,227,180	15.39	22.55	8.97	$268,536	$1,213,666	$665,287	$415,470	$1,654,883	DOMINATED
Daclizumab	$1,158,813	14.78	22.55	9.14	$235,675	$1,117,044	$420,302	$279,185	$1,322,401	$1,769,239
Natalizumab	$1,279,611	12.88	22.69	9.82	$226,005	$1,072,278	$244,209	$238,152	$1,131,086	$197,007
Ocrelizumab	--	13.55	22.88	10.54	--	--	--	--	--	--
Alemtuzumab	$581,941	11.62	23.34	12.27	$36,470	$158,554	$47,226	DOMINANT	DOMINANT	DOMINANT

Table E25. Scenario 9 Results: Constant Discontinuation Rate for all DMTs of 10% for the First 2 Years and 3% Annually Thereafter

					Compared to Supportive Care			Compared to GA 20 mg (Glatopa)		
Drug	Cost	Relapses	Life-Years	QALYs	Cost per Additional QALY	Cost per Additional Life-Year	Cost per Relapse Avoided	Cost per Additional QALY	Cost per Additional Life-Year	Cost per Relapse Avoided
	Results for RRMS				Pairwise Results for RRMS					
Teriflunomide 7 mg	$1,090,465	15.26	22.19	7.46	$418,294	$2,001,729	$511,396	DOMINATED	DOMINATED	DOMINATED
Interferon β-1a 22 mcg (Rebif)	$1,147,728	14.94	22.28	7.84	$370,986	$1,754,673	$451,728	DOMINATED	DOMINATED	DOMINATED
Interferon β-1a 30 mcg (Avonex)	$1,091,763	16.03	22.31	7.89	$337,408	$1,514,555	$1,080,899	DOMINATED	DOMINATED	DOMINATED
Glatiramer acetate 20 mg (Copaxone)	$1,187,464	14.66	22.41	8.42	$307,188	$1,434,184	$409,339	Cost-Increasing	Cost-Increasing	Cost-Increasing
Glatiramer acetate 20 mg (Glatopa)	$874,107	14.66	22.41	8.42	$193,452	$903,181	$257,782	--	--	--
Interferon β-1a 44 mcg (Rebif)	$1,186,589	14.78	22.43	8.48	$300,531	$1,386,366	$434,493	$5,376,476	$15,842,999	DOMINATED
Teriflunomide 14mg	$1,153,323	15.07	22.45	8.55	$282,313	$1,289,521	$491,079	$2,292,017	$7,028,422	DOMINATED
Interferon β-1b 250 mcg (Betaseron)	$1,059,007	15.17	22.57	9.05	$212,448	$949,818	$461,176	$296,321	$1,115,916	DOMINATED
Interferon β-1b 250 mcg (Extavia)	$963,378	15.17	22.57	9.05	$184,148	$823,293	$399,743	$143,065	$538,770	DOMINATED
Fingolimod	$1,214,527	13.42	22.55	9.11	$253,856	$1,199,465	$264,285	$496,654	$2,466,074	$275,153
Peginterferon β-1a	$1,248,154	15.13	22.64	9.32	$248,404	$1,102,572	$567,638	$417,318	$1,608,593	DOMINATED
Dimethyl fumarate	$1,254,455	14.17	22.67	9.53	$236,287	$1,070,459	$358,240	$342,587	$1,445,661	$789,233
Natalizumab	$1,300,099	12.34	22.81	10.24	$209,869	$970,748	$218,831	$234,800	$1,070,992	$184,039
Daclizumab	$1,331,572	13.80	22.85	10.28	$214,661	$957,151	$338,437	$246,096	$1,028,775	$532,580
Ocrelizumab	--	12.89	23.04	11.08	--	--	--	--	--	--
Alemtuzumab	$678,040	12.26	23.15	11.57	$57,063	$252,570	$75,443	DOMINANT	DOMINANT	DOMINANT
	Results for PPMS				Pairwise Results for PPMS					
OCR	--	--	16.09	3.32	--	--	--	--	--	--

Table E26. Scenario 10 Results: Removed Studies with Non-constant Follow-up Times from Discontinuation Calculation

					Compared to Supportive Care			Compared to GA 20 mg (Glatopa)		
Drug	Cost	Relapses	Life-Years	QALYs	Cost per Additional QALY	Cost per Additional Life-Year	Cost per Relapse Avoided	Cost per Additional QALY	Cost per Additional Life-Year	Cost per Relapse Avoided
	Results for RRMS				Pairwise Results for RRMS					
Teriflunomide 7 mg	$987,450	15.21	22.25	7.76	$309,692	$1,513,702	$426,125	DOMINATED	DOMINATED	DOMINATED
Interferon β-1a 22 mcg (Rebif)	$1,167,333	14.91	22.28	7.83	$381,954	$1,797,251	$455,808	DOMINATED	DOMINATED	DOMINATED
Interferon β-1a 30 mcg (Avonex)	$1,079,600	15.94	22.32	7.92	$327,916	$1,480,824	$942,833	DOMINATED	DOMINATED	DOMINATED
Interferon β-1a 44 mcg (Rebif)	$1,088,890	14.88	22.40	8.43	$271,192	$1,287,156	$406,089	DOMINATED	DOMINATED	DOMINATED
Glatiramer acetate 20 mg (Copaxone)	$1,170,362	14.68	22.41	8.43	$300,402	$1,412,389	$405,805	Cost-Increasing	Cost-Increasing	Cost-Increasing
Glatiramer acetate 20 mg (Glatopa)	$872,345	14.68	22.41	8.43	$192,442	$904,797	$259,964	--	--	--
Teriflunomide 14 mg	$1,075,083	15.08	22.42	8.49	$260,493	$1,224,858	$447,276	$3,547,542	$16,751,738	DOMINATED
Fingolimod	$1,105,475	13.96	22.49	8.94	$233,316	$1,130,539	$276,604	$452,149	$2,620,113	$323,835
Interferon β-1b 250 mcg (Betaseron)	$1,061,881	15.16	22.58	9.07	$211,621	$951,882	$460,348	$293,646	$1,114,425	DOMINATED
Interferon β-1b 250 mcg (Extavia)	$965,822	15.16	22.58	9.07	$183,418	$825,021	$398,996	$144,823	$549,623	DOMINATED
Peginterferon β-1a	$1,231,275	15.12	22.63	9.30	$244,984	$1,102,143	$556,308	$411,107	$1,627,523	DOMINATED
Dimethyl fumarate	$1,231,598	14.24	22.65	9.50	$232,322	$1,067,411	$358,944	$334,964	$1,453,758	$821,380
Natalizumab	$1,274,531	12.62	22.78	10.17	$207,126	$973,482	$227,360	$230,342	$1,081,968	$195,049
Daclizumab	$1,297,779	13.94	22.81	10.20	$211,256	$960,935	$343,594	$240,630	$1,041,634	$574,276
Alemtuzumab	$601,053	11.40	23.38	12.46	$38,277	$166,077	$48,787	DOMINANT	DOMINANT	DOMINANT

Appendix F. Patient Survey Questions

1. What is your current age? (numerical entry)

2. What is your gender?

    a) Female
    b) Male

3. Ethnicity (check ONLY one with which you MOST CLOSELY identify):

    a) Hispanic or Latino/a
    b) Not Hispanic or Latino
    c) Unknown
    d) Not Reported

4. Race (check those with which you identify):

    a) American Indian
    b) Asian
    c) Black
    d) Native Hawaiian/Pacific Islander
    e) Not Reported
    f) Unknown
    g) White

5. Do you live in the United States?

    a) Yes
    b) No

6. Do you **currently** have health insurance?

    a) Yes
    b) No

7. If Yes – What type(s) of health insurance do you have? (Please check all that apply)

    a) Any Private, Commercial or Pre-paid health plan (such as Aetna, BC/BS, Prudential, Oxford, COBRA, Kaiser, any other HMO or PPO)
    b) Medicare. Medicare is the federal health insurance program for people who are 65 or older, certain younger people with disabilities, and people with End-Stage Renal Disease

c) Medicaid. Medicaid is a health insurance program for low-income individuals and those with disabilities. Medicaid is a joint program, funded primarily by the federal government and run at the state level, where coverage (and the name of the coverage) may vary. Elderly low-income people are eligible for both Medicare and Medicaid.
d) Tri-Care (formerly CHAMPUS, CHAMP-VA)
e) Department of Veterans Affairs OR Canadian Forces
f) Indian Health Service OR Non-Insured Health Benefits for First Nations, Inuit
g) Universal Health Care - Canadian
h) Supplemental Insurance (such as Medigap, Value Benefit Plans, AARP, etc.)
i) Other Primary Insurance (please specify)

8. Has your doctor diagnosed you with multiple sclerosis (MS)?

a) Yes
b) No
c) Unsure

9. If Q8 is yes – What type of MS do you have?

a) Clinically Isolated Syndrome (CIS)
b) Relapsing-remitting (sometimes referred to as relapsing) MS
c) Secondary progressive MS
d) Primary progressive MS
e) Progressive relapsing MS
f) I'm not sure

10. If Q8 is yes – In what year were you diagnosed with MS? (date entry)

11. If Q8 is yes – Are you currently taking one or more of the following drugs for your MS?

a) Yes
b) No → go to question 13

12. If yes, please select the drug(s) you are taking:

a) Aubagio® (teriflunomide)
b) Avonex® (Interferon beta-1a)
c) Betaseron® (interferon beta-1b)
d) Cellcept (mycophenolate mofetil)
e) Copaxone® (glatiramer acetate)
f) Extavia® (interferon beta-1b)
g) Gilenya® (fingolimod)
h) Glatopa (glatiramer acetate)

i) Imuran (azathioprine)
j) Lemtrada™ (alemtuzumab)
k) Novantrone® (mitoxantrone)
l) Ocrevus® (ocrelizumab)
m) Plegridy® (peginterferon beta-1a)
n) Rebif® (interferon beta-1a)
o) Rituxan® (rituximab)
p) Steroids
q) Tecfidera® (dimethyl fumarate)
r) Tysabri® (natalizumab)
s) Zinbryta™ (daclizumab)
t) Clinical trial drug (please specify)

13. Are you currently on the MS drug that you prefer to be on?

a) Yes
b) No, the drug that I'm currently on is not my top choice
c) No, I'm not on a MS drug at this time but would prefer to be on one
d) Not applicable—I'm not on a MS drug at this time and do not wish to be on one

14. If (b) or (c) above – What factor(s) are preventing you from being on your preferred drug? (check all that apply)

a) Out of pocket costs
b) Insurance restrictions/Risk of side effects
c) Doctor or health care provider won't prescribe it
d) Inconvenience/access issues (time, transportation, drug storage, etc.)
e) My preferred drug is not approved for my form of MS
f) Other (please specify)

15. If Q8=Yes and Q11=Yes – How important were the following factors in selection of the drug you are currently taking? (Not Important, Slightly Important, Moderately Important, Important, Very Important)

a) Restrictions that my insurance plan puts on access to certain drugs
b) Costs that I pay every month for the drug (co-pay, coinsurance, etc.)
c) Doctor or healthcare professional recommendation
d) The way I take the drug (for example: by mouth, injected by myself, or infused in a healthcare setting)
e) How often I need to take the drug (for example: daily injectable, weekly injectable, infused once or twice per year)

f) Risk of progressive multifocal leukoencephalopathy or PML
g) Risk of serious infection other than PML
h) Other long term risks such as liver problems, cancer, other infections, thyroid problems, kidney problems, bleeding problems, change in vision, breathing problems
i) Risks during pregnancy to unborn child (only answer if you are a woman of childbearing age)
j) Risk of side effects such as flu-like symptoms, skin reactions from injections, slow heartbeat, upset stomach, hair loss, infusion reactions
k) The need for frequent or prolonged monitoring and/or blood tests
l) The drug's effectiveness in preventing relapses and reducing new MRI lesion
m) The drug's effectiveness in delaying disability
n) The drug's effectiveness in allowing me to continue working and/or performing normal daily activities
o) Other (please describe)

16. Since you have been taking your MS drug have you: (Yes, No, Not sure, N/A)

a) Had fewer relapses (episodes of new or returning symptoms)
b) Had less or no progression (worsening) of MS symptoms
c) Missed less time from work or other daily activities
d) Been hospitalized less frequently

17. Do you feel that you had input into the decision making for your MS drug?

a) Yes, my doctor and I discussed the drug and made the decision together
b) Yes, my doctor gave me the drug information and told me to make the decision
c) No, my doctor decided and prescribed the drug

18. Did you consult with others in making your drug decision?

a) Care Partner
b) Spouse
c) Parent
d) Friend
e) Other (please specify)

19. If 18=Yes – What was their role in helping you make the decision? (please describe)

20. Have you had trouble starting the prescribed MS drug for any of the following reasons?

a) My health plan does not cover the drug
b) I must try another drug before my insurance company will approve the drug that my doctor prescribed

c) I am unaware of or do not qualify for patient assistance programs, so I cannot afford my drug
d) I do not have trouble getting the drug prescribed by my doctor

21. What, if anything, sometimes prevents you from taking your MS drug as it is prescribed? (check all that apply)

a) Nothing, I almost always take my MS drug as prescribed
b) Changes in my health plan that interferes with regular drug access
c) Changes in my specialty pharmacy that interferes with regular shipments
d) Difficulties completing manufacturer's patient assistance program forms and/or enrolling in the program
e) Side effects of the drug
f) I don't like to take it
g) I forget to take it
h) Lack of transportation to a drug infusion location
i) The amount I pay for the drug
j) Other (please specify)

22. If Q11=No – If you are <u>not</u> taking a drug for your MS, please select all that apply:

a) I am not a candidate for these drugs
b) I do not want to use any of these drugs
c) I do not have health insurance
d) I have health insurance but cannot afford the costs that apply to these drugs
e) I stopped due to experiencing bad side effects/adverse events
f) I am planning or trying to become pregnant or are currently pregnant
g) Other (please specify)

23. If Q8=Yes – Are you currently working?

a) Yes, full-time
b) Yes, part-time
c) No

24. If Q23=a or b – How many days of work did you miss because of your last relapse?

a) 1-5 days
b) 6-10 days
c) 11-15 days
d) 16-20 days
e) 21 days or more

f) I did not miss work because of my last relapse

25. If Q8=Yes, and Q24=B-F – How many days of work did someone who helps you when you are ill miss because of your last relapse?

a) 1-5 days
b) 6-10 days
c) 11-15 days
d) 16-20 days
e) 21 days or more
f) I do not have someone who helps care for me when I am ill
g) The person who helps me did not miss work because of my last relapse (or is paid to help me)

Appendix G. Public Comments

This section includes summaries of the public comments prepared for the CTAF Public Meeting on February 16, 2016 in Oakland, CA. These summaries were prepared by those who delivered the public comments at the meeting and are presented in order of delivery. Three speakers did not submit summaries of their public comments.

A video recording of all comments can be found on our site here, at minute 1:24:10. Conflict of interest disclosures are included at the bottom of each statement for each speaker who is not employed by a pharmaceutical manufacturer.

Mark Rametta, DO, FACOI, FACP, Bayer
Medical Director, US Medical Affairs, Neurology

We commend ICER for conducting this evaluation. However, there is one particular limitation that we would like to address which compromises the ability to use this report to influence treatment choice.

From the publication of the initial scoping document, Bayer has requested that ICER include CIS as part of the model structure rather than beginning with clinically-definite MS. In the report, ICER notes that while "some of the early trials in CIS provide provocative data," "…many patients with CIS never go on to MS, so the results are not directly applicable to the role of DMTs in RRMS." This is somewhat misleading as the FDA has acknowledged the strength of evidence by expanding the indication of several DMTs to include treatment for CIS. If ICER feels comfortable including products under review by the FDA, it is unclear why they refer to the evidence for early treatment of MS as "early" and "suggestive".

The BENEFIT trial was designed to assess the impact of early treatment on ARR, EDSS, cognitive outcomes, resource utilization, and employment at 2, 3, 5, 8, and 11 years after initial randomization. The results indicate that early treatment with Betaseron had a long-lasting, beneficial effect on disease activity in study participants. Thus, cost-effectiveness models focused solely on clinically-definite MS will not accurately reflect the full value of DMTs. By excluding CIS and the outcomes of the BENEFIT trial from the cost-effectiveness analysis, we believe that ICER has seriously underrepresented the full value of some of the treatments evaluated.

Kathleen Hawker, MD, EMD Serono
Vice President, Neurology and Immunology, US Medical Affairs
EMD Serono is committed to credible, evaluable, and replicable assessments to inform clinical decision-making at the point of care. We appreciate ICER's contribution to this vital dialogue, and

we are thankful to the many people who have bravely shared their journeys with MS throughout this assessment process.

We are committed to patient access to treatment, and support an open access policy for all DMTs, enabling the delivery of the right treatment, to the right patient, at the right time. MS is an extremely heterogenic disease. Each patient is unique, and there is no 'one size fits all' therapy for patients with MS. The availability of a large therapeutic arsenal is critical for enabling patient-centered MS care, as DMTs of varying clinical profiles can be customized for distinct clinical scenarios and specific patient preferences. We believe that patients should have access to quality care through broad formulary coverage of all DMTs, as well as comprehensive patient assistance programs.

While patients have many concerns related to their MS, a key concern is access to effective treatments. As highlighted by the MS Coalition, "patients want their provider to be able to choose the medication that is best for them without restriction, but feel that their choice of therapy is driven by insurance coverage". We believe that the results from this report should not be used by payers to jeopardize patient access to treatment. All stakeholders need to listen closely to the patient's voice, and work in concert to optimize patient outcomes.

Peter S Chin, MD, MSHS, Genentech
Group Medical Director, Neuroscience

Genentech is committed to advancing research and innovating therapies in MS. We support well-conducted frameworks that enable meaningful discussions on value and believe that treatment decisions should be made by the physician and patient. We have concerns that ICER's report may compromise patient access. Below are our recommendations:

- Consider a broader range of efficacy assessments and systematically incorporate benefit and risk into ratings.
- Increase transparency by providing economic models for manufacturer feedback.
- Revise the report's clinical and economic sections once ocrelizumab is FDA-approved and price is available.

Ocrelizumab, an investigational drug product, is the first and only disease modifying MS medicine to demonstrate Phase 3 efficacy in both relapsing and primary progressive MS (PPMS).

- The OPERA I and OPERA II trials were robustly designed and represent the first pivotal trial program in relapsing MS (RMS) to consist of two 2-year, double blind, double-dummy, head-to-head trials that demonstrated superiority over subcutaneous interferon beta-1a across major efficacy outcomes including relapse rate, disability progression and MRI parameters.

- ORATORIO is the first and only Phase 3 trial to demonstrate efficacy in PPMS, showing statistically significant effects of ocrelizumab compared to placebo on disability progression, timed ambulation, MRI lesion volume and brain volume loss.
- These three studies revealed a safety profile with similar rates of adverse events (AEs) and serious AEs including serious infections as subcutaneous interferon beta-1a in RMS and placebo in PPMS. The most common AEs observed were infusion-related reactions and infections, which were mostly mild to moderate in severity.

Norman Putzki, MD, Novartis
Vice President and Head of Medical Business Unit, Neuroscience

At Novartis, our mission is to provide better care to patients to positively impact their lives. Since no one MS patient is the same, treatment decisions should be based on the needs of each individual patient.

Although ICER provided a public forum to discuss MS medications, there is a need to improve the methodology and transparency of the net health benefit ratings, cost-effectiveness model, and network-meta analysis. More importantly, we have an obligation to highlight factors important to MS patients:

- MS Patients want a treatment option that best fits their lifestyle.[34,161] Novartis introduced fingolimod as the first oral disease-modifying therapy (DMT) more than 6 years ago as a first-line treatment for relapsing forms of MS.[162] Fingolimod is the only oral DMT proven to cut relapses in half in a head-to-head trial against an active comparator.[85]
- Patients rely on long-term experience. Fingolimod has an established benefit/risk profile in a variety of clinical practice settings. We have had the privilege of treating 184,000 patients with fingolimod,[163] which has been rigorously studied with up to 7 years of demonstrated safety and efficacy data.[164,165]
- Many patients opt for a more convenient, once daily oral therapy that is easy to tolerate for the long run. Several studies, including trials and real-world studies, have shown patients are satisfied with fingolimod and more likely to be adherent versus other oral and injectable DMTs.[166-172]

Novartis is committed to research that incorporates the patient perspective to advance treatment options for relapsing and progressive forms of MS.

Laura Saltonstall, MD, MBA, Sanofi-Genzyme
Senior Medical Director, US Medical Affairs

Sanofi Genzyme appreciates the opportunity to comment and engage with ICER.

1. We acknowledge that ICER incorporated patient perspectives, but the report inadequately addresses patient heterogeneity and differing treatment preferences or responses. MS patients must have access to all approved DMTs so individualized treatment choices can be made.

2. NMA flaws and inaccuracies, including persistent data errors, result in misleading conclusions. Examples:
   - Inclusion of an inappropriate study impacting results in favor of glatiramer acetate
   - Persistent errors (primarily use of imputed data when actual, observed data is available) in data inputs
   - Pooled findings regardless of differences in power, endpoints, or duration introduce bias

3. The CEA and threshold analyses include inconsistencies and counterintuitive results.
   - Generic GA cannot be meaningfully described as dominating teriflunomide 14 mg, given the products are reported as equally efficacious until the first decimal point for life-years and QALYs.
   - Teriflunomide dominates (in cost per additional QALY) two interferon β-1a products and branded GA but is reported as less cost-effective at a WAC of $0, without adequate explanation.

4. Figure 5 subjectively and inaccurately characterizes safety and efficacy of products.

5. Despite flaws in the analyses, we are not surprised by the positive findings for alemtuzumab given its dosing schedule and demonstrated efficacy.

6. We recognize the importance of understanding the value of DMTs for the treatment of MS, but due to significant limitations of these analyses, it is imperative that results are used responsibly and do not limit patients' access to treatments.

Kathleen Costello, MS, National MS Society
Vice President, Healthcare Access

The National MS Society appreciates the opportunity to provide public comments on ICER's evidence report on treatments for MS. We commend ICER for their effort in seeking to address this expensive class of medications and for their effort in working with patient groups throughout the process. MS is highly heterogeneous and requires individualized treatment plans determined through collaborative decision making that considers efficacy, risk profile and tolerance, side effects, ability to adhere, treatment goals and cost. It is our belief that people with MS and their

providers require access to the full range of DMTs so that all factors can be considered in treatment decision making.

ICER's model emphasized a reliance on randomized controlled trials (RCTs) although RCTs are not designed, controlled, conducted, or powered to establish cost effectiveness nor do they provide necessary data on real-world treatment impact or information on patient reported outcomes. While the report narrative noted many factors that are important to people living with MS, none were considered within the modeling. The exclusion of this important data is detrimental to the review and diminishes the utility of the report. We remain concerned that this review and value assessment could be employed to limit access to MS treatments.

Limited comparative data exist for this type of review. Therefore, we believe that the evidence review and value comparison are premature in the MS disease space and that as more comparative effectiveness data become available, ICER should revisit the MS disease space with a revised evidence report.

No personal conflicts of interest declared. The National MS Society receives less than 25% of its overall funding through contributions from pharmaceutical companies.

Jeffrey English, MD, MS Center of Atlanta (on behalf of the MS Coalition)
Director of Clinical Research

As is stated in the MS Coalition's "The Use of Disease-Modifying Therapies in Multiple Sclerosis," we maintain that all people living with MS should have access to the full range of DMT's. The heterogeneity of multiple sclerosis mandates availability of all DMT's and all treatment options as each person experiences the disease differently.

People with MS have individual preferences and strong opinions about the choice of DMT and the resulting consequences on their respective lifestyles. Shared decision-making is critical in the selection of DMT therapy. It is hoped that any conclusions reached through this analysis will not diminish the importance of the patient's perspective and involvement in decision-making.

After initial discussions with ICER staff, continued concern about patient input prompted the MS Coalition to develop and distribute a survey to over 16,000 people living with MS. The MS Coalition is extremely disappointed that these survey results were not incorporated into the network meta-analyses in order to contribute important information from the patient perspective to the overall results of the ICER review.

The review lacks the analytical precision necessary to place high confidence in the results.

Patient access to disease-modifying therapies must not be negatively affected by this review. The Coalition urges payers and regulatory bodies to use caution in the application of the ICER review's results.

Dr. English declared receipt or potential receipt of anything of monetary value, including but not limited to, salary or other payments for services such as consulting fees or honoraria in excess of $5,000; and manufacturer support of research in the clinical area of this meeting. Dr. English has conducted research for Biogen, EMD Serono, Genzyme, Genentech, Teva, and Novartis. Dr. English has served on Advisory Boards, performed group and independent consulting, and has been a speaker for the following companies in the previous year: Biogen, EMD Serono, Genzyme, Genentech, and Teva.

Appendix H. Conflict of Interest Disclosures

Tables H1 through H3 contain conflict of interest (COI) disclosures for all participants at the February 16, 2017 Public meeting of the California Technology Assessment Forum.

Table H1. ICER Staff and Consultant COI Disclosures

Name	Organization	Disclosures
Josh Carlson, PhD, MPH	University of Washington	Prior consultancies with Genentech, Sandoz
Marita Zimmermann, MPH, PhD	University of Washington	Prior consultancy with Genentech
Daniel Ollendorf, PhD	ICER	None
Steven Pearson, MD, MSc	ICER	None
Matt Seidner, BS	ICER	None
Jeff Tice, MD	University of California, San Francisco	None
Margaret Webb, BA	ICER	None

Table H2. CTAF Panel Member COI Disclosures

Name	Organization	Disclosures
Ralph G. Brindis, MD, MPH, MACC, FSCAI, FAHA	UCSF	*
Robert Collyar	Patient Advocates in Research	*
Meg Durbin, MD	Canopy Health	*
Rena Fox, MD	UCSF	*
Luanda Grazette, MD, MPH, FACC	USC	*
Kimberly Gregory, MD, MPH	Cedars-Sinai Medical Center	*
Paul Heidenreich, MD, MS	Stanford University	*
Jeff Klingman, MD	The Permanente Medical Group	*
Joy Melnikow, MD, MPH	UC Davis	*
Robert E. Rentschler, MD	Beaver Medical Group	*
Rita F. Redberg, MD, MSc, FACC	UCSF	*
Alexander Smith, MD, MPH	UCSF	*
Daniel J. Ullyot, MD (Chair)	Retired, UCSF	*
Gerald R. Winslow, PhD	Loma Linda University Medical Center	*

* No relevant conflicts of interest to disclose, defined as more than $10,000 in healthcare company stock or more than $5,000 in honoraria or consultancies during the previous year from health care manufacturers or insurers.

Table H3. Policy Roundtable Participant Disclosures

Name	Title	Disclosures
Sara Alvarez, PharmD, BCPS	Manager of Pharmacoeconomic Evaluations, UnitedHealthcare	UHC Employee
Peter Chin, MD, MSHS	Group Medical Director for Neuroscience, USMA, Genentech Inc.	Genentech Employee
David Jones, MD	Assistant Professor of Neurology, UVA; MS Section Chair, AAN	Honoraria: Biogen, Genentech (<$5k each) Salary Support: Consortium of MS Centers (CMSC), Biogen (PI of clinical trial) Board Position: CMSC, Can Do MS
Annette Langer-Gould, MD, PhD, MS	Research Scientist, Kaiser Permanente Department of Research and Evaluation; MS Specialist, Los Angeles Medical Center	None
Bari Talente, JD	Executive Vice President, Advocacy, National MS Society	None
Philip Posner, PhD	MS Patient	None
John Yao, MD, MPH, MBA, MPA, FACP	Staff Vice President of Medical Policy and Technology Assessment, Anthem	Anthem Employee