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

Draft Evidence Report

November 22, 2016

Prepared for

ICER Staff and Consultants	University of Washington School of Pharmacy Modeling Group
Jeffrey A. Tice, MD Associate Professor of Medicine University of California, San Francisco **Rick Chapman, PhD, MS** Director of Health Economics Institute for Clinical and Economic Review **Varun Kumar, MBBS, MPH, MSc** Health Economist Institute for Clinical and Economic Review **Anne M. Loos, MA** Senior Research Associate Institute for Clinical and Economic Review **Shanshan Liu, MS, MPH** Research Associate Institute for Clinical and Economic Review **Matt Seidner, BS** Program Manager Institute for Clinical and Economic Review **Daniel A. Ollendorf, PhD** Chief Scientific Officer Institute for Clinical and Economic Review **David Rind, MD** Chief Medical Officer Institute for Clinical and Economic Review **Steven D. Pearson, MD, MSc** President Institute for Clinical and Economic Review	**Marita Zimmermann, MPH, PhD** Research Fellow Pharmaceutical Outcomes Research and Policy Program, Department of Pharmacy University of Washington **Elizabeth Brouwer, MPH** Graduate Student Pharmaceutical Outcomes Research and Policy Program, Department of Pharmacy University of Washington **Josh J. Carlson, PhD, MPH** Associate Professor Pharmaceutical Outcomes Research and Policy Program, Department of Pharmacy University of Washington *The role of the University of Washington (UW) School of Pharmacy Modeling Group is limited to the development of the cost-effectiveness model, and the resulting ICER reports do not necessarily represent the views of the UW.*

DATE OF PUBLICATION: November 22, 2016

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

About ICER

The Institute for Clinical and Economic Review (ICER) is an independent non-profit research organization that evaluates medical evidence and convenes public deliberative bodies to help stakeholders interpret and apply evidence to improve patient outcomes and control costs. ICER receives funding from government grants, non-profit foundations, health plans, provider groups, and health industry manufacturers. For a complete list of funders, visit http://www.icer-review.org/about/support/. Through all its work, ICER seeks to help create a future in which collaborative efforts to move evidence into action provide the foundation for a more effective, efficient, and just health care system. More information about ICER is available at http://www.icer-review.org

About CTAF

The California Technology Assessment Forum (CTAF) – a core program of ICER – provides a public venue in which the evidence on the effectiveness and value of health care services can be discussed with the input of all stakeholders. CTAF seeks to help patients, clinicians, insurers, and policymakers interpret and use evidence to improve the quality and value of health care.

The CTAF Panel is an independent committee of medical evidence experts from across California, with a mix of practicing clinicians, methodologists, and leaders in patient engagement and advocacy. All Panel members meet strict conflict of interest guidelines and are convened to discuss the evidence summarized in ICER reports and vote on the comparative clinical effectiveness and value of medical interventions. More information about CTAF is available at https://icer-review.org/programs/ctaf/.

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/

Clinical Expert Reviewer

David E. Jones, MD
Assistant Professor of Neurology
University of Virginia Health System

Additional Clinical Expert Input

Jeffrey Klingman, MD
Chief of Neurology
Kaiser Permanente Walnut Creek

Table of Contents

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

Executive Summary

An executive summary will be included in the Evidence Report to be released in January 2017.

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 a decision date of December 28, 2016.[7] 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.[8]

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)

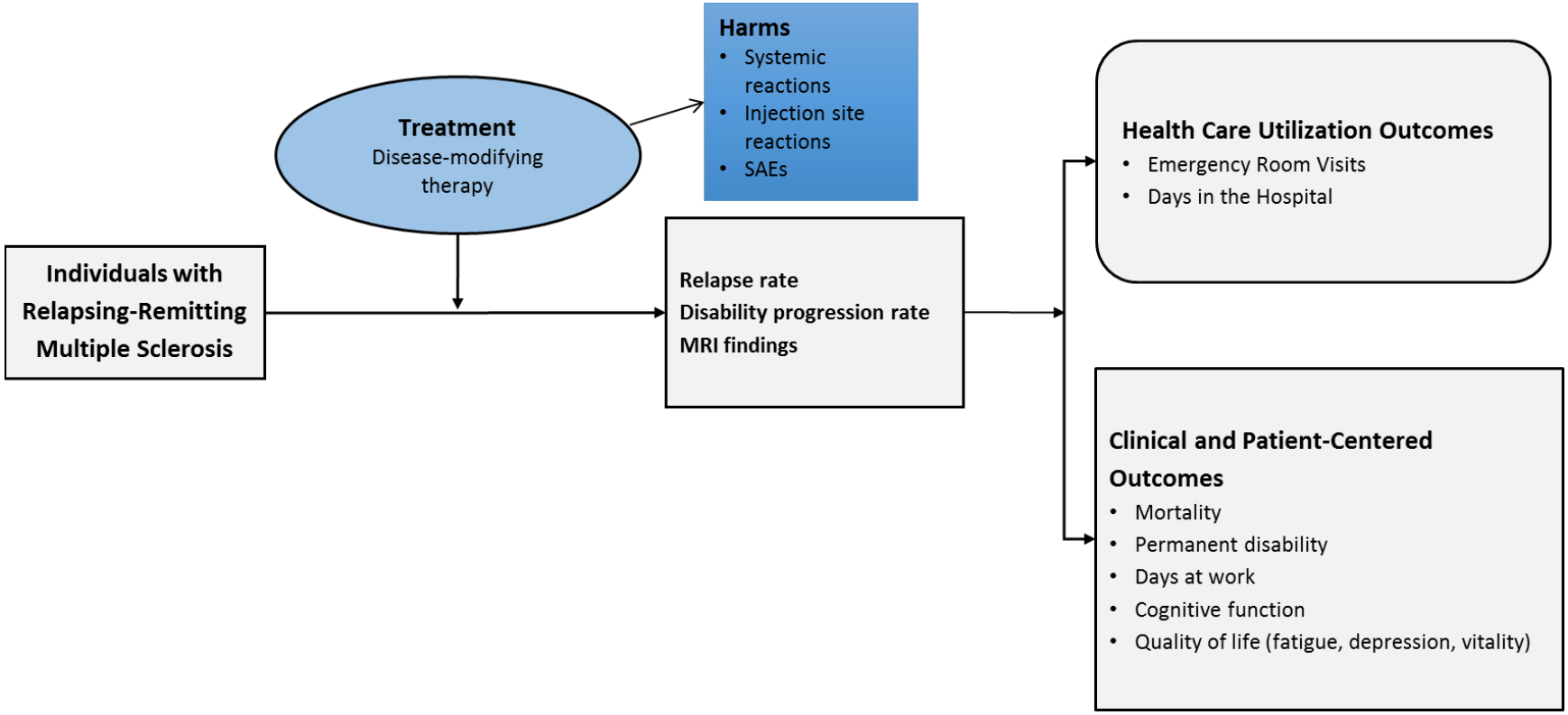
For PPMS, the included interventions were ocrelizumab and rituximab.

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 and number needed to treat 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.[9,10] 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.[11-16]

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 encephalopathy (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.[17] 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.[18] 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 also are not reviewing 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.[19-23] 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 December 2016 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	$75,881
Interferon β-1b (Betaseron®, Bayer)	IFN β-1b 250 mcg	Interferon	250 mcg every other day	$69,220
Interferon β-1b (Extavia®, Novartis)	IFN β-1b 250 mcg	Interferon	250 mcg every other day	$57,743
Glatiramer acetate (Copaxone®, Teva)	GA 20 mg	Mixed polymers	20 mg daily	$80,215
Glatiramer acetate (Copaxone®, Teva)	GA 40 mg	Mixed polymers	40 mg three times weekly	$70,445
Glatiramer acetate (Glatopa®, Sandoz)	GA 20 mg (Glatopa)	Mixed polymers	20 mg daily	$63,192
Interferon β-1a (Rebif®, EMD Serono)	IFN β-1a 22 mcg or 44 mcg	Interferon	22 mcg or 44 mcg three times weekly	$77,827
Peginterferon β-1a (Plegridy®, Biogen)	PEG	Interferon	125 mcg every 14 days	$73,017
Daclizumab (Zinbryta™, Biogen and AbbVie)	DAC	Anti-IL2 monoclonal antibody	150 mg every 4 weeks	$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	$76,832
Intravenous infusion				
Natalizumab (Tysabri®, Biogen)	NAT	Anti α4β1/ α4β7 integrin monoclonal antibody	300 mg every 4 weeks	$75,569
Alemtuzumab (Lemtrada®, Sanofi Genzyme)	ALE	Anti-CD52 monoclonal antibody	12 mg per day for 3 days every year	$101,219

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	1000 mg every 6 months	$16,062

WAC: wholesale acquisition cost

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.[21]

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.[24] 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[24]

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.[25]

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.[26,27] 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. Though not reflected in the Table, which examined a 2016 formulary, UHC recently announced that they would include peginterferon β-1a and remove step therapy requirements for fingolimod and teriflunomide from their 2017 formularies.[28]

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.[29] 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[30]	Anthem[31]	Cigna[32]	Humana[33]	UHC[34]	Health Net[35]	BSCA[36,37]
Interferon β-1a 30 mcg (Avonex)							
Tier	5	4	2	5	2	SP	SP
ST	Yes	No	No	No	No	No	No
PA	Yes	Yes	Yes	Yes	Yes	Yes	No
Preferred Agent	No		Yes	No			
Inteferon β-1b 250 mcg (Betaseron, Extavia)							
Tier	5	4	N/C	5	2	SP	SP
ST	Yes	No		No	No	No	Yes
PA	Yes	Yes		Yes	Yes	Yes	Yes
Preferred Agent	No			No			
Glatiramer Acetate 20 mg (Copaxone)							
Tier	5	4	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	5	3	SP	SP
ST	No*[29]	No	No	Yes*[38]	No	No	No
PA	Yes	Yes	Yes	Yes	Yes	Yes	No
Preferred Agent	No		Yes	No			
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	N/A	Yes	No			

	Aetna[30]	Anthem[31]	Cigna[32]	Humana[33]	UHC[34]	Health Net[35]	BSCA[36,37]
Interferon β-1a 22/44 mcg (Rebif)							
Tier	4 (preferred)	4	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	N/A	Yes				
Daclizumab (Zinbryta)							
Tier	5	4	N/C	NL	NL	SP	N/C
ST	Yes	Yes*[39]		Yes*[40]		No	
PA	Yes	Yes				Yes	
Preferred Agent	No					N/A	
Fingolimod (Gilenya)							
Tier	4 (preferred)	4	2	5	3	SP	4
ST	No	No	No	No	Yes	No	No
PA	Yes	Yes	Yes	Yes	Yes	Yes	No
Preferred Agent	Yes		Yes	No			
Teriflunomide 7/14 mg (Aubagio)							
Tier	5	4	2	5	3	SP	SP
ST	Yes	No	No	No	Yes	No	Yes
PA	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Preferred Agent	No		Yes	No			

	Aetna[30]	Anthem[31]	Cigna[32]	Humana[33]	UHC[34]	Health Net[35]	BSCA[36,37]
Dimethyl Fumarate (Tecfidera)							
Tier	5	4	2	5	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	NL	5	NL	NL	NL
ST	Yes*	Yes*[41]	Yes*[42]	No		Yes*[43]	
PA	Yes	Yes		Yes			
Preferred Agent	No			No			
Alemtuzumab (Lemtrada)							
Tier	5	4	NL	NL	NL	NL	NL
ST	Yes	Yes*[39]	Yes*[42]	Yes*[44]	Yes*[45]		
PA	Yes	Yes		Yes	Yes*[45]		
Preferred Agent	No						
Rituximab (Rituxan)							
Tier	N/A	N/C[46]	N/C[42]	N/C[47]	N/C[48]		
ST	Yes*[29]						
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[49]

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 not use these agents in patients who test positive for JC virus antibodies. 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[50]

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[51]

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).

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[52]

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.[53] We conducted the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[54] 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. 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.

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. 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."[55]

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.*

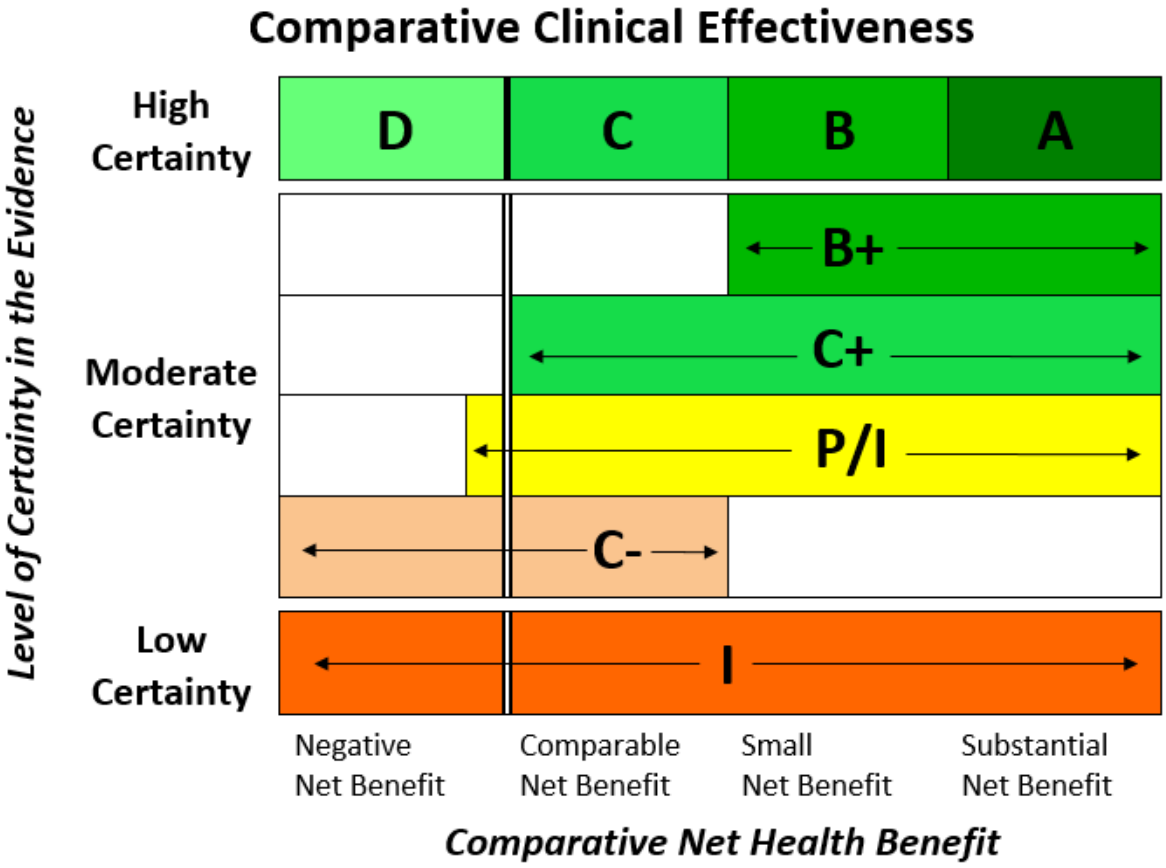
Poor: *Any of the following fatal flaws exists: groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are 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.[56]

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 39 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 39 studies randomized 22,936 participants to one or more of the DMTs considered in this review or to placebo. The oldest trial[57] was published in 1987 and the most recent trial was presented at a conference in 2015, but is not yet published.[58] Eleven of the trials used the Poser definition of clinically-definite MS to define their patient population and the remaining 28 trials used the McDonald criteria to define their eligible population. Nine 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 3.3 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 17 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 only three of the trials included in our NMA to be of good quality (Appendix Table C3).[59-61] 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 23 publications to be of fair quality. We rated the remaining 12 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.[62] 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 (11%) 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<0.001) for daclizumab compared to placebo. The hazard ratio (HR) for confirmed disability progression sustained for at least 12 weeks was 0.45 (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<0.001) 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<0.001), 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, 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).[63] 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 the number of relapses in the year prior to study entry as well as 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 placebo. The HR for confirmed disability progression sustained for at least 12 weeks was 0.84 (0.66-1.07, p=0.016). 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 placebo. 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.[58] 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 fair quality because they have only been presented in abstract form at a conference and due to relatively high loss to follow-up (14% and 18% respectively). 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. The number of new or enlarging T2 lesions was reduced with ocrelizumab (77% and 83% respectively, p<0.0001 for both trials) as was the reduction in the rate of brain

volume loss (24% decrease in rate for both, p<0.001). SAEs, infections, and nervous system disorders were all 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 were similar 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.[64] 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.[65] 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).[66] 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.[67] 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.[68-70] 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 beta-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.[71-74] Fogarty and colleagues published the most recent NMA.[71] 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[72] 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.[8] 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 presented at the 31st Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS), but has not yet been published, which makes a full assessment of the trial difficult.[75] 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). 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). 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 25-26% 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 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-three head-to-head studies, seven which also included a placebo arm, and an additional 16 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 ranged from 0.11 to 1.35 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 6 trials published before 2000 ranged from 0.82 to 1.35[57,59,76-79], while those published since 2010 ranged from 0.26-0.50.[60,62,66,67,80-85] The explanation for the change in ARR over time has been studied, but no conclusive reason has been identified.[86-89] 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.

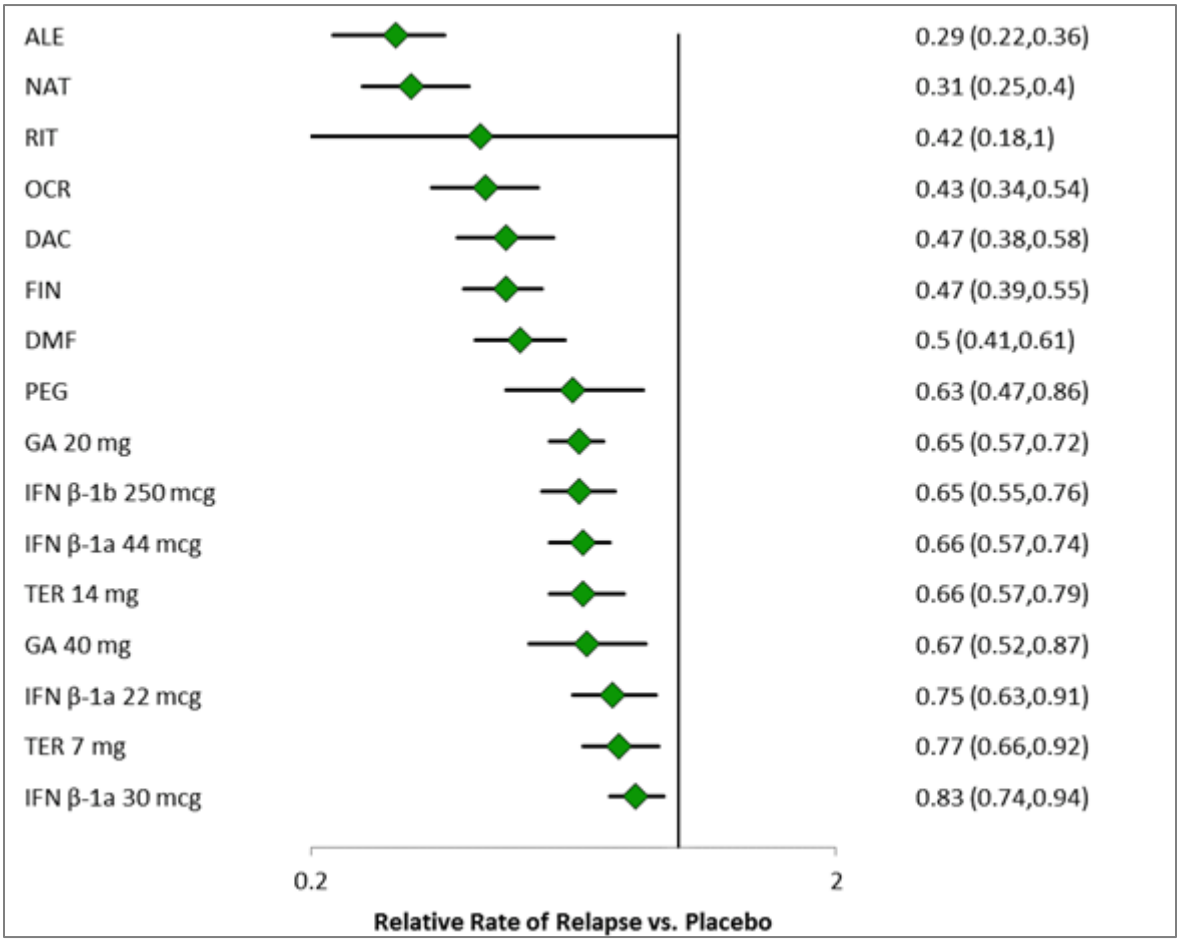
We identified 39 studies that randomized a total of 22,936 participants to one or more of the DMTs considered in this review or to placebo. The oldest trial[57] was published in 1987 and the most recent trial was presented at a conference in 2015, but is not yet published.[58] Eleven of the trials used the Poser definition of clinically-definite MS to define their patient population and the remaining 28 trials used the McDonald criteria to define their eligible population. Nine 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 mean EDSS grade at baseline ranged from 2.0 to 3.3 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.[60-62,64,67,83,90]. The one exception is teriflunomide, which reduced ARR by 20%-40% compared to placebo.[81,84,91]. There are no placebo controlled trials of alemtuzumab; all three of the alemtuzumab randomized trials used interferon beta-1a 44 mcg as an active control.

In our NMA, alemtuzumab and natalizumab had the greatest reduction in ARR (approximately 70% reduction compared to placebo). The 95% credible interval for those two drugs did not include 1 when compared to any of the other drugs (Table 6). Rituximab, ocrelizumab, daclizumab, fingolimod, and dimethyl fumarate were the next most effective (50% to 58% 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 and natalizumab 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 ocrelizumab, the other anti-CD20 drug, as well as those for 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.

The pooled relapse rate for the placebo group was 0.56 relapses per year. Assuming this as the background rate, we estimated that the number needed to treat (NNT) with a DMT to prevent one relapse ranges from 3 to 11 (Table 5 below). For example, 11 patients with MS need to be treated with interferon β-1a 30 mcg to prevent one relapse, while only 3 patients need to be treated with

natalizumab or alemtuzumab to prevent one relapse. These NNTs were are all relatively low, and all of the DMTs were effective at decreasing the number of relapses.

Table 5. Number Needed to Treat (NNT) to Prevent One Relapse*

Drug	NNT
Interferon β-1a 30 mcg (Avonex)	11
Teriflunomide 7 mg (Aubagio)	8
Interferon β-1a 22 mcg (Rebif)	8
Glatiramer acetate 40 mg (Copaxone)	6
Teriflunomide 14 mg (Aubagio)	6
Interferon β-1a 44 mcg (Rebif)	6
Interferon β-1b 250 mcg (Betaseron)	6
Glatiramer acetate 20 mg (Copaxone)	6
Peginterferon β-1a (Plegridy)	5
Dimethyl fumarate (Tecfidera)	4
Fingolimod (Gilenya)	4
Daclizumab (Zinbryta)	4
Ocrelizumab (Ocrevus)	4
Rituximab (Rituxan)	4
Natalizumab (Tysabri)	3
Alemtuzumab (Lemtrada)	3

*Assuming a background relapse rate of 0.5622 relapses per year

Table 6 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.

Table 6. League Table for Annualized Relapse Rate, Base Case

ALE															
0.93 (0.65-1.27)	NAT														
0.69 (0.28-1.64)	0.74 (0.30-1.78)	RIT													
0.67 (0.49-0.90)	0.73 (0.53-1.03)	0.98 (0.41-2.37)	OCR												
0.63 (0.45-0.83)	**0.67 (0.49-0.94)**	0.91 (0.38-2.16)	0.93 (0.70-1.21)	DAC											
0.62 (0.44-0.81)	**0.67 (0.50-0.91)**	0.91 (0.38-2.16)	0.92 (0.70-1.20)	0.99 (0.77-1.30)	FIN										
0.58 (0.43-0.78)	**0.63 (0.46-0.86)**	0.85 (0.36-2.05)	0.87 (0.64-1.15)	0.94 (0.70-1.24)	0.94 (0.72-1.21)	DMF									
0.46 (0.31-0.66)	**0.49 (0.34-0.73)**	0.67 (0.27-1.65)	**0.68 (0.46-0.98)**	0.74 (0.50-1.06)	0.74 (0.52-1.04)	0.79 (0.55-1.13)	PEG								
0.45 (0.35-0.57)	**0.49 (0.38-0.65)**	0.66 (0.28-1.57)	**0.67 (0.53-0.85)**	**0.73 (0.58-0.92)**	**0.73 (0.59-0.89)**	**0.77 (0.63-0.97)**	0.99 (0.71-1.38)	GA 20 mg							
0.45 (0.34-0.57)	**0.48 (0.36-0.65)**	0.65 (0.27-1.56)	**0.67 (0.51-0.86)**	**0.72 (0.56-0.93)**	**0.72 (0.57-0.90)**	**0.76 (0.61-0.98)**	0.97 (0.70-1.39)	0.99 (0.85-1.15)	IFNß-1b 250 mcg						
0.45 (0.37-0.53)	**0.48 (0.37-0.64)**	0.65 (0.28-1.56)	**0.66 (0.52-0.84)**	**0.71 (0.57-0.91)**	**0.72 (0.59-0.89)**	**0.76 (0.61-0.97)**	0.97 (0.71-1.37)	0.98 (0.85-1.14)	1.00 (0.83-1.20)	IFNß-1a 44 mcg					
0.44 (0.32-0.57)	**0.47 (0.35-0.63)**	0.64 (0.27-1.52)	**0.65 (0.48-0.85)**	**0.70 (0.53-0.92)**	**0.71 (0.55-0.89)**	**0.75 (0.58-0.96)**	0.96 (0.68-1.35)	0.97 (0.78-1.17)	0.98 (0.77-1.21)	0.99 (0.79-1.19)	TER 14 mg				
0.44 (0.30-0.60)	**0.47 (0.33-0.67)**	0.64 (0.26-1.54)	**0.65 (0.45-0.90)**	**0.70 (0.50-0.98)**	**0.70 (0.51-0.95)**	0.75 (0.54-1.03)	0.95 (0.64-1.42)	0.96 (0.71-1.27)	0.98 (0.71-1.31)	0.98 (0.72-1.29)	0.99 (0.73-1.36)	GA 40 mg			
0.39 (0.29-0.49)	**0.42 (0.31-0.56)**	0.56 (0.24-1.36)	**0.58 (0.42-0.76)**	**0.62 (0.47-0.81)**	**0.62 (0.48-0.78)**	**0.66 (0.51-0.86)**	0.84 (0.59-1.20)	0.86 (0.68-1.04)	0.86 (0.68-1.07)	0.86 (0.71-1.03)	0.88 (0.69-1.12)	0.89 (0.64-1.21)	IFNß-1a 22 mcg		
0.38 (0.28-0.48)	**0.41 (0.30-0.54)**	0.55 (0.23-1.30)	**0.56 (0.41-0.72)**	**0.60 (0.46-0.78)**	**0.61 (0.47-0.75)**	**0.64 (0.50-0.83)**	0.92 (0.58-1.15)	0.83 (0.67-1.00)	0.84 (0.66-1.04)	0.85 (0.68-1.02)	0.86 (0.72-1.02)	0.86 (0.63-1.16)	0.97 (0.77-1.23)	TER 7 mg	
0.35 (0.27-0.44)	**0.37 (0.29-.050)**	0.51 (0.22-1.20)	**0.52 (0.42-0.63)**	**0.56 (0.46-0.68)**	**0.56 (0.46-0.68)**	**0.60 (0.48-0.75)**	0.76 (0.55-1.06)	**0.77 (0.67-0.89)**	**0.78 (0.66-0.92)**	**0.78 (0.67-0.90)**	**0.79 (0.66-0.98)**	0.80 (0.61-1.07)	0.90 (0.74-1.12)	0.93 (0.77-1.15)	IFNß-1a 30 mcg
0.29 (0.22-0.36)	**0.31 (0.25-0.40)**	0.42 (0.18-1.00)	**0.43 (0.34-0.54)**	**0.47 (0.38-0.58)**	**0.47 (0.39-0.55)**	**0.50 (0.41-0.61)**	**0.63 (0.47-0.86)**	**0.65 (0.57-0.72)**	**0.65 (0.55-0.76)**	**0.66 (0.57-0.74)**	**0.66 (0.57-0.79)**	**0.67 (0.52-0.87)**	**0.75 (0.63-0.91)**	**0.77 (0.66-0.92)**	**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.

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 Table D1). There were two estimates in the direct meta-analysis for alemtuzumab and ocrelizumab that were substantially different from the base-case NMA estimate. For alemtuzumab, there are no placebo controlled trials, so there are no direct meta-analysis results versus placebo. For ocrelizumab, the phase II study is the only placebo controlled trial of ocrelizumab and the reduction in relapse rates with ocrelizumab in that study was greater than in the phase III studies. The remaining sensitivity analyses produced values 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 7 below).[71-74] The Cochrane NMA estimated the relative rates over both 12- and 24-month follow-up periods.

Table 7. 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	0.65
40 TIW					0.65	0.67
Interferon β-1a (Rebif)	0.87	0.86				
22 mcg			0.71	0.71	0.72	0.75
44 mcg			0.67	0.66	0.67	0.66
Peginterferon β-1a (Plegridy)	0.89	NR	NR	0.65	0.64	0.63
Daclizumab (Zinbryta)	0.79	NR	NR	NR	NR	0.47
Fingolimod (Gilenya)	0.63	0.72	0.44	NR	0.47	0.47
Teriflunomide (Aubagio)	0.84	0.88		NR		
7 mg			0.69		0.67	0.77
14 mg			0.68			0.66
Dimethyl fumarate (Tecfidera)	0.78	0.89	0.50	NR	0.50	0.50
Natalizumab (Tysabri)	0.56	0.56	0.32	NR	0.31	0.31
Alemtuzumab (Lemtrada)	0.40	0.46	0.30	NR	0.31	0.29
Ocrelizumab (Ocrevus)	NR	NR	NR	NR	NR	0.43
Rituximab (Rituxan)	NR	NR	NR	NR	NR	0.42

NR: not reported

Disability Progression

A primary long-term goal for patients is to avoid permanent disability. Ideally, studies would measure disability progression over at least five years.[92] 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). Twelve 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).

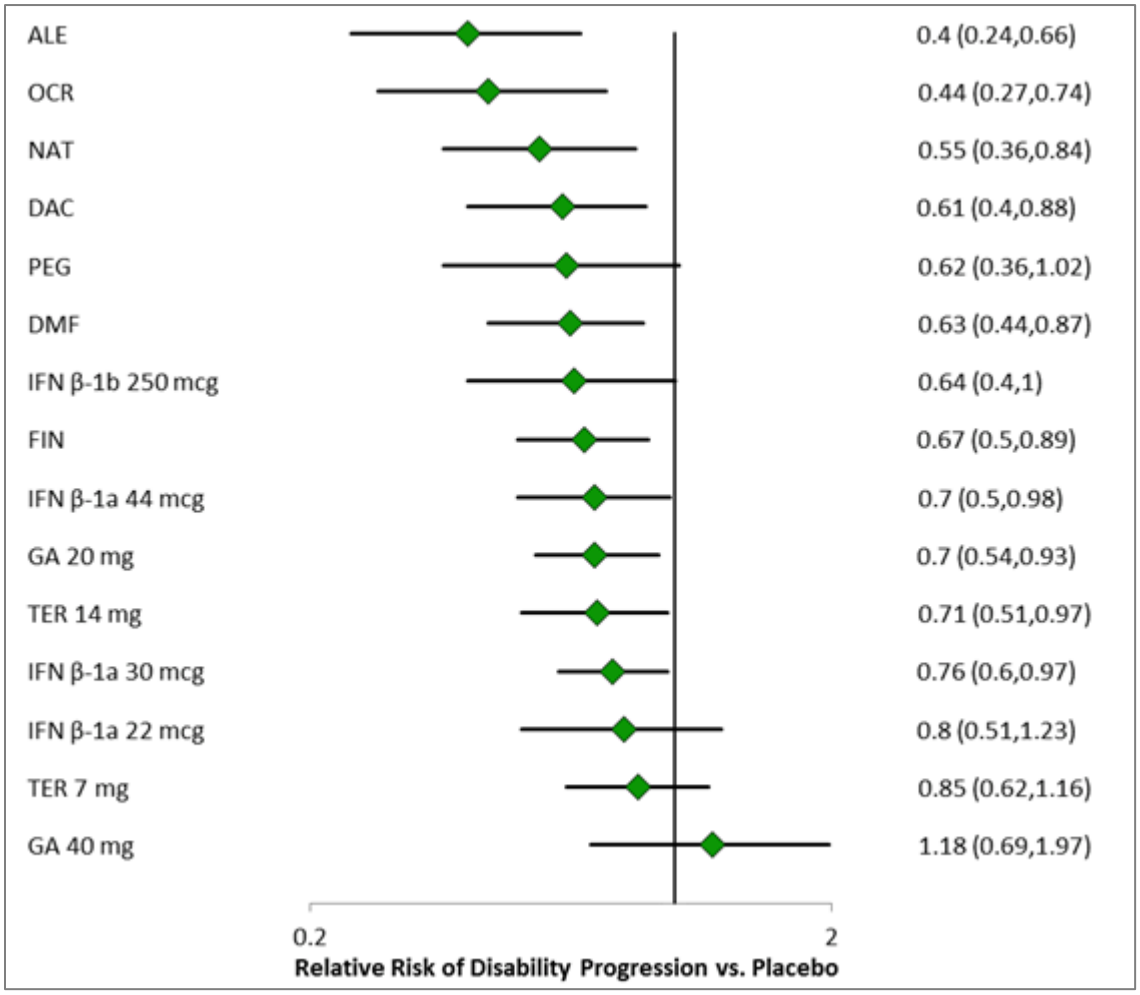
Studies reported confirmed disability progression sustained for 12 or 24 weeks (Appendix Tables C6 and C5), and as noted earlier, disability progression sustained for 24 weeks was the preferred outcome. In studies the reported both outcomes, the relative risk for disability progression was usually lower 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 beta-1a 44 mcg (RR 0.25 and 0.42) and the DECIDE study of daclizumab versus interferon beta-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, daclizumab).

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 20% to 38% for the interferons and glatiramer acetate compared to placebo and 33% to 60% 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 (56% to 60% reduction compared to placebo respectively), followed by natalizumab (45%). Fingolimod, dimethyl fumarate, interferon β-1b 250 mcg, peginterferon β-1a, and daclizumab were next (33% to 39%). Teriflunomide, glatiramer acetate, and the remaining interferons were less effective (15% to 30%). Three of the drugs were not significantly better than placebo (peginterferon β-1a, interferon β-1b 250 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.[93] 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).[94]

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 9), which compares each DMT to the others, only alemtuzumab and ocrelizumab are significantly better than other DMTs (interferon β-1a 22/44 mcg, glatiramer acetate 20/40 mg, and teriflunomide 7/14 mg).

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, natalizumab, daclizumab, peginterferon β-1a, dimethyl fumarate, interferon β-1b 250 mcg, fingolimod, and teriflunomide 14 mg (see Table 9). Alemtuzumab is superior to interferon β-1a (22, 44, and 30 mcg doses), teriflunomide 7 mg, and glatiramer acetate (20 and 40 mg doses).

The pooled risk of sustained disability progression for the placebo group was 0.176. Assuming this as the background rate, the number needed to treat with a DMT to prevent one patient from sustained disability progression ranges from 10 to 24 (Table 8).

Table 8. Number Needed to Treat to Prevent One Disability Progression*

Drug	NNT
Glatiramer acetate 40 mg (Copaxone)	-
Interferon β-1a 22 mcg (Rebif)	-
Rituximab (Rituxan)	-
Teriflunomide 7 mg (Aubagio)	-
Interferon β-1a 30 mcg (Avonex)	24
Teriflunomide 14 mg (Aubagio)	20
Glatiramer acetate 20 mg (Copaxone)	19
Interferon β-1a 44 mcg (Rebif)	19
Fingolimod (Gilenya)	18
Interferon β-1b 250 mcg (Betaseron)	16
Dimethyl fumarate (Tecfidera)	16
Peginterferon β-1a (Plegridy)	15
Daclizumab (Zinbryta)	15
Natalizumab (Tysabri)	13
Ocrelizumab (Ocrevus)	11
Alemtuzumab (Lemtrada)	10

*Assuming a background risk for disability progression of 0.176. The NNT is **not** calculated if the 95% credible interval contains 1.

Table 9 below includes a complete set of pairwise comparisons for all agents included in the network.

Table 9. League Table for Disability Progression, Base Case

ALE															
0.91 (0.53-1.53)	OCR														
0.73 (0.38-1.41)	0.81 (0.41-1.57)	NAT													
0.67 (0.37-1.22)	0.73 (0.40-1.37)	0.91 (0.52-1.64)	DAC												
0.65 (0.32-1.34)	0.71 (0.35-1.49)	0.89 (0.46-1.75)	0.97 (0.51-1.87)	PEG											
0.64 (0.37-1.14)	0.70 (0.40-1.27)	0.87 (0.52-1.53)	0.96 (0.60-1.55)	0.99 (0.52-1.84)	DMF										
0.63 (0.32-1.22)	0.69 (0.35-1.36)	0.85 (0.46-1.61)	0.94 (0.52-1.69)	0.97 (0.48-1.91)	0.98 (0.56-1.69)	IFNβ-1b 250 mcg									
0.60 (0.34-1.07)	0.66 (0.37-1.19)	0.82 (0.49-1.37)	0.91 (0.56-1.42)	0.93 (0.50-1.66)	0.94 (0.60-1.43)	0.96 (0.56-1.64)	FIN								
0.58 (0.40-0.82)	**0.63 (0.43-0.92)**	0.78 (0.45-1.33)	0.87 (0.53-1.36)	0.89 (0.47-1.59)	0.90 (0.57-1.34)	0.92 (0.52-1.58)	0.95 (0.62-1.46)	IFNβ-1a 44 mcg							
0.57 (0.34-0.94)	0.63 (0.37-1.05)	0.78 (0.46-1.28)	0.87 (0.54-1.30)	0.89 (0.48-1.55)	0.90 (0.63-1.20)	0.91 (0.55-1.50)	0.95 (0.64-1.38)	1.00 (0.70-1.40)	GA 20 mg						
0.57 (0.31-1.03)	0.62 (0.34-1.14)	0.77 (0.45-1.32)	0.85 (0.51-1.40)	0.88 (0.47-1.59)	0.89 (0.54-1.39)	0.91 (0.51-1.57)	0.94 (0.61-1.45)	0.99 (0.62-1.57)	0.99 (0.66-1.52)	TER 14 mg					
0.53 (0.32-0.87)	**0.58 (0.35-0.97)**	0.73 (0.44-1.17)	0.80 (0.55-1.09)	0.82 (0.45-1.41)	0.83 (0.56-1.16)	0.85 (0.51-1.39)	0.88 (0.62-1.22)	0.93 (0.65-1.30)	0.93 (0.69-1.23)	0.94 (0.62-1.39)	IFNβ-1a 30 mcg				
0.51 (0.28-0.89)	0.55 (0.31-1.00)	0.69 (0.37-1.26)	0.76 (0.43-1.33)	0.78 (0.39-1.51)	0.79 (0.45-1.33)	0.81 (0.43-1.50)	0.83 (0.50-1.42)	0.88 (0.57-1.38)	0.88 (0.55-1.44)	0.89 (0.52-1.54)	0.95 (0.60-1.56)	IFNβ-1a 22 mcg			
0.47 (0.26-0.85)	**0.52 (0.28-0.94)**	0.64 (0.38-1.09)	0.71 (0.43-1.15)	0.73 (0.39-1.31)	0.74 (0.46-1.14)	0.75 (0.43-1.29)	0.78 (0.51-1.19)	0.82 (0.52-1.30)	0.82 (0.54-1.25)	0.83 (0.60-1.15)	0.89 (0.60-1.33)	0.94 (0.54-1.59)	TER 7 mg		
0.34 (0.17-0.71)	**0.37 (0.18-0.78)**	**0.47 (0.24-0.93)**	**0.51 (0.27-0.98)**	0.62 (0.36-1.02)	0.53 (0.28-1.01)	0.54 (0.27-1.09)	0.57 (0.31-1.05)	0.59 (0.32-1.12)	0.59 (0.33-1.10)	0.60 (0.33-1.13)	0.64 (0.37-1.17)	0.68 (0.34-1.36)	0.72 (0.40-1.34)	GA 40 mg	
0.40 (0.24-0.66)	**0.44 (0.27-0.74)**	**0.55 (0.36-0.84)**	**0.61 (0.40-0.88)**	0.62 (0.36-1.02)	**0.63 (0.44-0.87)**	0.64 (0.40-1.00)	**0.67 (0.50-0.89)**	**0.70 (0.50-0.98)**	**0.70 (0.54-0.93)**	**0.71 (0.51-0.97)**	**0.76 (0.60-0.97)**	0.80 (0.51-1.23)	0.85 (0.62-1.16)	1.18 (0.69-1.97)	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 beta-1a 44 mcg changed from 0.70 to a non-significant 0.99 under the McDonald criteria. 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 0.40). 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 D6).

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 10 below).[71-74] The Cochrane and CADTH NMAs used confirmed disability progression sustained at 24 weeks for their analyses.[73,74] 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.

Table 10: 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	0.76
Interferon β-1b 250 mcg (Betaseron)	0.79	0.74	0.82	0.54	0.83	0.31	0.63
Glatiramer acetate (Copaxone)							
20 mg QD	0.77	0.83	0.82	0.70	0.81	0.75	0.70
40 mg TIW							1.18
Interferon β-1a (Rebif)	0.86						
22 mcg		0.89	0.77		0.81		0.80
44 mcg		0.84	0.69	0.78	0.72	0.77	0.70
Peginterferon β-1a (Plegridy)	0.89			0.43	0.62	0.45	0.62
Daclizumab (Zinbryta)	0.79						0.61
Fingolimod (Gilenya)	0.86	0.76			0.75	0.69	0.67
Teriflunomide (Aubagio)	0.87						
7 mg		0.85			0.72		0.85
14 mg		0.80					0.71
Dimethyl fumarate (Tecfidera)	0.80	0.73			0.62	0.65	0.64
Natalizumab (Tysabri)	0.64	0.67			0.55	0.46	0.55
Alemtuzumab (Lemtrada)	0.35	0.56			0.32	0.41	0.40
Ocrelizumab (Ocrevus)							0.44
Rituximab (Rituxan)							

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.[95,96] 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 beta-1b trial, MRI changes during the trial explained none of the variability in disability progression.[97] 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

Quality of life is worse in patients with MS compared to age- and sex-matched individuals in the general population.[98,99] 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, including one trial of interferon beta-1a 44 mcg[78], one trial of fingolimod[80], three trials of teriflunomide[66,81,84], and two trials of daclizumab.[62,63] . Trials reporting QoL outcomes used a variety of instruments including the Multiple Sclerosis Quality of Life Questionnaire 54, the Multiple Sclerosis Impact Scale (MSIS-29), the EuroQOL-5D, the SF-12, the SF-36, the Beck Hopelessness scale, the Center for Epidemiologic Studies depression mood scale, the Global Health Questionnaire, the Treatment Satisfaction Questionnaire, the Sickness Impact Profile and the Fatigue Impact Scale.

Since there was no quality of life measure used consistently in the trials, no summary estimates or comparisons across DMTs are possible. There were no differences from control group in the measures assessed for interferon beta-1a 44 mcg or fingolimod. In two of the three trials of teriflunomide there were small, but statistically-significant differences between the teriflunomide 14 mg group and placebo group on one of the four subscales of the SF-36 that were reported and in

the change in the Fatigue Impact Score from baseline to last visit (p=0.043), but not baseline to week 48. There were no significant differences with the teriflunomide 7 mg dose. Finally, in the daclizumab trials there were significant differences between the daclizumab 150 mg group and the placebo group in the MSIS-29 physical impact score, but not the psychological impact score. There were also significant differences in favor of daclizumab on the EQ-visual analog scale, the EQ-5D summary health index, and the SF-12 physical and mental health components.

Harms

The harms of the DMTs are summarized in Table 11. 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. 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 11. 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%

Drug (Brand name)	Major safety concerns	D/C rates	SAEs
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%). Only available through **REMS.***	12%	10%
Teriflunomide (Aubagio)	Boxed warning for hepatotoxicity (including fatal liver failure) and teratogenicity. ↓ WBC, ↑ risk of infection, peripheral neuropathy (1.4 – 1.9%); ↑ BP (3-4%). Hair thinning.	13%	13%
Dimethyl fumarate (Tecfidera)	Anaphylaxis, angioedema, PML, ↓ WBC, 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, ↑ risk of malignancies. Infusion reactions (92%), rash (53%), lymphopenia (99.9%). Only available through **REMS**.*	2%	33%
Ocrelizumab (Ocrevus)	Risk of infection, possible ↑ risk for PML (due more to being related to rituximab and ofatumumab)[100]	3%	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: discontinuation, 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 are 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 focuses 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.

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).[101] 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).[101]

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.[100] 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.[102] 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 extention trial of glatiramer acetate and the 21-year extension trial of interferon beta-1b did not identify any new significant adverse events.

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.[86-89,103] 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. 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. 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.[104,105] 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-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, and only one of the 39 reviewed RCTs studied a population that had received at least one prior treatment with a DMT.[70]

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.

The trials of ocrelizumab for both RRMS and PPMS are encouraging, but the studies have not been published, so fewer data are available, and it is difficult to fully assess the quality of the trials. In addition, 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.

Summary

RRMS: DMTs Compared to Best Supportive Care

The data are most robust comparing DMTs to placebo. Of all the agents included in this review, natalizumab and alemtuzumab were the most effective drugs in reducing relapses and they were significantly better than the other DMTs. They were also two of the top three most effective drugs at reducing disability progression, although the separation from other DMTs was not as substantial. The differences in efficacy between the alemtuzumab and natalizumab were relatively small and non-significant. We gave each of these drugs 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.

The next most effective group for relapse reduction included rituximab, ocrelizumab, daclizumab, 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). In addition to greatly reducing relapses, ocrelizumab is one of the top two DMTs at reducing disability progression and to date, it has few know severe adverse events. However, the clinical trials establishing the benefits of ocrelizumab have not yet been published and there is no real-world evidence supporting its efficacy. Thus, we judge it to produce incremental or better net health benefits when compared to placebo, a "B+" rating. Similarly, 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. The pivotal trials for daclizumab, findgolimod, and dimethyl fumarate have been published, so there is greater certainty in the evidence supporting their safety and effectiveness. 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[72], or those agents plus teriflunomide.[71,73,74] 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

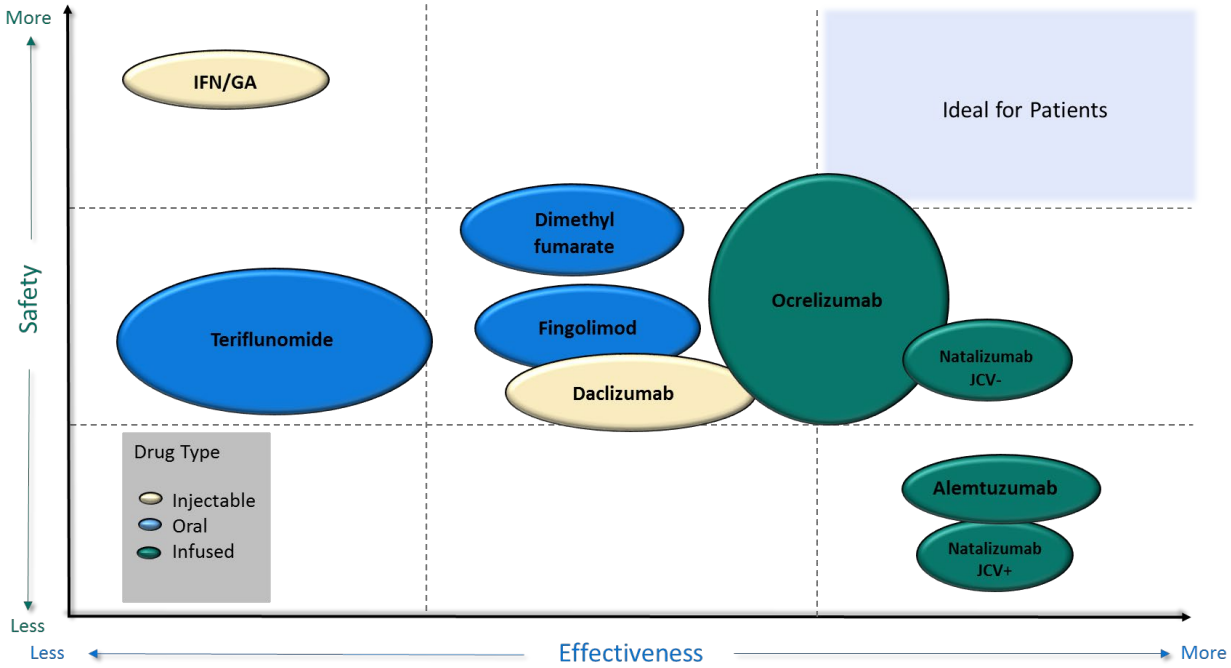
frequently and teriflunomide is taken orally. These differences be important for patients when choosing among different options, but the clinical differences in important outcomes are small. As such, we judged with high certaintly that these nine DMTs provide incremental net health benefits compared to placebo ("B").

Table 12. 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 qualitativiely 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 effectivenss 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 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 inteferons and glatiramer acetate is of greater interest to many stakeholders (Table 13). 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 is 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, the trials have not been published and 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 teriflunomide has comparable net health benefits to the interferons and glatiramer acetate.

Table 13. 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)	C+
Alemtuzumab (Lemtrada)	B+
Ocrelizumab (Ocrevus)	B+
Rituximab (Rituxan)	P/I

RRMS: Additional Key Comparisons

One of the specific comparisons we were asked to assess was the comparative effectiveness of interferon β-1a 44 mcg SC TIW (Rebif) to interferon β-1a 30 mcg IM once weekly (Avonex). In the NMA, Rebif had a significantly lower relapse rate than Avonex (RR 0.78, 95% CrI 0.67-0.90) and a non-significantly lower disability progression (RR 0.93, 95% CrI 0.65-1.30). 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). 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 (i.e., B+).

There are insufficient data to compare rituximab to ocrelizumab. The two drugs target the same molecule (CD20), but ocrelizumab is a fully-humanized monoclonal antibody, which is likely why it appears to 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. 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 disease progression sustained for at least 12 weeks, the primary endpoint of the trial, was significantly lower in the (HR 0.76, 95% CI 0.59 - 0.98, p=0.032) 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. The primary concern with the results is that they have not been published. We judge there to be moderate certainty of small to substantial net benefit, tempered primarily by increased uncertainty due to the preliminary nature of the data (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 14. 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)

The route of administration is important for patients with a choice of DMTs.[106,107] For many years, their only option was to 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.

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.

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 cost-effectiveness of various DMTs for patients with 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 amount of time, on average, patients spent in each health state, which were defined by EDSS category. Unadjusted and utility-adjusted time spent in each health state were summed 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, as glatiramer acetate is the most commonly used product and the generic version was the lowest priced version. Cost-effectiveness ratios were also calculated versus no DMT (i.e., best supportive care). 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 vs. no DMT / best supportive care
    - Costs per additional QALY vs. generic glatiramer acetate 20 mg
    - Costs per additional life-year vs. no DMT / best supportive care
    - Costs per additional life-year vs. generic glatiramer acetate 20 mg
    - Cost per relapse avoided vs. no DMT / best supportive care (RRMS model only)
    - Cost per relapse avoided vs. 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,[24] which has been widely used to describe MS progression in clinical trials.[108] 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.[109-116]

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 decribed 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 decribed above.

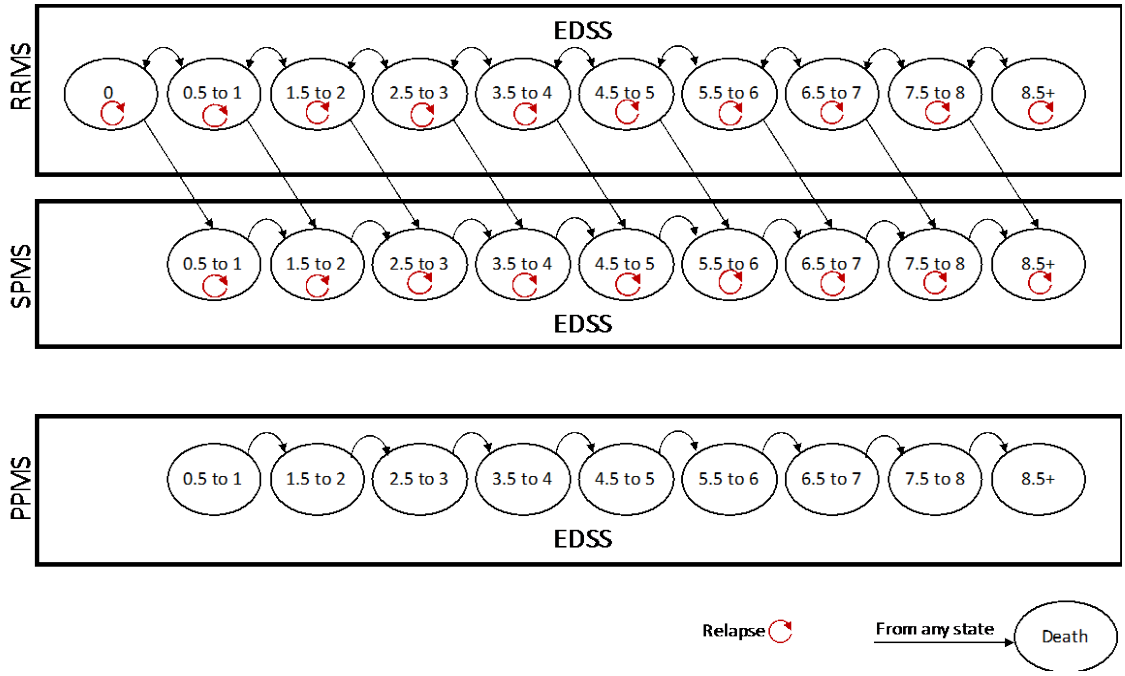
The RRMS model consisted of 20 health states: EDSS 0–9 for RRMS patients, EDSS 1–9 for SPMS patients, and death (Figure 6). At baseline, a cohort of patients was distributed among the 10 RRMS health states according to the expected distribution of newly diagnosed MS patients.[67,83,117-119] These patients 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.

The PPMS model consisted of 10 health states: EDSS 1-9 and death (Figure 6). As with the RRMS model, a cohort of patients was distributed among the 10 PPMS health states, patients transitioned 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. Costs were inflated to 2016 US dollars using the US consumer price index (CPI) for medical care.[120]

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).[121] The modeled population for PPMS had an assumed mean age at onset of disease of 42 years (range for SA 33-50).[122]

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, as there was insufficient evidence on disability progression to include it 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. The model was informed by several assumptions, which are represented in Table 15 along with the rationale for each assumption.

Table 15. 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.
The DMT discontinuation rate was constant for all DMTs and EDSS levels.	Trial discontinuation rates were not considered representative of real-world discontinuation rates, and there was insufficient observational data to inform different discontinuation rates for all DMTs.
Patients continued treatment after transitioning to SPMS states.	Current clinical opinion supports the continued use of treatment after transitioning to SPMS.
Patients receiving DMT therapy 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, and alemtuzumab. In the case that the first-line DMT was one of these three, the second line treatment was distributed equally over the remaining two.	These three DMTs are commonly used for second-line treatment in clinical practice.
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 slide deck[117].

Although there may be differences in discontinuation rates between DMTs, well documented and consistent data on these rates are not currently available. We chose not to use trial discontinuation rates because they were not deemed to be reflective of real-world rates and were subject to trial-specific, protocol-driven biases. Therefore, we assumed equal rates across DMTs, and assumed that patients discontinue initial DMTs at a rate of 10% per year for the first two years of treatment, then at a rate of 3% per year until they reached EDSS 7, at which point all patients discontinue.[123] After discontinuation, all patients transitioned to second line treatment or supportive care (see methods below).

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).[67,83,117-119] For the PPMS population, the initial distribution of EDSS states from the ORATORIO[117] 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[116] that used data from the DEFINE and CONFIRM clinical trial supplementary data, along with London, Ontario cohort data.[14,67,83] As there was not sufficient data available on PPMS transition probabilities, we assumed that PPMS transition probabilities were the same as SPMS transition probabilities.

ARRs in the absence of DMTs were based on an existing study[116] that extrapolated from observational data in Patzold and Pocklington (Appendix Table E8).[124] 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. For patients who experience relapses, 18.7% were assumed to be severe, with the remainder being mild/moderate in severity.[125] We assumed that PPMS patients did not experience relapses.

Background mortality rates were based on age-specific US life tables.[126] These were adjusted for MS-specific mortality using an EDSS-specific mortality multiplier calculated from Pokorski et al.[127] via the following equation, $Multiplier=0.0219*EDSS^3-0.1972*EDSS^2+0.6069*EDSS+1$, and are presented in Table 16.

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

EDSS State	Mortality Multiplier*[127]	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[116], and that used data from the DEFINE and CONFIRM trials for RRMS and a UK survey for SPMS (Table 17).[67,83,124] 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.[128] 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.[129]

Table 17. Utility Scores by Health State[116]

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. 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. Due to its severity, we also included PML, though only 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 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[130]
ALT increased	$284.30	2 specialist visits; 4 liver function tests	0	Mauskopf 2016[116]
Cholelithiasis	$4,476.85	DRG 446	0.005	Cook 1994[131]
Influenza	$5,687.24	DRG 194	0.016	Mauskopf 2016[116]
Serious infection	$11,176.56	DRG 177	0.005	Jakubowiak 2016[130]
Trigeminal neuralgia	$7,829.06	DRG 073	0.44	Tölle 2006[132]
Depression	$3,884.28	DRG 881	0.56	Mauskopf 2016[116]
PML	$23,444.88	ICD diagnosis code 046.3	0.4	Campbell 2013[133]

Economic Inputs

Drug Acquisition Costs

Each DMT was associated with an annual cost based on the wholesale acquisition cost (WAC), dosing, administration, and monitoring. For drug costs, we obtained 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. Data on the approved agents of interest were current through the third quarter of 2016.[134] 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[135] for each medication to arrive at an estimated net price. Average discounts applied to each drug are shown in Table 19.

For alemtuzumab, costs were applied as calculated for year 1 and year 2. For years 3-5, the year 2 cost was applied to 19%, 13%, 16%, and 9% of patients who received an additional course in that year.[119] As no price is available for ocrelizumab, the annual net price was assumed to be the average of the net price (including discount) for the two most recently approved monoclonal antibodies (alemtuzumab and daclizumab) plus 10%. For this calculation, a blended average of the year 1 and year 2 alemtuzumab cost was used. 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)	30mcg	$5,821.00 / 4EA	20%	$60,705	$60,705
Interferon β-1b 250 mcg (Betaseron)	300 mcg	$6,218.71 / 14EA	35%	$44,993	$43,910
Interferon β-1b 250 mcg (Extavia)	300 mcg	$5,558.21 / 15EA	35%	$37,533	$36,630
Glatiramer Acetate 20 mg (Copaxone)	20mg	$6,593.00 / 30EA	15%	$68,183	$68,183
Glatiramer Acetate 20 mg (Glatopa)	20mg	$5,193.92 / 30EA	35%	$41,075	$41,075
Glatiramer Acetate 40 mg (Copaxone)	40mg	$5,404.00 / 12EA	15%	$59,878	$59,878
Interferon β-1a 22/44 mcg (Rebif)	22/44 mcg	$6,283.57 / 0.5ml	15%	$66,153	$69,624
Peginterferon β-1a 125 mcg (Plegridy)	125mg	$5,821.00 / 1ml	10%	$65,715	$68,293
Daclizumab 150 mg (Zinbryta)	150mg	$6,833.33 / 1ml	5%	$77,900	$77,900
Fingolimod 0.5 mg (Gilenya)	0.5mg	$6743.26 / 30EA	10%	$73,839	$73,839
Teriflunomide 7/14 mg (Aubagio)	7/14 mg	$5,877.08 / 28EA	10%	$68,951	$68,951
Dimethyl Fumarate 240 mg (Tecfidera)	240mg	$6,315.00 / 60EA	10%	$69,149	$69,149
Natalizumab 20 mg (Tysabri)	20mg	$5,797.00 / 15ml	5%	$71,790	$71,790
Alemtuzumab 10 mg (Lemtrada)	10mg	$20,243.75 / 1.2ml	5%	$96,158	$57,695
Ocrelizumab 600 mg (Ocrevus) (RRMS and PPMS)	300mg	N/A	N/A	$85,154‡	$85,154‡

EA: each

*Redbook updated October 7, 2016

†Varied ± 20% in sensitivity analysis

‡Calculated as average of alemtuzumab and daclizumab plus 10%

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, and is expected to continue in perpetuity, we assumed no monitoring costs from the payer perspective for alemtuzumab.[119] Daclizumab has additional monitoring after the final dose, which was captured in the first year after discontinuation.

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.[136] 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 = 4,427.7*EDSS + 27,443; and indirect costs = 1,594.1*EDSS + 2,217.5.

Table 20. Annual costs per EDSS state

EDSS State	Annual Direct Costs (2016 $)[136]*	Annual Indirect Costs (2016 $)[136]*
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.[136], 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.[128] 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.[128]

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, and alemtuzumab, which are all commonly used as second-line agents.[137] These three DMTs were assumed to be equally distributed in the second line. In the case where one of natalizumab, fingolimod, or alemtuzumab was the first-line DMT, the second-line average was comprised of the remaining two. 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. 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).

Scenario Analyses

We conducted several scenario analyses, listed below:

1. Higher untreated ARR by EDSS states[116] (based on trial data, Appendix Table E7)
2. Lower untreated ARR by EDSS states[138] (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.

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 a 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[116,138-145]. 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 $346,000 for supportive care, and ranged from approximately $660,000 for alemtuzumab to $1.4 million for ocrelizumab. The projected number of relapses was 15.1 for supportive care, and ranged from 11.0 for alemtuzumab to 14.5 for interferon β-1a 30 mcg. Discounted life expectancy from age of DMT initiation (age 29 years for RRMS) was 21.2 years for supportive care, and ranged narrowly from 21.2 years for glatiramer acetate 40 mg to 22.5 years for alemtuzumab. Finally, projected discounted QALYs were 4.9 for supportive care, and ranged from 4.7 for glatiramer acetate 40 mg to 10.2 for alemtuzumab.

Among patients with PPMS, projected discounted costs, life-years, and QALYs for supportive care were approximately $260,000, 15.6 years, and 2.7 years, respectively, compared to approximately $750,000, 16.1 years, and 3.3 years for ocrelizumab.

Table 21. Results for Base-case Analysis

Drug	Cost	Relapses	Life-Years	QALYs
RRMS				
Glatiramer acetate 40 mg (Copaxone)	$847,211	12.5	21.2	4.7
Supportive Care	$346,212	15.1	21.2	4.9
Teriflunomide 7 mg (Aubagio)	$1,021,284	13.7	21.5	6.2
Interferon β-1a 22 mcg (Rebif)	$1,043,049	13.8	21.6	6.5
Interferon β-1a 30 mcg (Avonex)	$989,533	14.5	21.7	6.7
Teriflunomide 14 mg (Aubagio)	$1,082,080	13.4	21.8	7.2
Interferon β-1a 44 mcg (Rebif)	$1,088,217	13.5	21.8	7.3
Glatiramer acetate 20 mg (Copaxone)	$1,079,620	13.4	21.8	7.3
Glatiramer acetate 20 mg (Glatopa)	$831,341	13.4	21.8	7.3
Fingolimod (Gilenya)	$1,125,413	12.1	21.9	7.8
Interferon β-1b 250 mcg (Betaseron)	$881,383	13.7	21.9	7.8
Interferon β-1b 250 mcg (Extavia)	$810,836	13.7	21.9	7.8
Dimethyl fumarate (Tecfidera)	$1,116,280	12.4	21.9	7.9
Peginterferon β-1a (Plegridy)	$1,118,174	13.5	22.0	7.9
Daclizumab (Zinbryta)	$1,218,763	12.3	22.0	8.2
Natalizumab (Tysabri)	$1,185,451	11.1	22.1	8.8
Ocrelizumab (Ocrevus)*	$1,406,137	12.4	22.4	9.8
Alemtuzumab (Lemtrada)	$664,033	11.0	22.5	10.2
PPMS				
Supportive Care	$264,334	N/A	15.6	2.7
Ocrelizumab (Ocrevus)*	$751,097	N/A	16.1	3.3

*Using assumed price calculated as average of alemtuzumab and daclizumab plus 10%

Projected life-years and QALYs were lower for glatiramer acetate 40 mg than for supportive care because the relative risk for progression was greater than 1 (see NMA results above). Life-years and QALYs inversely correlated with relative risk for progression, as expected, with the exception of QALYs for interferon β-1b 250 mcg (Extavia) and dimethyl fumarate, though results were very similar. Although the relative risks for progression were similar between the two drugs, QALYs for interferon β-1b 250 mcg (Extavia) were slightly lower because it had a higher 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, fingolimod had fewer projected relapses than ocrelizumab despite having a higher rate ratio for relapses (0.47 vs. 0.43) because fingolimod had a higher relative risk for progression (0.67 vs. 0.44) and therefore more fingolimod 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 $60,000 per QALY for alemtuzumab to $518,000 for teriflunomide; costs per additional life-year ranged from approximately $624,000 per year for interferon β-1b 250 mcg (Extavia) to $1.9 million for teriflunomide; and costs per relapse avoided ranged from approximately $77,000 for alemtuzumab to $946,000 for interferon β-1a 30 mcg. Glatiramer acetate 40 mg was dominated for cost per additional QALY and cost per additional life-year, meaning it had higher costs and lower projected QALYs and life-years compared to supportive care.

For PPMS, ocrelizumab had a cost per additional QALY of approximately $854,000 and a cost per additional life year of approximately $1 million compared to supportive care. These higher figures are reflective, in part, of the large differences in projected cost between ocrelizumab and best supportive care.

Table 22. Pairwise Results for DMTs Compared to Supportive Care

Drug	Cost per Additional QALY	Cost per Additional Life-Year	Cost per Relapse Avoided
RRMS			
Glatiramer acetate 40 mg (Copaxone)	DOMINATED*	DOMINATED	$191,049
Teriflunomide 7 mg (Aubagio)	$517,764	$1,920,477	$482,101
Interferon β-1a 22 mcg (Rebif)	$432,633	$1,626,742	$508,612
Interferon β-1a 30 mcg (Avonex)	$352,949	$1,300,347	$946,187
Teriflunomide 14 mg (Aubagio)	$320,696	$1,259,173	$432,990
Interferon β-1a 44 mcg (Rebif)	$314,864	$1,229,920	$445,299
Glatiramer acetate 20 mg (Copaxone)	$308,808	$1,215,669	$421,467
Glatiramer acetate 20 mg (Glatopa)	$204,268	$804,132	$278,789
Fingolimod (Gilenya)	$270,066	$1,119,254	$253,402
Interferon β-1b 250 mcg (Betaseron)	$183,617	$718,215	$359,069
Interferon β-1b 250 mcg (Extavia)	$159,412	$623,539	$311,736
Dimethyl fumarate (Tecfidera)	$260,631	$1,063,912	$283,560
Peginterferon β-1a (Plegridy)	$256,255	$1,006,675	$478,512
Daclizumab (Zinbryta)	$270,373	$1,106,004	$302,209
Natalizumab (Tysabri)	$215,180	$900,185	$205,442
Ocrelizumab (Ocrevus)†	$217,385	$865,621	$380,162
Alemtuzumab (Lemtrada)	$60,209	$244,311	$76,655
PPMS			
Ocrelizumab (Ocrevus)†	$854,020	$1,012,599	N/A

*DOMINATED indicates the DMT had higher projected costs and worse projected health outcomes (fewer projected QALYs or life-years) compared to supportive care.
†Using assumed price calculated as average of alemtuzumab and daclizumab plus 10%

When compared to generic glatiramer acetate 20 mg, six DMTs were dominated for cost per additional QALY, cost per additional life-year, and cost per relapse avoided. This indicates that the DMT had higher projected costs and worse projected health outcomes (lower QALYs or life-years, or higher relapses). Among those DMTs with better health outcomes compared to generic glatiramer acetate 20 mg, costs per additional QALY ranged from approximately $93,000 per QALY for interferon β-1b 250 mcg (Betaseron) to approximately $576,000 per QALY for fingolimod; costs per additional life-year ranged from approximately $326,000 per year for interferon β-1b 250 mcg (Betaseron) to $3.2 million per life-year for fingolimod; and costs per relapse avoided ranged from approximately $18,000 for glatiramer acetate 40 mg to $548,000 for ocrelizumab. Both alemtuzumab and interferon β-1b 250 mcg (Extavia) were dominant for both cost per additional

QALY and cost per additional life-year, meaning that projected costs were lower and projected QALYs and life-years were higher than glatiramer acetate. Alemtuzumab was also dominant for cost per relapse avoided, indicating it had lower projected costs and fewer projected relapses. Interferon β-1b 250 mcg (Extavia) had lower projected costs compared to generic glatiramer acetate 20 mg, but also had more projected relapses. As branded and generic glatiramer acetate 20 mg were assumed to have equivalent effectiveness, the more expensive branded product was considered dominated by the generic.

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

Drug	Cost per Additional QALY	Cost per Additional Life-Year	Cost per Relapse Avoided
RRMS			
Glatiramer acetate 40 mg (Copaxone)	DOMINATED*	DOMINATED	$17,988
Teriflunomide 7 mg (Aubagio)	DOMINATED	DOMINATED	DOMINATED
Interferon β-1a 22 mcg (Rebif)	DOMINATED	DOMINATED	DOMINATED
Interferon β-1a 30 mcg (Avonex)	DOMINATED	DOMINATED	DOMINATED
Teriflunomide 14 mg (Aubagio)	DOMINATED	DOMINATED	DOMINATED
Interferon β-1a 44 mcg (Rebif)	DOMINATED	DOMINATED	DOMINATED
Glatiramer acetate 20 mg (Copaxone)	DOMINATED	DOMINATED	DOMINATED
Glatiramer acetate 20 mg (Glatopa)	--	--	--
Fingolimod (Gilenya)	$576,325	$3,166,043	$220,307
Interferon β-1b 250 mcg (Betaseron)	$92,731	$352,790	DOMINATED
Interferon β-1b 250 mcg (Extavia)	DOMINANT†	DOMINANT	Lower costs, more relapses
Dimethyl fumarate (Tecfidera)	$491,563	$2,364,400	$292,071
Peginterferon β-1a (Plegridy)	$449,924	$1,753,818	DOMINATED
Daclizumab (Zinbryta)	$454,588	$2,087,109	$337,736
Natalizumab (Tysabri)	$232,172	$1,076,321	$151,011
Ocrelizumab (Ocrevus)‡	$229,842	$925,341	$548,493
Alemtuzumab (Lemtrada)	DOMINANT	DOMINANT	DOMINANT
PPMS			
Ocrelizumab (Ocrevus)‡	N/A	N/A	N/A

*DOMINATED indicates the DMT had higher projected costs and worse projected health outcomes (fewer projected QALYs or life-years, more projected relapses) compared to glatiramer acetate 20 mg (Glatopa).
†DOMINANT indicates the DMT had lower projected costs and better projected health outcomes (more projected QALYs or life-years, fewer projected relapses) compared to glatiramer acetate 20 mg (Glatopa).
‡Using assumed price calculated as average of alemtuzumab and daclizumab plus 10%

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 that our projected life-years and QALYs were equivalent when using similar ages.

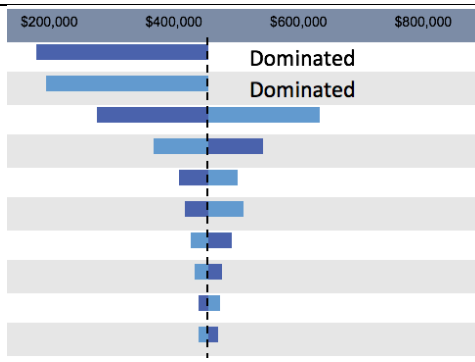
Sensitivity Analysis Results – One Way

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 illustrative examples, the impacts of varying each of the parameters in the model over ranges reflecting their uncertainty are shown in Figure 7 for both daclizumab and ocrelizumab compared to generic glatiramer acetate 20 mg for RRMS. For those DMTs that were either dominant or dominated by 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 and Ocrelizumab Compared to Generic Glatiramer Acetate 20 mg for RRMS

Cost per additional QALY

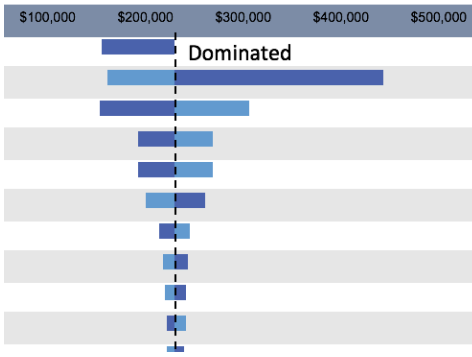
RRMS DAC vs GA 20 mg (Glatopa)



Parameter	Low Value	High Value
Relative Risk, Progression, DAC	0.40	0.88
Relative Risk, Progression, GA 20 mg (Glatopa)	0.54	0.93
WAC, DAC	5467	8200
WAC, GA 20 mg (Glatopa)	4155	6233
Discount from WAC, GA 20 mg (Glatopa)	0.28	0.42
Rate Ratio, Relapse, DAC	0.38	0.58
Rate Ratio, Relapse, GA 20 mg (Glatopa)	0.57	0.72
Annual Utiity, RRMS, EDSS 2	0.62	0.94
Age at beginning treatment, RRMS	23	35
Annual Utiity, RRMS, EDSS 0	0.70	1.05

Cost per additional QALY

RRMS OCR vs GA 20 mg (Glatopa)



Parameter	Low Value	High Value
Relative Risk, Progression, OCR	0.27	0.74
Relative Risk, Progression, GA 20 mg (Glatopa)	0.54	0.93
Annual Cost, OCR	68124	102185
WAC, DAC	5467	8200
WAC, ALE	16195	24293
WAC, GA 20 mg (Glatopa)	4155	6233
Discount from WAC, GA 20 mg (Glatopa)	0.28	0.42
Annual Utiity, RRMS, EDSS 2	0.62	0.94
Annual Utiity, RRMS, EDSS 0	0.70	1.05
Rate Ratio, Relapse, OCR	0.34	0.54

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 $174,427 to $544,389 when compared to supportive care and from $139,264 to dominated when compared to to generic glatiramer acetate 20 mg.

Sensitivity Analysis Results – Scenarios

Results from the scenario analyses can be found in Appendix Tables E17-E23. For the majority of pairwise comparisons, the scenario analyses did not yield major differences in conclusions from the base case. However, when using only 12-week NMA results, we note the following exceptions for the cost per QALY results: 1) fingolimod compared to generic glatiramer acetate 20 mg decreased from approximately $576,000 in the base case to approximately $120,000, 2) interferon β-1b 250 mcg (Betaseron) compared to generic glatiramer acetate 20 mg went from approximately $93,000 to dominated (higher cost with worse outcomes), and 3) interferon β-1b 250 mcg (Extavia) compared to generic glatiramer acetate 20 mg went from dominant to less costly and less effective. When using only 24-week NMA results, we note the following exceptions for the cost per QALY results: 1) interferon β-1a 22 mcg, interferon β-1b 250 mcg (Betaseron), and interferon β-1b 250 mcg (Extavia) compared to supportive care changed to being less than $150,000 per QALY; 2) interferon β-1a 22 mcg compared to generic glatiramer acetate 20 mg, decreased from dominated to $76,621. Including indirect costs (i.e., a societal perspective) did not influentially change results.

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 from a structural, population, perspective, and setting standpoint.

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.[146] 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 [7.9 QALYs] was greater than that of interferon β-1a 44 mcg and glatiramer acetate 20 mg [7.3 QALYs each]).

Another manufacturer-funded study by Mauskopf et al. (2016) compared dimethyl fumarate to glatiramer acetate 20 mg and fingolimod in RRMS patients.[147] Dimethyl fumarate dominated both comparators, with an incremental QALY gain of 0.45 and 0.359 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.[143,148-150] 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 (6.7), and interferon β-1b 250 mcg had the highest QALYs gained (7.8). 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 vs. interferon β-1a 30 mcg (in this case, 6.8 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.[145] While a societal perspective was employed in this model, productivity costs were not included under the

assumption that these effects were captured in the QALYs. 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 interferon beta-1a 30 mcg in ours. A minimal relative difference in QALYs was seen between fingolimod and teriflunomide, with lower QALYs gained for interferon β-1a 30 mcg and higher for dimethyl fumarate, similar to the pattern seen in our model.

6.5 Potential Budget Impact

We used the cost-effectiveness model to estimate the potential total budgetary 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). We also assessed the potential budgetary impact of ocrelizumab as the first agent likely to secure FDA approval in PPMS. In both cases, we assumed specific patterns of product uptake. 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 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 our assumed price, which we calculated as the average of the net prices for alemtuzumab and daclizumab plus a 10% mark-up. 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. 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.[151] 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. Briefly, our calculations assume that the utilization of new drugs occurs without any payer, provider group, or pharmacy benefit management controls in place, to provide an estimate of "unmanaged" drug uptake by five years after launch.

In general, we examine six characteristics of the drug or device and the marketplace to estimate "unmanaged" uptake. These characteristics are listed below:

- Magnitude of improvement in clinical safety and/or effectiveness
- Patient-level burden of illness
- Patient preference (ease of administration)
- Proportion of eligible patients currently being treated
- Primary care vs. specialty clinician prescribing/use
- Presence or emergence of competing treatments of equal or superior effectiveness

Based on our assessment of these criteria, we assign a new drug or device to one of four categories of unmanaged drug uptake patterns: 1) very high (75% uptake by year 5); 2) high (50% uptake by year 5); 3) intermediate (25% uptake by year 5); and 4) low (10% uptake by year 5). In this analysis, we assumed a 10% uptake for daclizumab and 25% uptake for ocrelizumab in the RRMS cohort. We assumed a lower uptake for daclizumab based on its relatively modest effectiveness, its likely use mainly in JC virus-positive patients (i.e., assuming that JC virus-negative patients would use natalizumab), and its potential displacement of only one other drug. Ocrelizumab uptake was assumed to be greater given its clinical performance and potential use in more segments of the market. We assumed a 50% uptake of ocrelizumab in the PPMS cohort, due to the current lack of any approved DMT for these patients as well as ocrelizumab's promising results in this population. We did not assume a higher uptake, however, given the potential for some off-label use of rituximab in PPMS and the possibility of approval of other compounds currently in development.

Using this approach to estimate potential budget impact, we then compared our estimates to a 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://www.icer-review.org/wp-content/uploads/2014/01/Slides-on-value-framework-for-national-webinar1.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. Calculations are performed as shown in Table 24.

For 2015-16, therefore, the five-year annualized potential budget impact threshold that should trigger policy actions to manage affordability is calculated to total approximately $904 million per year for new drugs.

Table 24. Calculation of Potential Budget Impact Threshold

Item	Parameter	Estimate	Source
1	Growth in US GDP, 2015-2016 (est.) +1%	3.75%	World Bank, 2015
2	Total health care spending ($)	$3.08 trillion	CMS NHE, 2014
3	Contribution of drug spending to total health care spending (%)	13.3%	CMS National Health Expenditures (NHE), Altarum Institute, 2014
4	Contribution of drug spending to total health care spending ($) (Row 2 x Row 3)	$410 billion	Calculation
5	Annual threshold for net health care cost growth for ALL new drugs (Row 1 x Row 4)	$15.4 billion	Calculation
6	Average annual number of new molecular entity approvals, 2013-2014	34	FDA, 2014
7	Annual threshold for average cost growth per individual new molecular entity (Row 5 ÷ Row 6)	$452 million	Calculation
8	Annual threshold for estimated potential budget impact for each individual new molecular entity (doubling of Row 7)	$904 million	Calculation

Potential Budget Impact Model: Results

Table 25 below presents the potential budget impact of one year and five years of utilization of each drug in the candidate population, assuming the uptake patterns previously described. Results are presented for both one-year and five-year time horizons.

Results from the potential budget impact model showed that in the first year, with the uptake pattern assumptions described above, daclizumab and ocrelizumab would be given to an estimated 8,218 and 20,545 RRMS patients, respectively, and ocrelizumab to 7,251 PPMS patients. Over the entire five-year time horizon, we estimate that "unmanaged" uptake in the RRMS cohort would lead to approximately 41,090 patients receiving daclizumab, and 102,725 patients receiving ocrelizumab. Over the five-year time horizon, an estimated 36,255 PPMS patients would receive ocrelizumab.

Across the five-year time horizon, the weighted potential budgetary impact (adjusted for differing periods of drug utilization and associated cost-offsets) is approximately $14,500 per RRMS patient taking daclizumab. Using our assumed price for ocrelizumab, the weighted potential budgetary impact is estimated to be approximately $36,600 per RRMS patient and approximately $208,400 for every PPMS patient taking ocrelizumab. Total potential budgetary impact of daclizumab over five years is approximately $594 million, with an average budget impact per year of approximately $118.8 million. For ocrelizumab, the total annualized potential budgetary impact for the RRMS population is approximately $752 million, but totals $1.5 billion for the PPMS population given the larger cost differences versus supportive care. The annualized budget impact of daclizumab is 13% of the budget impact threshold of $904 million, while the annualized budget impacts for ocrelizumab were 83% and 167% of this threshold for the RRMS and PPMS cohorts, respectively.

Table 25. Estimated Annualized Potential Budget Impact (BI) of Daclizumab and Ocrelizumab for Treatment of Multiple Sclerosis

Drug	Eligible Population	Analytic Horizon = 1 Year			Analytic Horizon = 5 Years		
		Number Treated	Annual BI per Patient*	Total BI (millions)	Number Treated	Weighted BI per Patient*	Annualized BI per year (millions)
RRMS							
Daclizumab	410,892	8,218	$4,520	$37.1	41,090	$14,454	$118.8
Ocrelizumab†	410,892	20,545	$13,225	$271.7	102,725	$36,625	$752.4
PPMS							
Ocrelizumab†	72,510	7,251	$85,582	$620.5	36,255	$208,436	$1,511.4

*Weighted budget impact calculated by subtracting cost offsets from drug costs for one-year horizon. 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.

†Using assumed price calculated as average of alemtuzumab and daclizumab plus 10%

6.5 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 net price 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 $60,000 for alemtuzumab, but exceeded the commonly-cited threshold of $150,000

per QALY for all other DMTs (range: $159,000 for Interferon β-1b 250 mcg [Extavia] to $518,000 for teriflunomide). Alemtuzumab provided the highest number of QALYs gained while costing less than all other treatments except supportive care. The two newest agents, daclizumab and ocrelizumab, produced estimates of approximately $270,000 and $217,000 per QALY gained, respectively (using our assumed price for ocrelizumab). Among patients with PPMS, ocrelizumab produced a cost per additional QALY of $854,000 and a cost per additional life year of approximately $1 million 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 dominated (i.e., more costly and less effective). Among those DMTs with better health outcomes compared to generic glatiramer acetate 20 mg, costs per additional QALY ranged from approximately $93,000 per QALY for interferon β-1b 250 mcg (Betaseron) to $576,000 per QALY for fingolimod. Both alemtuzumab and interferon β-1b 250 mcg (Extavia) were dominant, meaning that projected costs were lower and projected QALYs and life-years were higher than glatiramer acetate. The cost-effectiveness of daclizumab and ocrelizumab was estimated to be approximately $455,000 and $230,000 per QALY gained, respectively.

Our budget impact estimates for daclizumab and ocrelizumab suggest that their use in RRMS will not increase costs to a level that has the potential to strain health-system budgets, but that the expected brisk uptake of ocrelizumab in PPMS has the potential to generate $1.5 billion in incremental costs over supportive care each year, suggesting the need for policy interventions to manage these costs.

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 six key limitations of our analysis.

First, 24-week 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. Fifth, we were not able to identify consistent data sources for all DMTs on real-world discontinuation rates. Finally, the cost of ocrelizumab has not yet been released; we therefore calculated an annual cost for this DMT based on current price of recently approved MS drugs. If the true price differs substantially from our calculated price, our results will not reflect the true value of 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. Results for the two new agents of primary interest, daclizumab and ocrelizumab, suggested that, even at current best estimates for discounted prices, their estimated cost-effectiveness exceeds $200,000 per QALY regardless of comparator, or in the case of ocrelizumab, type of MS.

****

This is the first CTAF review of DMTs for MS.

References

1. Harrison DM. In the clinic. Multiple sclerosis. *Ann Intern Med.* 2014;160(7):ITC4-2-ITC4-18; quiz ITC14-16.
2. Niedziela N, Adamczyk-Sowa M, Pierzchala K. Epidemiology and clinical record of multiple sclerosis in selected countries: a systematic review. *The International journal of neuroscience.* 2014;124(5):322-330.
3. Ma VY, Chan L, Carruthers KJ. Incidence, prevalence, costs, and impact on disability of common conditions requiring rehabilitation in the United States: stroke, spinal cord injury, traumatic brain injury, multiple sclerosis, osteoarthritis, rheumatoid arthritis, limb loss, and back pain. *Arch Phys Med Rehabil.* 2014;95(5):986-995 e981.
4. Weinshenker BG, Bass B, Rice GP, et al. The natural history of multiple sclerosis: a geographically based study. I. Clinical course and disability. *Brain : a journal of neurology.* 1989;112 (Pt 1):133-146.
5. Goodin DS. The epidemiology of multiple sclerosis: insights to disease pathogenesis. *Handbook of clinical neurology.* 2014;122:231-266.
6. National Multiple Sclerosis Society. Primary progressive MS (PPMS). http://www.nationalmssociety.org/What-is-MS/Types-of-MS/Primary-progressive-MS. Accessed July 13, 2016.
7. FDA Grants Priority Review for Genentech's OCREVUS (Ocrelizumab) Biologic's License Application [press release]. June 27 2016.
8. Hawker K, O'Connor P, Freedman MS, et al. Rituximab in patients with primary progressive multiple sclerosis: results of a randomized double-blind placebo-controlled multicenter trial. *Annals of neurology.* 2009;66(4):460-471.
9. Poulos C, Kinter E, Yang JC, Bridges JF, Posner J, Reder AT. Patient Preferences for Injectable Treatments for Multiple Sclerosis in the United States: A Discrete-Choice Experiment. *The patient.* 2016;9(2):171-180.
10. Utz KS, Hoog J, Wentrup A, et al. Patient preferences for disease-modifying drugs in multiple sclerosis therapy: a choice-based conjoint analysis. *Therapeutic Advances in Neurological Disorders.* 2014;7(6):263-275.
11. Bermel RA, You X, Foulds P, et al. Predictors of long-term outcome in multiple sclerosis patients treated with interferon beta. *Annals of neurology.* 2013;73(1):95-103.
12. Bsteh G, Ehling R, Lutterotti A, et al. Long Term Clinical Prognostic Factors in Relapsing-Remitting Multiple Sclerosis: Insights from a 10-Year Observational Study. *PloS one.* 2016;11(7):e0158978.
13. Prosperini L, Gallo V, Petsas N, Borriello G, Pozzilli C. One-year MRI scan predicts clinical response to interferon beta in multiple sclerosis. *European journal of neurology.* 2009;16(11):1202-1209.
14. Scalfari A, Neuhaus A, Degenhardt A, et al. The natural history of multiple sclerosis: a geographically based study 10: relapses and long-term disability. *Brain : a journal of neurology.* 2010;133(Pt 7):1914-1929.
15. Tremlett H, Yousefi M, Devonshire V, Rieckmann P, Zhao Y. Impact of multiple sclerosis relapses on progression diminishes with time. *Neurology.* 2009;73(20):1616-1623.
16. von Gumberz J, Mahmoudi M, Young K, et al. Short-term MRI measurements as predictors of EDSS progression in relapsing-remitting multiple sclerosis: grey matter atrophy but not lesions are predictive in a real-life setting. *PeerJ.* 2016;4:e2442.

17. Dong-Si T, Gheuens S, Gangadharan A, et al. Predictors of survival and functional outcomes in natalizumab-associated progressive multifocal leukoencephalopathy. *J Neurovirol.* 2015;21(6):637-644.
18. Kappos L, Edan G, Freedman MS, et al. The 11-year long-term follow-up study from the randomized BENEFIT CIS trial. *Neurology.* 2016;87(10):978-987.
19. Freedman MS, Wolinsky JS, Wamil B, et al. Teriflunomide added to interferon-beta in relapsing multiple sclerosis: a randomized phase II trial. *Neurology.* 2012;78(23):1877-1885.
20. Goodman AD, Rossman H, Bar-Or A, et al. GLANCE: results of a phase 2, randomized, double-blind, placebo-controlled study. *Neurology.* 2009;72(9):806-812.
21. Lublin FD, Cofield SS, Cutter GR, et al. Randomized study combining interferon and glatiramer acetate in multiple sclerosis. *Annals of neurology.* 2013;73(3):327-340.
22. Rudick RA, Stuart WH, Calabresi PA, et al. Natalizumab plus interferon beta-1a for relapsing multiple sclerosis. *The New England journal of medicine.* 2006;354(9):911-923.
23. Wynn D, Kaufman M, Montalban X, et al. Daclizumab in active relapsing multiple sclerosis (CHOICE study): a phase 2, randomised, double-blind, placebo-controlled, add-on trial with interferon beta. *The Lancet Neurology.* 2010;9(4):381-390.
24. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology.* 1983;33(11):1444-1452.
25. Hoadley J, Cubanci J, Neuman T. *It Pays to Shop: Variation in Out-of-Piocket Costs for Medicare Part D Enrollees in 2016.* The Henry J. Kaiser Family Foundation; December 2015.
26. California Department of Health Care Services. Injections: Drug A-D Policy. 2015.
27. California Department of Health Care Services. Injections: Drugs N - R Policy. 2015.
28. Dangi-Garimella S. UnitedHealth's 2017 Formulary to Support Generic and Biosimilar Drugs. *American Journal of Managed Care.* September 23, 2016.
29. Aetna. Specialty Pharmacy Clinical Policy Bulletins Aetna Non-Medicare Prescription Drug Plan; Subject: Multiple Sclerosis. 2016; http://www.aetna.com/products/rxnonmedicare/data/2016/CNS/multiple_sclerosis.html. Accessed November 13, 2016.
30. Aetna. 2017 Aetna Drug Search for Value Five Tier Pharmacy Drug Guide. 2016; https://client.formularynavigator.com/Search.aspx?siteCode=0394671891. Accessed November 13, 2016.
31. Anthem. Drug list - Four (4) Tier Drug Plan. 2016; https://fm.formularynavigator.com/MemberPages/pdf/National4Tier-Official_6343_Full_1953.pdf. Accessed 2016, November 13.
32. Cigna. 2017 Value 3 Tier Drug List. 2016; http://www.cigna.com/prescription-drug-list?consumerID=cigna&indicator=nonIFP&pdlYearType=NY. Accessed November 13, 2016.
33. Humana. Provider Drug List Search (Rx5 Plus). 2016; http://apps.humana.com/UnsecuredDrugListSearch/Search.aspx. Accessed 2016, November 13.
34. UnitedHealthcare. 2016 Prescription Drug List. 2016; https://www.unitedhealthcareonline.com/ccmcontent/ProviderII/UHC/en-US/Assets/ProviderStaticFiles/ProviderStaticFilesPdf/Tools%20and%20Resources/Pharmacy%20Resources/UHC_Physician_PDL_Booklet_716_7.pdf. Accessed November 13, 2016.
35. Health Net. Pharmacy Information: 3-Tier with Specialty Drug List. 2016; https://www.healthnet.com/portal/provider/content/iwc/provider/unprotected/pharmacy_info/book/pharmacy_information.action. Accessed November 13, 2016.

36. Blue Shield of California. Blue Shield Standard Drug Formulary: January 2017. 2016; https://fm.formularynavigator.com/MemberPages/pdf/CommercialStandard2017_Closed_10143_BS%20CA%20Standard_2810.pdf. Accessed November 13, 2016.
37. Blue Shield of California. Specialty Drug List for Standard Drug Formulary. 2016; https://www.blueshieldca.com/bsca/documents/pharmacy/Specialty_Drugs_List_Standard_Formulary.pdf. Accessed November 13, 2016.
38. Humana. Glatopa (glatiramer acetate injection) Pharmacy Coverage Policy. 2016.
39. Anthem. Medical Policy: Daclizumab (Zinbryta). 2016; https://www11.anthem.com/ca/medicalpolicies/policies/mp_pw_c191086.htm. Accessed November 13, 2016.
40. Humana. Zinbryta (dazlicumab) Pharmacy Coverage Policy. 2016.
41. Anthem. Clinical UM Guideline: Natalizumab (Tysabri). 2016; https://www11.anthem.com/ca/medicalpolicies/guidelines/gl_pw_c178382.htm. Accessed 2016, November 13.
42. Cigna. Cigna Drug and Biologic Coverage Policy; Subject: Multiple Sclerosis Therapy. 2016; https://cignaforhcp.cigna.com/public/content/pdf/coveragePolicies/pharmacy/ph_1402_pharmacycoverageposition_multiple_sclerosis.pdf. Accessed November 13, 2016.
43. Health Net. Prior Authorization Protocol: CIMZIAR (certolizumab pegol), ENBRELR (etanercept), HUMIRAR (adalimumab), KINERETR (anakinra), SIMPONIR, SIMPONIR ARIATM (golimumab), STELARATM (ustekinumab), REMICADE (infliximab), COSENTYX (secukinumab), OTEZLA (apremilast), ORENCIA abatacept), ACTEMRA (tocilizumab), ENTYVIO (vedolizumab), TYSABRI (natalizumab). 2016.
44. Humana. Lemtrada (alemtuzumab) Pharmacy Coverage Policy.
45. UnitedHealthcare. Drug Policy: Lemtrada (alemtuzumab). 2016.
46. Anthem. Medical Policy: Rituximab (Rituxan). 2016; https://www11.anthem.com/ca/medicalpolicies/policies/mp_pw_c103932.htm. Accessed November 13, 2016.
47. Humana. Rituxan (rituximab) Pharmacy Coverage Policy. 2016.
48. UnitedHealthcare. Drug Policy: Rituxan (rituximab). 2016.
49. Neurology AAo. Evidence-based practice guideline: Disease-modifying Therapies for Multiple Sclerosis (Draft). 2016.
50. Canadian Agency for Drugs and Technologies in Health. *CADTH Therapeutic Review: Recommendations for Drug Therapies for Relapsing-Remitting Multiple Sclerosis.* Ottawa October 2013.
51. MS Coalition. The Use of Disease-Modifying Therapies in Multiple Sclerosis: Principles and Current Evidence. 2016.
52. National Institute for Health and Care Excellence (NICE). Managing multiple sclerosis. https://pathways.nice.org.uk/pathways/multiple-sclerosis#path=view%3A/pathways/multiple-sclerosis/managing-multiple-sclerosis.xml&content=view-node%3Anodes-disease-modifying-therapies. Accessed November 13, 2016.
53. Cook DJ, Mulrow CD, Haynes RB. Systematic reviews: synthesis of best evidence for clinical decisions. *Ann Intern Med.* 1997;126(5):376-380.
54. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med.* 2009;151(4):264-269, w264.
55. Agency for Healthcare Research and Quality. U.S. Preventive Services Task Force Procedure Manual. 2008.

56. Ollendorf DA, Pearson SD. An integrated evidence rating to frame comparative effectiveness assessments for decision makers. *Medical care.* 2010;48(6 Suppl):S145-152.
57. Bornstein MB, Miller A, Slagle S, et al. A pilot trial of Cop 1 in exacerbating-remitting multiple sclerosis. *The New England journal of medicine.* 1987;317(7):408-414.
58. Hauser S, Comi G, Hartung HP, et al. Efficacy and Safety of Ocrelizumab in Relapsing Multiple Sclerosis - Results of the Phase III Double-blind, Interferon beta-1a-controlled OPERA I and II Studies. Congress of the European Committee for Treatment and Research in Multiple Sclerosis; 2015; Barcelona, Spain.
59. Jacobs LD, Cookfair DL, Rudick RA, et al. Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis. The Multiple Sclerosis Collaborative Research Group (MSCRG). *Annals of neurology.* 1996;39(3):285-294.
60. Kappos L, Radue EW, O'Connor P, et al. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. *The New England journal of medicine.* 2010;362(5):387-401.
61. Polman CH, O'Connor PW, Havrdova E, et al. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. *The New England journal of medicine.* 2006;354(9):899-910.
62. Gold R, Giovannoni G, Selmaj K, et al. Daclizumab high-yield process in relapsing-remitting multiple sclerosis (SELECT): a randomised, double-blind, placebo-controlled trial. *Lancet (London, England).* 2013;381(9884):2167-2175.
63. Kappos L, Wiendl H, Selmaj K, et al. Daclizumab HYP versus Interferon Beta-1a in Relapsing Multiple Sclerosis. *The New England journal of medicine.* 2015;373(15):1418-1428.
64. Hauser SL, Waubant E, Arnold DL, et al. B-cell depletion with rituximab in relapsing-remitting multiple sclerosis. *The New England journal of medicine.* 2008;358(7):676-688.
65. Cohen JA, Barkhof F, Comi G, et al. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. *The New England journal of medicine.* 2010;362(5):402-415.
66. Vermersch P, Czlonkowska A, Grimaldi LM, et al. Teriflunomide versus subcutaneous interferon beta-1a in patients with relapsing multiple sclerosis: a randomised, controlled phase 3 trial. *Multiple sclerosis (Houndmills, Basingstoke, England).* 2014;20(6):705-716.
67. Fox RJ, Miller DH, Phillips JT, et al. Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis. *The New England journal of medicine.* 2012;367(12):1087-1097.
68. Cohen JA, Coles AJ, Arnold DL, et al. Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomised controlled phase 3 trial. *Lancet (London, England).* 2012;380(9856):1819-1828.
69. Coles AJ, Compston DA, Selmaj KW, et al. Alemtuzumab vs. interferon beta-1a in early multiple sclerosis. *The New England journal of medicine.* 2008;359(17):1786-1801.
70. Coles AJ, Twyman CL, Arnold DL, et al. Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial. *Lancet (London, England).* 2012;380(9856):1829-1839.
71. Fogarty E, Schmitz S, Tubridy N, Walsh C, Barry M. Comparative efficacy of disease-modifying therapies for patients with relapsing remitting multiple sclerosis: Systematic review and network meta-analysis. *Mult Scler Relat Disord.* 2016;9:23-30.
72. Tolley K, Hutchinson M, You X, et al. A Network Meta-Analysis of Efficacy and Evaluation of Safety of Subcutaneous Pegylated Interferon Beta-1a versus Other Injectable Therapies for the Treatment of Relapsing-Remitting Multiple Sclerosis. *PloS one.* 2015;10(6):e0127960.
73. Tramacere I, Del Giovane C, Salanti G, D'Amico R, Filippini G. Immunomodulators and immunosuppressants for relapsing-remitting multiple sclerosis: a network meta-analysis. *The Cochrane database of systematic reviews.* 2015;9:Cd011381.

74. Tran K, Milev S, Jabr MF, et al. Comparative Clinical and Cost-Effectiveness of Drug Therapies for Relapsing-Remitting Multiple Sclerosis. *Comparative Clinical and Cost-Effectiveness of Drug Therapies for Relapsing-Remitting Multiple Sclerosis*. Ottawa (ON)2013.
75. Montalban X, Hemmer B, Rammohan KW, et al. Efficacy and Safety of Ocrelizumab in Primary Progress Multiple Sclerosis - Results of the Phase III Double-blind, Placebo-controlled ORATORIO Study. Congress of the European Committee for Treatment and Research in Multiple Sclerosis; 2015; Barcelona, Spain.
76. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. I. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. The IFNB Multiple Sclerosis Study Group. *Neurology.* 1993;43(4):655-661.
77. Johnson KP, Brooks BR, Cohen JA, et al. Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis: results of a phase III multicenter, double-blind placebo-controlled trial. The Copolymer 1 Multiple Sclerosis Study Group. *Neurology.* 1995;45(7):1268-1276.
78. Randomised double-blind placebo-controlled study of interferon beta-1a in relapsing/remitting multiple sclerosis. PRISMS (Prevention of Relapses and Disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis) Study Group. *Lancet (London, England).* 1998;352(9139):1498-1504.
79. Evidence of interferon beta-1a dose response in relapsing-remitting MS: the OWIMS Study. The Once Weekly Interferon for MS Study Group. *Neurology.* 1999;53(4):679-686.
80. Calabresi PA, Radue EW, Goodin D, et al. Safety and efficacy of fingolimod in patients with relapsing-remitting multiple sclerosis (FREEDOMS II): a double-blind, randomised, placebo-controlled, phase 3 trial. *The Lancet Neurology.* 2014;13(6):545-556.
81. Confavreux C, O'Connor P, Comi G, et al. Oral teriflunomide for patients with relapsing multiple sclerosis (TOWER): a randomised, double-blind, placebo-controlled, phase 3 trial. *The Lancet Neurology.* 2014;13(3):247-256.
82. De Stefano N, Curtin F, Stubinski B, et al. Rapid benefits of a new formulation of subcutaneous interferon beta-1a in relapsing-remitting multiple sclerosis. *Multiple sclerosis (Houndmills, Basingstoke, England).* 2010;16(7):888-892.
83. Gold R, Kappos L, Arnold DL, et al. Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis. *The New England journal of medicine.* 2012;367(12):1098-1107.
84. O'Connor P, Wolinsky JS, Confavreux C, et al. Randomized trial of oral teriflunomide for relapsing multiple sclerosis. *The New England journal of medicine.* 2011;365(14):1293-1303.
85. Vollmer TL, Sorensen PS, Selmaj K, et al. A randomized placebo-controlled phase III trial of oral laquinimod for multiple sclerosis. *J Neurol.* 2014;261(4):773-783.
86. Inusah S, Sormani MP, Cofield SS, et al. Assessing changes in relapse rates in multiple sclerosis. *Multiple sclerosis (Houndmills, Basingstoke, England).* 2010;16(12):1414-1421.
87. Nicholas R, Straube S, Schmidli H, Pfeiffer S, Friede T. Time-patterns of annualized relapse rates in randomized placebo-controlled clinical trials in relapsing multiple sclerosis: a systematic review and meta-analysis. *Multiple sclerosis (Houndmills, Basingstoke, England).* 2012;18(9):1290-1296.
88. Steinvorth SM, Rover C, Schneider S, Nicholas R, Straube S, Friede T. Explaining temporal trends in annualised relapse rates in placebo groups of randomised controlled trials in relapsing multiple sclerosis: systematic review and meta-regression. *Multiple sclerosis (Houndmills, Basingstoke, England).* 2013;19(12):1580-1586.

89. Stellmann JP, Neuhaus A, Herich L, et al. Placebo cohorts in phase-3 MS treatment trials - predictors for on-trial disease activity 1990-2010 based on a meta-analysis and individual case data. *PloS one.* 2012;7(11):e50347.
90. Kappos L, Li D, Calabresi PA, et al. Ocrelizumab in relapsing-remitting multiple sclerosis: a phase 2, randomised, placebo-controlled, multicentre trial. *Lancet (London, England).* 2011;378(9805):1779-1787.
91. O'Connor PW, Li D, Freedman MS, et al. A Phase II study of the safety and efficacy of teriflunomide in multiple sclerosis with relapses. *Neurology.* 2006;66(6):894-900.
92. European Medicines Agency. Guideline on clinical investigation of medicinal products for the treatment of Multiple Sclerosis, Rev. 2.26. 2015. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/03/WC500185161.pdf. Accessed November 2, 2016.
93. Khan O, Rieckmann P, Boyko A, Selmaj K, Zivadinov R. Three times weekly glatiramer acetate in relapsing-remitting multiple sclerosis. *Annals of neurology.* 2013;73(6):705-713.
94. Khan O, Rieckmann P, Boyko A, et al. Efficacy and safety of a three-times-weekly dosing regimen of glatiramer acetate in relapsing-remitting multiple sclerosis patients: 3-year results of the Glatiramer Acetate Low-Frequency Administration open-label extension study. *Multiple sclerosis (Houndmills, Basingstoke, England).* 2016.
95. Sormani MP, Bonzano L, Roccatagliata L, Cutter GR, Mancardi GL, Bruzzi P. Magnetic resonance imaging as a potential surrogate for relapses in multiple sclerosis: a meta-analytic approach. *Annals of neurology.* 2009;65(3):268-275.
96. Sormani MP, Bruzzi P. MRI lesions as a surrogate for relapses in multiple sclerosis: a meta-analysis of randomised trials. *The Lancet Neurology.* 2013;12(7):669-676.
97. Goodin DS, Traboulsee A, Knappertz V, et al. Relationship between early clinical characteristics and long term disability outcomes: 16 year cohort study (follow-up) of the pivotal interferon beta-1b trial in multiple sclerosis. *Journal of neurology, neurosurgery, and psychiatry.* 2012;83(3):282-287.
98. Rudick RA, Miller D, Hass S, et al. Health-related quality of life in multiple sclerosis: effects of natalizumab. *Annals of neurology.* 2007;62(4):335-346.
99. Zivadinov R, Zorzon M, Tommasi MA, et al. A longitudinal study of quality of life and side effects in patients with multiple sclerosis treated with interferon beta-1a. *Journal of the neurological sciences.* 2003;216(1):113-118.
100. Willis MD, Harding KE, Pickersgill TP, et al. Alemtuzumab for multiple sclerosis: Long term follow-up in a multi-centre cohort. *Multiple sclerosis (Houndmills, Basingstoke, England).* 2016;22(9):1215-1223.
101. Bloomgren G, Richman S, Hotermans C, et al. Risk of natalizumab-associated progressive multifocal leukoencephalopathy. *The New England journal of medicine.* 2012;366(20):1870-1880.
102. Cohen JA, Khatri B, Barkhof F, et al. Long-term (up to 4.5 years) treatment with fingolimod in multiple sclerosis: results from the extension of the randomised TRANSFORMS study. *Journal of neurology, neurosurgery, and psychiatry.* 2016;87(5):468-475.
103. Rover C, Nicholas R, Straube S, Friede T. Changing EDSS Progression in Placebo Cohorts in Relapsing MS: A Systematic Review and Meta-Regression. *PloS one.* 2015;10(9):e0137052.
104. Cofield SS, Lublin F, Cutter G, Gustafson T, Wolinsky JS. Functional System Changes Associated with Relapse: The CombiRx Experience *Neurology.* 2015;84(14):285.

105. Meyer-Moock S, Feng YS, Maeurer M, Dippel FW, Kohlmann T. Systematic literature review and validity evaluation of the Expanded Disability Status Scale (EDSS) and the Multiple Sclerosis Functional Composite (MSFC) in patients with multiple sclerosis. *BMC neurology.* 2014;14:58.
106. Ridyard CH, Dawoud DM, Tuersley LV, Hughes DA. A Systematic Review of Patients' Perspectives on the Subcutaneous Route of Medication Administration. *The patient.* 2016.
107. Ting J, Liu Y, Petrillo J, Giannattasio G, Sabatella G. Treatment Satisfaction With Disease Modifying Therapies In Multiple Sclerosis: A Systematic Review of Studies Using The Treatment Satisfaction Questionnaire For Medication (Tsqm). *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research.* 2015;18(7):A760-761.
108. Sormani MP, Bonzano L, Roccatagliata L, Mancardi GL, Uccelli A, Bruzzi P. Surrogate endpoints for EDSS worsening in multiple sclerosis. A meta-analytic approach. *Neurology.* 2010;75(4):302-309.
109. Chevalier J, Chamoux C, Hammes F, Chicoye A. Cost-Effectiveness of Treatments for Relapsing Remitting Multiple Sclerosis: A French Societal Perspective. *PloS one.* 2016;11(3):e0150703.
110. Chilcott J, McCabe C, Tappenden P, et al. Modelling the cost effectiveness of interferon beta and glatiramer acetate in the management of multiple sclerosis. *British Medical Journal (England).* 2003;326:522-525.
111. National Institute for Health and Care Excellence. Dimethyl fumarate for relapsing-remitting multiple sclerosis. 2014.
112. Gani R, Giovannoni G, Bates D, Kemball B, Hughes S, Kerrigan J. Cost-effectiveness analyses of natalizumab (Tysabri) compared with other disease-modifying therapies for people with highly active relapsing-remitting multiple sclerosis in the UK. *PharmacoEconomics.* 2008;26:617-627.
113. Maruszczak MJ, Montgomery SM, Griffiths MJ, Bergvall N, Adlard N. Cost-utility of fingolimod compared with dimethyl fumarate in highly active relapsing-remitting multiple sclerosis (RRMS) in England. *J Med Econ.* 2015;18(11):874-885.
114. Su W, Kansal A, Vicente C, Deniz B, Sarda S. The cost-effectiveness of delayed-release dimethyl fumarate for the treatment of relapsing-remitting multiple sclerosis in Canada. *J Med Econ.* 2016;19(7):718-727.
115. Tappenden P, McCabe C, Chilcott J, et al. Cost-effectiveness of disease-modifying therapies in the management of multiple sclerosis for the Medicare population. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research.* 2009;12(5):657-665.
116. Mauskopf J, Fay M, Iyer R, Sarda S, Livingston T. Cost-effectiveness of delayed-release dimethyl fumarate for the treatment of relapsing forms of multiple sclerosis in the United States. *Journal of Medical Economics.* 2016;6998:1-11.
117. Genentech I. Data on File.
118. Sanofi Genzyme. Teriflunomide US adaptation for AMCP dossiers.
119. Sanofi Genzyme. Data on File.
120. United States Bureau of Labor Statistics. Consumer Price Index - All Urban Consumers. 2016; http://data.bls.gov/timeseries/CUUR0000SAM?output_view=pct_12mths. Accessed August 20, 2016.
121. Palace J, Bregenzer T, Tremlett H, et al. UK multiple sclerosis risk-sharing scheme: a new natural history dataset and an improved Markov model. *BMJ open.* 2014;4(1):e004073.
122. Koch M, Kingwell E, Rieckmann P, Tremlett H. The natural history of primary progressive multiple sclerosis. *Neurology.* 2009;73(23):1996-2002.

123. Tappenden P, McCabe C, Chilcott J, et al. Cost-effectiveness of disease-modifying therapies in the management of multiple sclerosis for the medicare population. *Value in Health.* 2009;12:657-665.
124. Patzold U, Pocklington PR. Course of multiple sclerosis. First results of a prospective study carried out of 102 MS patients from 1976-1980. *Acta neurologica Scandinavica.* 1982;65(4):248-266.
125. Nickerson M, Cofield SS, Tyry T, Salter AR, Cutter GR, Marrie RA. Impact of multiple sclerosis relapse: The NARCOMS participant perspective. *Mult Scler Relat Disord.* 2015;4(3):234-240.
126. CDC/NCHS National Vital Statistics System. Life table for the total population: United States, 2011.
127. Pokorski RJ. Long-term survival experience of patients with multiple sclerosis. *Journal of insurance medicine (New York, NY).* 1997;29(2):101-106.
128. Oleen-Burkey M, Castelli-Haley J, Lage MJ, Johnson KP. Burden of a Multiple Sclerosis Relapse. *The Patient - Patient-Centered Outcomes Research.* 2012;5(1):57-69.
129. Patrick DL, Starks HE, Cain KC, Uhlmann RF, Pearlman RA. Measuring preferences for health states worse than death. *Medical decision making : an international journal of the Society for Medical Decision Making.* 1994;14(1):9-18.
130. Jakubowiak AJ, Campioni M, Benedict A, et al. Cost-effectiveness of adding carfilzomib to lenalidomide and dexamethasone in relapsed multiple myeloma from a US Perspective. *J Med Econ.* 2016:1-44.
131. Cook J, Richardson J, Street A. A cost utility analysis of treatment options for gallstone disease: Methodological issues and results. *Health Economics.* 1994;3(3):157-168.
132. Tolle T, Dukes E, Sadosky A. Patient burden of trigeminal neuralgia: results from a cross-sectional survey of health state impairment and treatment patterns in six European countries. *Pain practice : the official journal of World Institute of Pain.* 2006;6(3):153-160.
133. Campbell JD, McQueen RB, Miravalle A, Corboy JR, Vollmer TL, Nair K. Comparative effectiveness of early natalizumab treatment in JC virus-negative relapsing-remitting multiple sclerosis. *The American journal of managed care.* 2013;19:278-285.
134. US Brand Rx Net Price (access restricted document). 2016. Accessed November 4.
135. Truven Health Analytics. Redbook Online (online database). 2016.
136. Kobelt G, Berg J, Atherly D, Hadjimichael O. Costs and quality of life in multiple sclerosis: A cross-sectional study in the United States. *Neurology.* 2006;66:1696-1702.
137. Gajofatto A, Benedetti MD. Treatment strategies for multiple sclerosis: When to start, when to change, when to stop? *World Journal of Clinical Cases : WJCC.* 2015;3(7):545-555.
138. Hernandez L, Guo S, Kinter E, Fay M. Cost-effectiveness analysis of peginterferon beta-1a compared with interferon beta-1a and glatiramer acetate in the treatment of relapsing-remitting multiple sclerosis in the United States. *Journal of Medical Economics.* 2016;19(7):684-695.
139. Chevalier J, Chamoux C, Hammès F, Chicoye A. Cost-Effectiveness of Treatments for Relapsing Remitting Multiple Sclerosis: A French Societal Perspective. *PloS one.* 2016;11:e0150703.
140. Lee S, Baxter DC, Limone B, Roberts MS, Coleman CI. Cost-effectiveness of fingolimod versus interferon beta-1a for relapsing remitting multiple sclerosis in the United States. *Journal of medical economics.* 2012;15:1088-1096.
141. Maruszczak MJ, Montgomery SM, Griffiths MJS, Bergvall N, Adlard N. Cost-utility of fingolimod compared with dimethyl fumarate in highly active relapsing-remitting multiple sclerosis (RRMS) in England. *Journal of Medical Economics.* 2015;6998:1-24.

142. National Institute for Health and Care Excellence. *Dimethyl fumarate for treating relapsing-remitting multiple sclerosis.* 2013.
143. Noyes K, Bajorska A, Chappel A, et al. Cost-effectiveness of disease-modifying therapy for multiple sclerosis: a population-based study. *Neurology.* 2011;77(4):355-363.
144. Su W, Kansal A, Vicente C, Deniz B, Sarda S. The cost-effectiveness of delayed-release dimethyl fumarate for the treatment of relapsing-remitting multiple sclerosis in Canada. *Journal of Medical Economics.* 2016:1-10.
145. Zhang X, Hay JW, Niu X. Cost effectiveness of fingolimod, teriflunomide, dimethyl fumarate and intramuscular interferon-β1a in relapsing-remitting multiple sclerosis. *CNS drugs.* 2015;29:71-81.
146. Hernandez L, Guo S, Kinter E, Fay M. Cost-effectiveness analysis of peginterferon beta-1a compared with interferon beta-1a and glatiramer acetate in the treatment of relapsing-remitting multiple sclerosis in the United States. *Journal of medical economics.* 2016;19(7):684-695.
147. Mauskopf J, Fay M, Iyer R, Sarda S, Livingston T. Cost-effectiveness of delayed-release dimethyl fumarate for the treatment of relapsing forms of multiple sclerosis in the United States. *Journal of medical economics.* 2016;19(4):432-442.
148. Minden S, Hoaglin D, Jureidini S, et al. Disease-modifying agents in the Sonya Slifka Longitudinal Multiple Sclerosis Study. *Multiple sclerosis (Houndmills, Basingstoke, England).* 2008;14(5):640-655.
149. Minden SL, Frankel D, Hadden L, Perloffp J, Srinath KP, Hoaglin DC. The Sonya Slifka Longitudinal Multiple Sclerosis Study: methods and sample characteristics. *Multiple sclerosis (Houndmills, Basingstoke, England).* 2006;12(1):24-38.
150. Minden SL, Frankel D, Hadden LS, Srinath KP, Perloff JN. Disability in elderly people with multiple sclerosis: An analysis of baseline data from the Sonya Slifka Longitudinal Multiple Sclerosis Study. *NeuroRehabilitation.* 2004;19(1):55-67.
151. Dilokthornsakul P, Valuck RJ, Nair KV, Corboy JR, Allen RR, Campbell JD. Multiple sclerosis prevalence in the United States commercially insured population. *Neurology.* 2016;86(11):1014-1021.
152. Agency for Healthcare Research and Quality. *U.S. Preventive Services Task Force Procedure Manual.* 2008.
153. Calabrese M, Bernardi V, Atzori M, et al. Effect of disease-modifying drugs on cortical lesions and atrophy in relapsing-remitting multiple sclerosis. *Multiple sclerosis (Houndmills, Basingstoke, England).* 2012;18(4):418-424.
154. Durelli L, Verdun E, Barbero P, et al. Every-other-day interferon beta-1b versus once-weekly interferon beta-1a for multiple sclerosis: results of a 2-year prospective randomised multicentre study (INCOMIN). *Lancet (London, England).* 2002;359(9316):1453-1460.
155. Etemadifar M, Janghorbani M, Shaygannejad V. Comparison of Betaferon, Avonex, and Rebif in treatment of relapsing-remitting multiple sclerosis. *Acta neurologica Scandinavica.* 2006;113(5):283-287.
156. Cadavid D, Wolansky LJ, Skurnick J, et al. Efficacy of treatment of MS with IFNbeta-1b or glatiramer acetate by monthly brain MRI in the BECOME study. *Neurology.* 2009;72(23):1976-1983.
157. O'Connor P, Filippi M, Arnason B, et al. 250 microg or 500 microg interferon beta-1b versus 20 mg glatiramer acetate in relapsing-remitting multiple sclerosis: a prospective, randomised, multicentre study. *The Lancet Neurology.* 2009;8(10):889-897.

158. Comi G, Filippi M, Wolinsky JS. European/Canadian multicenter, double-blind, randomized, placebo-controlled study of the effects of glatiramer acetate on magnetic resonance imaging--measured disease activity and burden in patients with relapsing multiple sclerosis. European/Canadian Glatiramer Acetate Study Group. *Annals of neurology.* 2001;49(3):290-297.
159. Panitch H, Goodin DS, Francis G, et al. Randomized, comparative study of interferon beta-1a treatment regimens in MS: The EVIDENCE Trial. *Neurology.* 2002;59(10):1496-1506.
160. Mikol DD, Barkhof F, Chang P, et al. Comparison of subcutaneous interferon beta-1a with glatiramer acetate in patients with relapsing multiple sclerosis (the REbif vs Glatiramer Acetate in Relapsing MS Disease [REGARD] study): a multicentre, randomised, parallel, open-label trial. *The Lancet Neurology.* 2008;7(10):903-914.
161. Calabresi PA, Kieseier BC, Arnold DL, et al. Pegylated interferon beta-1a for relapsing-remitting multiple sclerosis (ADVANCE): a randomised, phase 3, double-blind study. *The Lancet Neurology.* 2014;13(7):657-665.
162. Saida T, Kikuchi S, Itoyama Y, et al. A randomized, controlled trial of fingolimod (FTY720) in Japanese patients with multiple sclerosis. *Multiple sclerosis (Houndmills, Basingstoke, England).* 2012;18(9):1269-1277.
163. Brown S, Hutton B, Clifford T, et al. A Microsoft-Excel-based tool for running and critically appraising network meta-analyses—an overview and application of NetMetaXL. *Systematic Reviews.* 2014;3(1):110.
164. Center for Medicare and Medicaid Services. 2016 National Physician Fee Schedule Relative Value File January Release. 2016.
165. Center for Medicare and Medicaid Services. 2016 Clinical Diagnostic Laboratory Fee Schedule 2016.
166. Abbvie. Data on File.

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.

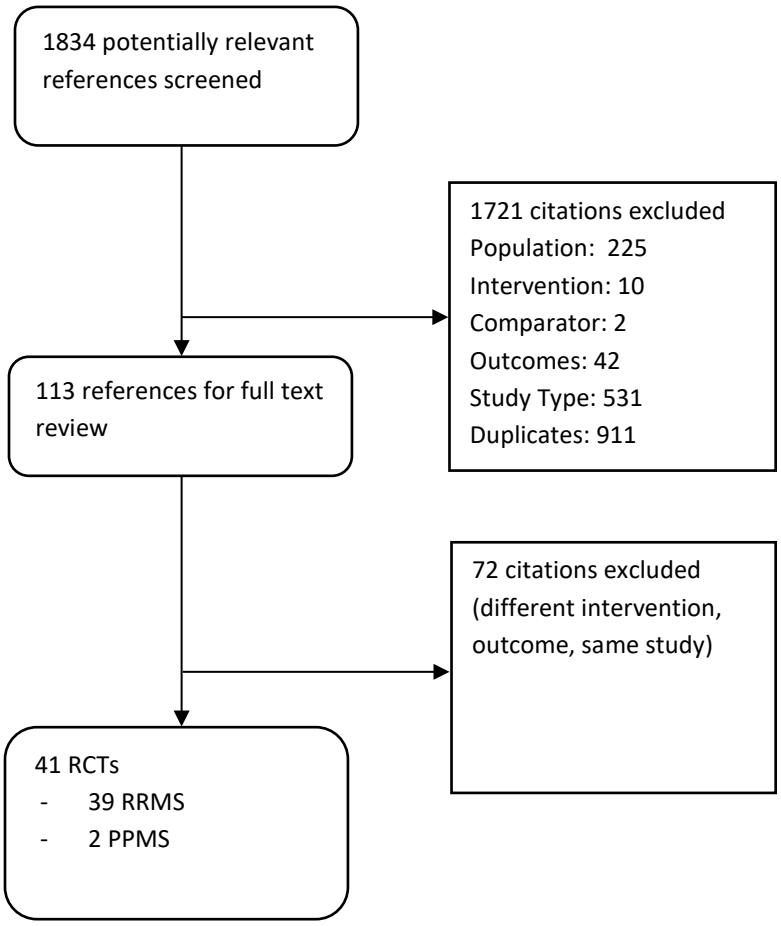
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.
Risk of bias across studies	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 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 monhts 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, adrenocorticotriopic 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 300 mg IFN B-1a (Rebif) 22 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 300 mg IFN B-1a (Rebif) 22 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 300 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
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)[152] 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 (months)	MS Definition	Prior Treatment
Interferon β-1a 30 mcg (Avonex)						
Jacobs 1996[59]	-	IFN β-1a 30 mcg IM Q week Placebo IM Q week	158 143	24	Poser	No
Calabrese 2012[153]	-	IFN β-1a 30 mcg IM Q week IFN β-1a 44 mcg SC TIW Glatiramer 20 mg SC QD	55 55 55	24	McDonald	Mixed
Lublin 2013[21]	CombiRx	IFN β-1a 30 mcg IM Q week Glatiramer 20 mg SC QD	250 259	36	McDonald	No
Vollmer 2014[85]	BRAVO	IFNβ-1a 30 mcg IM Q week Placebo IM Q week	447 450	24	McDonald	Mixed
Interferon β-1b 250 mcg (Betaseron)						
IFNβ Multiple Sclerosis Study Group 1993[76]	-	IFN β-1b 250 SC mcg QOD Placebo	124 123	24	Poser	No
Durelli 2002[154]	INCOMIN	IFN β-1b 250 SC mcg QOD IFN β-1a 30 mcg IM Q week	96 92	24	Poser	No
Etemadifar 2006[155]	-	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	24	Poser	No
Cadavid 2009[156]	BECOME	IFN β-1b 250 SC mcg QOD Glatiramer 20 mg SC QD	36 39	24	McDonald	No
O'Connor 2009[157]	BEYOND	IFN β-1b 250 SC mcg QOD Glatiramer 20 mg SC QD	897 448	24+	McDonald	No
Glatiramer Acetate (Copaxone)						
Bornstein 1987[57]	-	Glatiramer 20 mg SC QD Placebo SC QD	25 23	24	Poser	No
Johnson 1995[77]	-	Glatiramer 20 mg SC QD Placebo SC QD	125 126	24	Poser	Mixed
Comi 2001[158]	-	Glatiramer 20 mg SC QD Placebo SC QD	119 120	9	Poser	Mixed

Reference	Study	Group*	N	F/U (months)	MS Definition	Prior Treatment
Khan 2013[93]	GALA	Glatiramer 40 mg SC TIW Placebo SC QD	943 461	12	McDonald	Mixed
Interferon β-1a 22/44 mcg (Rebif)						
PRISMS 1998[78]	PRISMS	IFN β-1a 22 mcg SC TIW IFN β-1a 44 mcg SC TIW Placebo SC TIW	189 184 187	24	Poser	Mixed
OWIMS 1999[79]	OWIMS	IFN β-1a 22 mcg SC TIW IFN β-1a 44 mcg SC TIW Placebo SC TIW	95 98 100	11	Poser	No
Panitch 2002[159]	EVIDENCE	IFN β-1a 44 mcg SC TIW IFN β-1a 30 mcg IM Q week	339 338	6	Poser	Mixed
Mikol 2008[160]	REGARD	IFN β-1a 44 mcg SC TIW Glatiramer 20 mg SC QD	386 378	22	McDonald	No
De Stefano 2010[82]	IMPROVE	IFN β-1a 44 mcg SC TIW Placebo SC TIW	120 60	4	McDonald	Unclear
Peginterferon β-1a (Plegridy)						
Calabresi 2014[161]	ADVANCE	PEG β-1a 125 mcg SC Q 14 d Placebo SC Q 14 d	512 500	11	McDonald	Mixed
Fingolimod (Gilenya)						
Cohen 2010[65]	TRANSFORMS	Fingolimod 0.5 mg PO QD IFN β-1a 30 mcg IM Q week	429 431	12	McDonald	Mixed
Kappos 2010[60]	FREEDOMS	Fingolimod 0.5 mg PO QD Placebo PO QD	425 418	24	McDonald	Mixed
Saida 2012[162]	-	Fingolimod 0.5 mg PO QD Placebo PO QD	57 57	6	McDonald	Mixed
Calabresi 2014[80]	FREEDOMS II	Fingolimod 0.5 mg PO QD Placebo PO QD	358 355	24	McDonald	Mixed

Reference	Study	Group*	N	F/U (months)	MS Definition	Prior Treatment
Teriflunomide (Aubagio)						
O'Connor 2006[91]	-	Teriflunomide 7 mg PO QD Teriflunomide 14 mg PO QD Placebo PO QD	61 57 61	8	Poser	Mixed
O'Connor 2011[84]	TEMSO	Teriflunomide 7 mg PO QD Teriflunomide 14 mg PO QD Placebo PO QD	365 358 363	24	McDonald	Mixed
Confavreux 2014[81]	TOWER	Teriflunomide 7 mg PO QD Teriflunomide 14 mg PO QD Placebo PO QD	407 370 388	19	McDonald	Mixed
Vermersch 2014[66]	TENERE	Teriflunomide 7 mg PO QD Teriflunomide 14 mg PO QD IFN β-1a 44 mcg SC TIW	109 111 104	15	McDonald	Mixed
Dimethyl fumarate (Tecfidera)						
Fox 2012[67]	CONFIRM	Dimethyl fumarate 240 mg PO BID Glatiramer 20 mg SC QD Placebo	359 350 363	24	McDonald	Mixed
Gold 2012[83]	DEFINE	Dimethyl fumarate 240 mg PO BID Placebo PO BID	410 408	24	McDonald	Mixed
Natalizumab (Tysabri)						
Polman 2006[61]	AFFIRM	Natalizumab 300 mg IV Q 4 weeks Placebo IV Q 4 weeks	627 315	24	McDonald	Mixed
Alemtuzumab (Lemtrada)						
Coles 2008[69]	CAMMS223	Alemtuzumab 12 mg IV Q year IFN β-1a 44 mcg SC TIW	112 111	36	McDonald	No
Cohen 2012[68]	CARE-MS I	Alemtuzumab 12 mg IV Q year IFN β-1a 44 mcg SC TIW	376 187	24	McDonald	No
Coles 2012[70]	CARE-MS II	Alemtuzumab 12 mg IV Q year IFN β-1a 44 mcg SC TIW	426 202	24	McDonald	Yes

Reference	Study	Group*	N	F/U (months)	MS Definition	Prior Treatment
Daclizumab (Zinbryta)						
Gold 2013[62]	SELECT	Daclizumab 150 mg SC Q 4 weeks Placebo SC Q 4 weeks	201 196	12	McDonald	Mixed
Kappos 2015[63]	DECIDE	Daclizumab 150 mg SC Q 4 weeks IFN β-1a 30 mcg IM Q week	919 922	25	McDonald	Mixed
Ocrelizumab (Ocrevus)						
Kappos 2011[90]	-	Ocrelizumab 600 mg IV Q 24 weeks IFN β-1a 30 mcg IM Q week Placebo IV Q 24 weeks	55 54 54	6	McDonald	Mixed
Hauser 2015[58]	OPERA I	Ocrelizumab 600 mg IV Q 24 weeks IFN β-1a 44 mcg SC TIW	410 411	12	McDonald	Mixed
Hauser 2015[58]	OPERA II	Ocrelizumab 600 mg IV Q 24 weeks IFN β-1a 44 mcg SC TIW	417 418	12	McDonald	Mixed
Rituximab (Rituxan)						
Hauser 2008[64]	HERMES	Rituximab 1000 mg IV Placebo IV	69 35	11	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[59]	IFN β-1a 30 mcg IM Q week Placebo IM Q week	37	73	92	6.5	204	1.2	NR
Calabrese 2012[153]	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[21] **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[85] **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 Group1993[76]	IFN β-1b 250 SC mcg QOD Placebo	35	70	94	NR	2.4	2 years: 2.6	4.3
Durelli 2002[154] **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[155]	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[156] **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[157] **BEYOND**	IFN β-1b 250 SC mcg QOD Glatiramer 20 mg SC QD	36	69	91	5.3	2.3	1.3	2.1
Glatiramer Acetate (Copaxone)								
Bornstein 1987[57]	Glatiramer 20 mg SC QD Placebo SC QD	31	56	96	5.6	3.0	2 years: 3.8	NR

Reference	Group	Age	% Female	% White	MS Duration	EDSS baseline	Relapses prior year	MRI GdE lesions
Johnson 1995[77]	Glatiramer 20 mg SC QD Placebo SC QD	34	73	94	6.9	2.6	2 years: 2.9	NR
Comi 2001[158]	Glatiramer 20 mg SC QD Placebo SC QD	34	NR	NR	8.1	2.4	2 years: 2.6	4.3
Khan 2013[93] **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[78] **PRISMS**	IFNβ-1a 22 mg SC TIW IFNβ-1a 44 mcg SC TIW Placebo SC TIW	35	69	NR	5.3	2.5	2years: 3.0	NR
OWIMS 1999[79] **OWIMS**	IFNβ-1a 22 mg SC TIW IFNβ-1a 44 mcg SC TIW Placebo SC TIW	35	73	NR	6.6	2.6	2 years: 2.4	NR
Panitch 2002[159] **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[160] **REGARD**	IFNβ-1a 44 mcg SC TIW Glatiramer 20 mg SC QD	37	71	94	6.2	2.3	NR	1.6
De Stefano 2010[82] **IMPROVE**	IFNβ-1a 44 mcg SC TIW Placebo SC TIW	NR	NR	NR	NR	NR	NR	NR
Peginterferon β-1a (Plegridy)								
Calabresi 2014[161] **ADVANCE**	PegINFβ-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[65] **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[60] **FREEDOMS**	Fingolimod 0.5 mg PO QD Placebo PO QD	37	70	94	NR	2.9	2 years: 3.4	NR
Saida 2012[162]	Fingolimod 0.5 mg PO QD Placebo PO QD	35	69	0	7.8	2.1	1.6	1.4

Reference	Group	Age	% Female	% White	MS Duration	EDSS baseline	Relapses prior year	MRI GdE lesions
Calabresi 2014[80] **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 2006[91]	Teriflunomide 7 mg PO QD Teriflunomide 14 mg PO QD Placebo PO QD	39	74	NR	9.2	2.3	1	NR
O'Connor 2011[84] **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
Confavreux 2014[81] **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[66] **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[67] **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[83] **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[61] **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[69] **CAMMS223**	Alemtuzumab 12 mg IV Q year IFNβ-1a 44 mcg SC TIW	32	64	90	NR	2.0	2 year: 2.7	NR

Reference	Group	Age	% Female	% White	MS Duration	EDSS baseline	Relapses prior year	MRI GdE lesions
Cohen 2012[68] **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[70] **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[62] **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[63] **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)								
Kappos 2011[90]	Ocrelizumab 600 mg IV Q 24 weeks IFNβ-1a 30 mcg IM Q week Placebo IV Q 24 weeks	37	65	97	5.5	3.3	NR	2.0
Hauser 2015[58] **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
Hauser 2015[58] **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[64] **HERMES**	Rituximab 1000 mg IV 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[59]	Yes	Yes – 8%	Yes	Yes	Yes	Yes	Yes	Good
Calabrese 2012[153]	Yes	Yes – 15%	No	Yes	Yes	No	No	Poor
Lublin 2013[21] CombiRx	Yes	Yes – 19%	No	No	Yes	Yes	Yes	Fair
Vollmer 2014[85] BRAVO	Yes	Yes – 18%	No	No	Yes	Yes	Yes	Fair
Interferon β-1b 250 mcg (Betaseron)								
IFNβ Multiple Sclerosis Study Group1993[76]	Unclear	No – 33%	Yes	Yes	Yes	Yes	Yes	Poor
Durelli 2002[154] INCOMIN	Yes	Yes – 16%	No	No	Yes	Yes	Yes	Fair
Etemadifar 2006[155]	No	Yes – 0%	No	No	Yes	No	Yes	Poor
Cadavid 2009[156] BECOME	Unclear	Yes – 15%	No	No	Yes	No	Yes	Fair
O'Connor 2009[157] BEYOND	Yes	Yes – 15%	No	No	Yes	No	Unclear	Fair
Glatiramer Acetate (Copaxone)								
Bornstein 1987[57]	Yes	Yes – 14%	No	No	Yes	No	Yes	Fair
Johnson 1995[77]	Unclear	Yes – 14%	Yes	Yes	Yes	No	Yes	Fair
Comi 2001[158]	Yes	Yes – 6%	Yes	Yes	Yes	No	Yes	Fair
Khan 2013[93] GALA	Yes	Yes – 8%	Yes	Yes	Yes	No	Yes	Fair
Interferon β-1a 22/44 mcg (Rebif)								
PRISMS 1998[78] PRISMS	Yes	Yes- 10%	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
OWIMS 1999[79] **OWIMS**	Yes	Yes – 8%	Yes	Yes	Yes	No	Yes	Fair
Panitch 2002[159] **EVIDENCE**	Yes	Yes – 4%	No	No	Yes	Yes	Yes	Fair
Mikol 2008[160] **REGARD**	Yes	Yes – 18%	No	No	Yes	Yes	Yes	Fair
De Stefano 2010[82] **IMPROVE**	Unclear	Unclear	Yes	Yes	Yes	No	Yes	Fair
Peginterferon β-1a (Plegridy)								
Calabresi 2014[161] **ADVANCE**	Yes	Yes – 12%	Yes	Yes	Yes	No	Yes	Fair
Fingolimod (Gilenya)								
Cohen 2010[65] **TRANSFORMS**	Yes	Yes – 11%	Yes	Yes	Yes	No	Yes	Fair
Kappos 2010[60] **FREEDOMS**	Yes	Yes – 19%	Yes	Yes	Yes	Yes	Yes	Good
Saida 2012[162]	Unclear	Yes – 14%	Yes	Yes	Yes	No	No	Poor
Calabresi 2014[80] **FREEDOMS II**	Yes	No - 26%	Yes	Yes	Yes	Yes	Yes	Poor
Teriflunomide (Aubagio)								
O'Connor 2006[91]	Unclear	Yes – 11%	Yes	Yes	Yes	No	Yes	Fair
O'Connor 2011[84] **TEMSO**	Yes	No – 27%	Yes	Yes	Yes	No	Yes	Poor
Confavreux 2014[81] **TOWER**	Yes	No – 33%	Yes	Yes	Yes	No	Yes	Poor
Vermersch 2014[66] **TENERE**	Unclear	No – 23%	No	No	Yes	No	Yes	Poor
Dimethyl fumarate (Tecfidera)								
Fox 2012[67] **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[83] DEFINE	Yes	No – 23%	Yes	Yes	Yes	No	Yes	Poor
Natalizumab (Tysabri)								
Polman 2006[61] AFFIRM	Yes	Yes – 9%	Yes	Yes	Yes	Yes	Yes	Good
Alemtuzumab (Lemtrada)								
Coles 2008[69] CAMMS223	Unclear	No – 25%	Yes	Yes	Yes	Yes	Yes	Poor
Cohen 2012[68] CARE-MS I	Yes	Yes – 9%	No	No	Yes	Yes	Yes	Fair
Coles 2012[70] CARE-MS II	Yes	Yes – 15%	No	No	Yes	Yes	Yes	Fair
Daclizumab (Zinbryta)								
Gold 2013[62] SELECT	Yes	Yes – 9%	Yes	Yes	Yes	No	Yes	Fair
Kappos 2015[63] DECIDE	Yes	No – 23%	Yes	Yes	Yes	No	Yes	Poor
Ocrelizumab (Ocrevus)								
Kappos 2011[90]	Yes	Yes – 11%	Yes	Yes	Yes	No	Yes	Fair
Hauser 2015[58] OPERA I	Unclear	Yes – 14%	Yes	Yes	Yes	Yes	Yes	Fair
Hauser 2015[58] OPERA II	Unclear	Yes – 18%	Yes	Yes	Yes	Yes	Yes	Fair
Rituximab (Rituxan)								
Hauser 2008[64] 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[59]	-	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[153]	-	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[21]	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[85]	BRAVO	IFN β-1a 30 mcg IM Q week	447	825	214	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 Group1993[76]	-	IFN β-1b 250 SC mcg QOD	124	207	173	0.78	0.70-0.88
		Placebo	123	207	266	1.12	1.02-1.23
Durelli 2002[154]	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[155]	-	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[156]	BECOME	IFN β-1b 250 SC mcg QOD	36	68.04	25	0.37	0.62-0.87
		Glatiramer 20 mcg SC QD	39	70.59	23	0.33	0.24-0.53
O'Connor 2009[157]	BEYOND	IFN β-1b 250 SC mcg QOD	897	2260	814	0.36	NR
		Glatiramer 20 mg SC QD	448	1099.5	374	0.34	NR
Glatiramer Acetate							
Bornstein 1987[57]	-	Glatiramer 20 mg SC QD	25	50	16	0.32	NR
		Placebo SC QD	23	46	62	1.35	NR
Johnson 1995[77]	-	Glatiramer 20 mg SC QD	125	230.3	136	0.59	0.5-0.7
		Placebo SC QD	126	231.8	195	0.84	0.73-0.97

Reference	Study	Group*	N	Person-years	Relapses	ARR	95% CI
Comi 2001[158]	-	Glatiramer 20 mg SC QD	119	80.6	65	0.81	NR
		Placebo SC QD	120	81.9	99	1.21	NR
Khan 2013[93]	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[78]	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
OWIMS 1999[79]	OWIMS	IFN β-1a 22 mcg SC TIW	95	83.1	97	1.17	NR
		IFN β-1a 44 mcg SC TIW	98	84	79	0.94	NR
		Placebo SC TIW	100	89.5	105	1.17	NR
Panitch 2002[159]	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[160]	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
De Stefano 2010[82]	IMPROVE	IFN β-1a 44 mcg SC TIW	120	55.2	8	0.14	0.09-0.23
		Placebo SC TIW	60	27.6	9	0.33	0.22-0.52
Peginterferon β-1a							
Calabresi 2014[161]	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[65]	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[60]	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
Saida 2012[162]	-	Fingolimod 0.5 mg PO QD	57	24.51	12	0.50	0.29-0.87
		Placebo PO QD	57	24.51	24	0.99	0.67-1.45
Calabresi 2014[80]	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

Reference	Study	Group*	N	Person-years	Relapses	ARR	95% CI
Teriflunomide							
O'Connor 2006[91]	-	Teriflunomide 7 mg PO QD	61	37.6	22	0.58	NR
		Teriflunomide 14 mg PO QD	57	35	19	0.55	NR
		Placebo PO QD	61	37.6	30	0.81	NR
O'Connor 2011[84]	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[81]	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
Vermersch 2014[66]	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[67]	CONFIRM	Dimethyl fumarate 240 mg PO BID	359	567.22	125	0.22	0.18-0.28
		Glatiramer 20 mg SC QD	350	553	160	0.29	0.23-0.35
		Placebo	363	573.54	229	0.40	0.33-0.49
Gold 2012[83]	DEFINE	Dimethyl fumarate 240 mg PO BID	410	631.4	107	0.17	0.14-0.21
		Placebo PO BID	408	628.32	226	0.36	0.30-0.44
Natalizumab							
Polman 2006[61]	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[69]	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[68]	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

Reference	Study	Group*	N	Person-years	Relapses	ARR	95% CI
Coles 2012[70]	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[64]	HERMES	Rituximab 1000 mg IV	69	31.3	11	0.37	0.23-0.60
		Placebo IV	35	15.9	13	0.84	0.53-1.31
Daclizumab							
Gold 2013[62]	SELECT	Daclizumab 150 mg SC Q 4 weeks	201	217.75	46	0.21	0.16-0.29
		Placebo SC Q 4 weeks	196	212.33	98	0.46	0.37-0.57
Kappos 2015[63]	DECIDE	Daclizumab 150 mg SC Q 4 weeks	919	1692.5	372	0.22	0.19-0.24
		IFN β-1a 30 mg IM Q week	922	1698	662	0.39	0.35-0.44
Ocrelizumab							
Kappos 2011[90]	-	Ocrelizumab 600 mg IV Q 24 weeks	55	25.3	3	0.13	0.03-0.29
		IFN β-1a 30 mcg IM Q week	54	24.8	9	0.36	0.22-0.60
		Placebo IV Q 24 weeks	54	24.8	16	0.64	0.43-0.94
Hauser 2015[58]	OPERA I	Ocrelizumab 600 mg IV Q 24 weeks	410	754.3	118	0.155	NR
		IFN β-1a 44 mcg SC TIW	411	756.2	223	0.290	NR
Hauser 2015[58]	OPERA II	Ocrelizumab 600 mg IV Q 24 weeks	417	767.2	119	0.155	NR
		IFN β-1a 44 mcg SC TIW	418	769.1	223	0.290	NR

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[59]	-	IFN β-1a 30 mcg IM Q week Placebo IM Q week	158 143	35 50	NR	P=0.02	Y
Calabrese 2012[153]	-	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[21]	CombiRx	IFN β-1a 30 mcg IM Q week Glatiramer 20 mg SC QD	241 246	52 61	NR	NS	Y
Vollmer 2014[85]	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[76]	-	IFN β-1b 250 SC mcg QOD Placebo	122 122	43 56	NR	NS	Y
Durelli 2002[154]	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[155]	-	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[156]	BECOME	IFNβ-1b 250 SC mcg QOD Glatiramer 20 mg SC QD	36 39	NR NR			N
O'Connor 2009[157]	BEYOND	IFNβ-1b 250 SC mcg QOD Glatiramer 20 mg SC QD	897 448	NR NR			N
Glatiramer Acetate (Copaxone)							
Bornstein 1987[57]	-	Glatiramer 20 mg SC QD Placebo SC QD	25 23	NR NR			N
Johnson 1995[77]	-	Glatiramer 20 mg SC QD Placebo SC QD	125 126	NR NR			N
Comi 2001[158]	-	Glatiramer 20 mg SC QD Placebo SC QD	119 120	NR NR			N

Reference	Study	Group	N	EDSS Prog24	HR	95% CI	Included in Base Case NMA?
Khan 2013[93]	GALA	Glatiramer 40 mg SC TIW Placebo SC QD	943 461	NR NR			N
Interferon β-1a 22/44 mcg (Rebif)							
PRISMS 1998[78]	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
OWIMS 1999[79]	OWIMS	IFN β-1a 22 mcg SC TIW IFN β-1a 44 mcg SC TIW Placebo SC TIW	95 98 100	NR NR NR			N
Panitch 2002[159]	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[160]	REGARD	IFN β-1a 44 mcg SC TIW Glatiramer 20 mg SC QD	386 378	45 33	NR	P=0.12	Y
De Stefano 2010[82]	IMPROVE	IFN β-1a 44 mcg SC TIW Placebo SC TIW	120 60	NR NR			N
Peginterferon β-1a (Plegridy)							
Calabresi 2014[161]	ADVANCE	PEG β-1a 125 mcg SC Q 14 d Placebo SC Q 14 d	512 500	NR NR			N
Fingolimod (Gilenya)							
Cohen 2010[65]	TRANSFORMS	Fingolimod 0.5 mg PO QD IFN β-1a 30 mcg IM Q week	429 431	NR NR			N
Kappos 2010[60]	FREEDOMS	Fingolimod 0.5 mg PO QD Placebo PO QD	425 418	53 79	0.63	0.44-0.90	Y
Saida 2012[162]	-	Fingolimod 0.5 mg PO QD Placebo PO QD	57 57	NR NR			N
Calabresi 2014[80]	FREEDOMS II	Fingolimod 0.5 mg PO QD Placebo PO QD	358 355	49 63	0.72	0.48-1.07	Y

Reference	Study	Group	N	EDSS Prog24	HR	95% CI	Included in Base Case NMA?
Teriflunomide (Aubagio)							
O'Connor 2006[91]	-	Teriflunomide 7 mg PO QD Teriflunomide 14 mg PO QD Placebo PO QD	61 57 61	NR NR NR			N
O'Connor 2011[84]	TEMSO	Teriflunomide 7 mg PO QD Teriflunomide 14 mg PO QD Placebo PO QD	365 358 363	NR NR NR			N
Confavreux 2014[81]	TOWER	Teriflunomide 7 mg PO QD Teriflunomide 14 mg PO QD Placebo PO QD	407 370 388	NR NR NR			N
Vermersch 2014[66]	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[67]	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[83]	DEFINE	Dimethyl fumarate 240 mg PO BID Placebo PO BID	409 408	NR NR			N
Natalizumab (Tysabri)							
Polman 2006[61]	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[69]	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[68]	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[70]	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

Reference	Study	Group	N	EDSS Prog24	HR	95% CI	Included in Base Case NMA?
Rituximab (Rituxan)							
Hauser 2008[64]	HERMES	Rituximab 1000 mg IV Placebo IV	69 35	NR NR			N
Daclizumab (Zinbryta)							
Gold 2013[62]	SELECT	Daclizumab 150 mg SC Q 4 weeks Placebo SC Q 4 weeks	201 196	NR NR			N
Kappos 2015[63]	DECIDE	Daclizumab 150 mg SC Q 4 weeks IFN β-1a 30 mcg IM Q week	919 922	NR NR	0.79	0.59-1.06	N
Ocrelizumab (Ocrevus)							
Kappos 2011[90]	-	Ocrelizumab 600 mg IV Q 24 weeks IFN β-1a 30 mcg IM Q week Placebo IV Q 24 weeks	55 54 54	NR NR NR			N
Hauser 2015[58]	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 2015[58]	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[59]	-	IFN β-1a 30 mcg IM Q week Placebo IM Q week	158 143	NR NR			N
Calabrese 2012[153]	-	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[21]	CombiRx	IFN β-1a 30 mcg IM Q week Glatiramer 20 mg SC QD	241 246	NR NR			N
Vollmer 2014[85]	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 Group1993[76]	-	IFN β-1b 250 SC mcg QOD Placebo	122 122	NR NR			N
Durelli 2002[154]	INCOMIN	IFN β-1b 250 SC mcg QOD IFN β-1a 30 mg IM Q week	96 92	NR NR			N
Etemadifar 2006[155]	-	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[156]	BECOME	IFN β-1b 250 SC mcg QOD Glatiramer 20 mg SC QD	36 39	NR NR			N
O'Connor 2009[157]	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[57]	-	Glatiramer 20 mg SC QD Placebo SC QD	25 23	NR NR			N
Johnson 1995[77]	-	Glatiramer 20 mg SC QD Placebo SC QD	125 126	27 31	NR	NS	Y
Comi 2001[158]	-	Glatiramer 20 mg SC QD Placebo SC QD	119 120	NR NR			N

Reference	Study	Group	N	EDSS Prog12	HR	95% CI	Included in Base Case NMA?
Khan 2013[93]	GALA	Glatiramer 40 mg SC TIW Placebo SC QD	943 461	42 17			Y
Interferon β-1a 22/44 mcg (Rebif)							
PRISMS 1998[78]	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
OWIMS 1999[79]	OWIMS	IFN β-1a 22 mcg SC TIW IFN β-1a 44 mcg SC TIW Placebo SC TIW	95 98 100	NR NR NR			N
Panitch 2002[159]	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[160]	REGARD	IFN β-1a 44 mcg SC TIW Glatiramer 20 mg SC QD	386 378	NR NR			N
De Stefano 2010[82]	IMPROVE	IFN β-1a 44 mcg SC TIW Placebo SC TIW	120 60	NR NR			N
Peginterferon β-1a (Plegridy)							
Calabresi 2014[161]	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[65]	TRANSFORMS	Fingolimod 0.5 mg PO QD IFN β-1a 30 mg IM Q week	429 431	25 34		NS	Y
Kappos 2010[60]	FREEDOMS	Fingolimod 0.5 mg PO QD Placebo PO QD	425 418	74 101	0.70	0.52-0.96	N
Saida 2012[162]	-	Fingolimod 0.5 mg PO QD Placebo PO QD	57 57	NR NR			N
Calabresi 2014[80]	FREEDOMS II	Fingolimod 0.5 mg PO QD Placebo PO QD	358 355	91 103	0.83	0.61-1.12	N

Reference	Study	Group	N	EDSS Prog12	HR	95% CI	Included in Base Case NMA?
Teriflunomide (Aubagio)							
O'Connor 2006[91]	-	Teriflunomide 7 mg PO QD Teriflunomide 14 mg PO QD Placebo PO QD	61 57 61	NR NR NR			N
O'Connor 2011[84]	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
Confavreux 2014[81]	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[66]	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[67]	CONFIRM	Dimethyl fumarate 240 mg PO BID Glatiramer 20 mg SC QD Placebo	359 350 363	13 16 17	.79 .93	0.52-1.19 0.63-1.37	Y
Gold 2012[83]	DEFINE	Dimethyl fumarate 240 mg PO BID Placebo PO BID	409 408	16 27	0.62	0.44-0.87	Y
Natalizumab (Tysabri)							
Polman 2006[61]	AFFIRM	Natalizumab 300 mg IV Q 4 weeks Placebo IV Q 4 weeks	627 315	NR NR			N
Alemtuzumab (Lemtrada)							
Coles 2008[69]	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[68]	CARE-MS I	Alemtuzumab 12 mg IV Q year IFN β-1a 44 mcg SC TIW	376 187	NR NR			N
Coles 2012[70]	CARE-MS II	Alemtuzumab 12 mg IV Q year IFN β-1a 44 mcg SC TIW	426 202	NR NR			N

Reference	Study	Group	N	EDSS Prog12	HR	95% CI	Included in Base Case NMA?
Rituximab (Rituxan)							
Hauser 2008[64]	HERMES	Rituximab 1000 mg IV Placebo IV	69 35	NR NR			N
Daclizumab (Zinbryta)							
Gold 2013[62]	SELECT	Daclizumab 150 mg SC Q 4 weeks Placebo SC Q 4 weeks	201 196	11 25	0.43	0.21-0.88	Y
Kappos 2015[63]	DECIDE	Daclizumab 150 mg SC Q 4 weeks IFN β-1a 30 mg IM Q week	919 922	121 140	0.84	0.66-1.07	Y
Ocrelizumab (Ocrevus)							
Kappos 2011[90]	-	Ocrelizumab 600 mg IV Q 24 weeks IFN β-1a 30 mcg IM Q week Placebo IV Q 24 weeks	55 54 54	NR NR NR			N
Hauser 2015[58]	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 2015[58]	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.

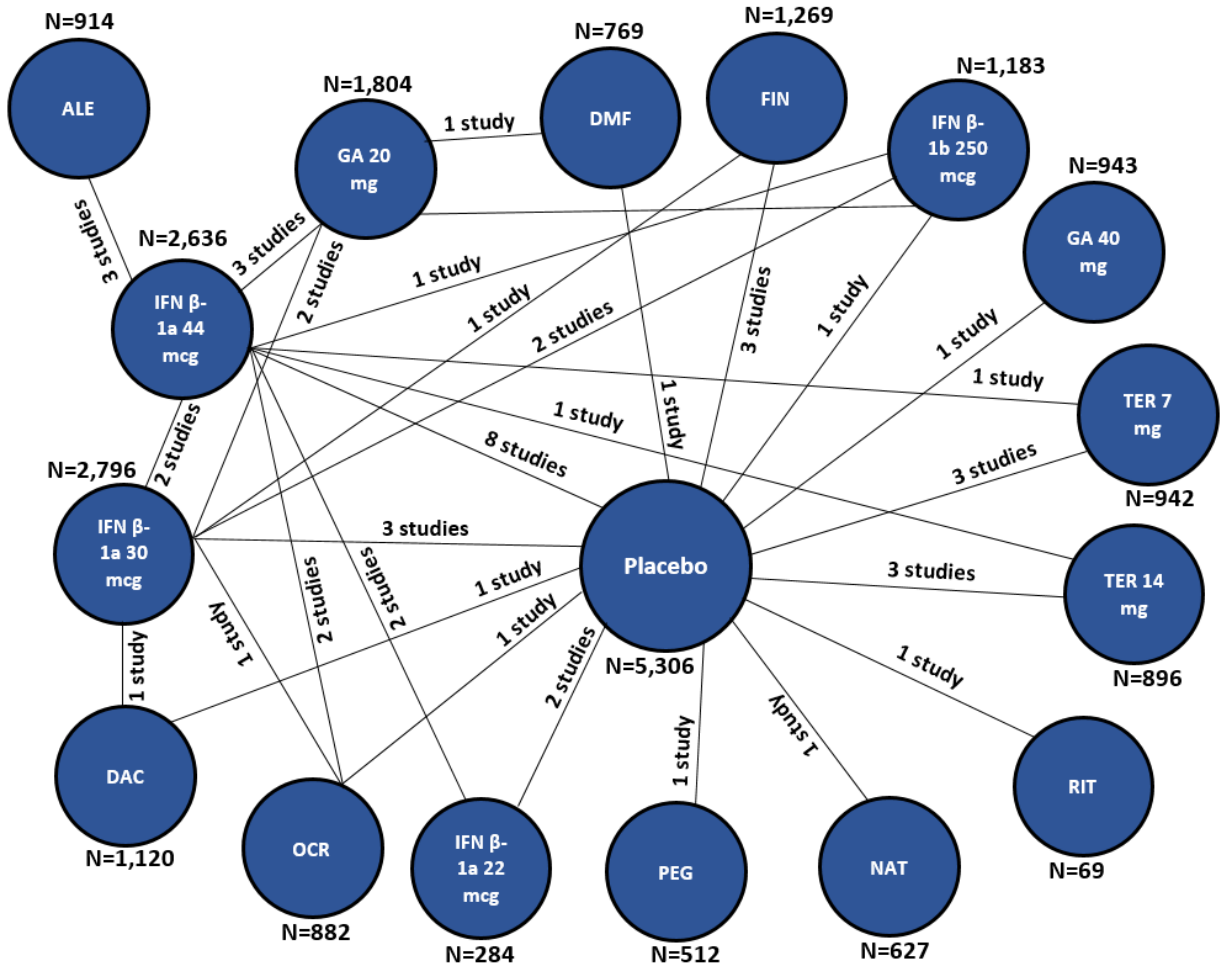


Table D1. NMA Subgroup Analyses for ARR

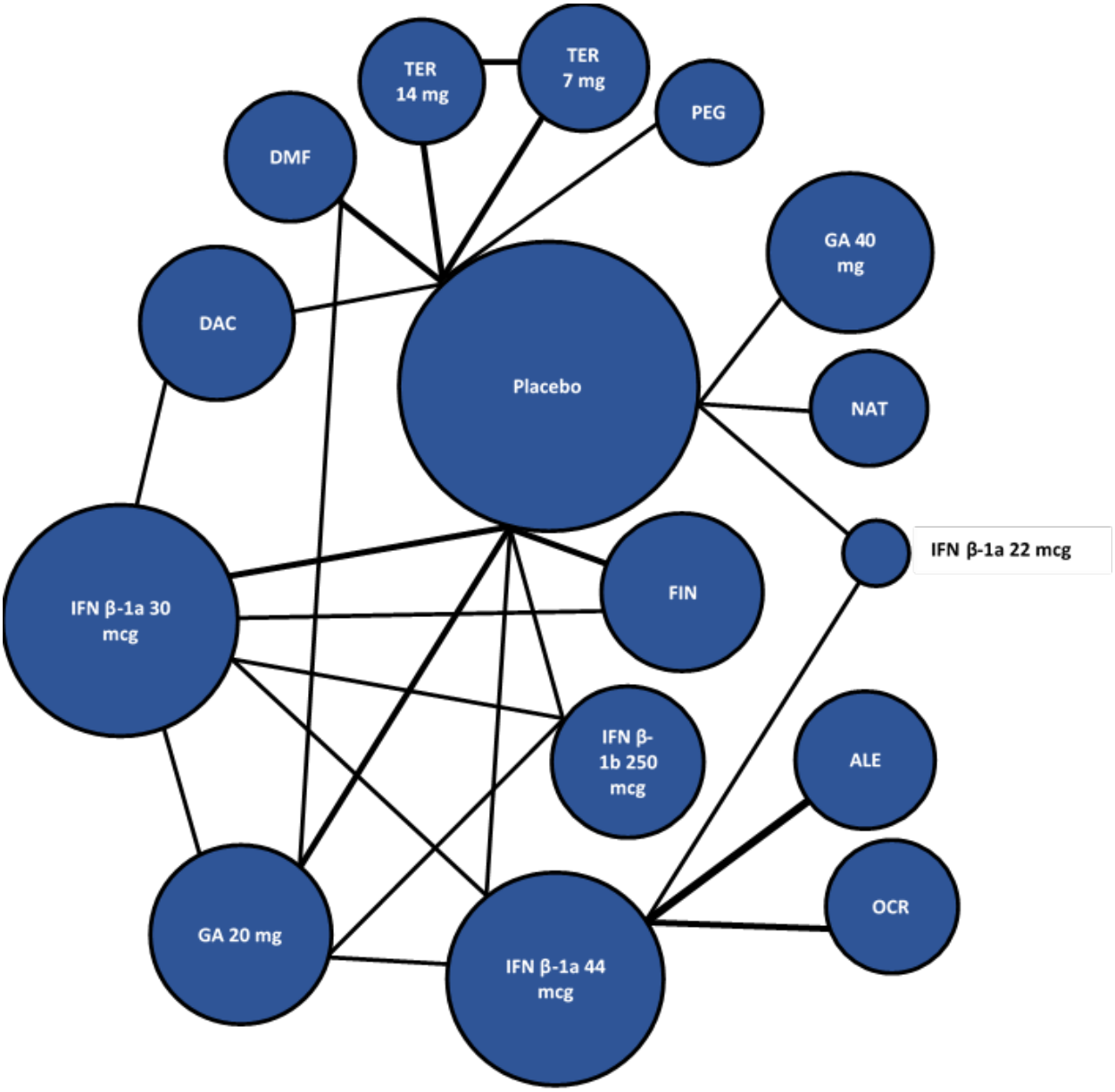
Treatment	Base Case ARR	Tx-naïve Population	Tx-naïve + Experienced Population	Exclude Trials with n<100	Trials Using Poser Criteria	Trials Using McDonald Criteria	Exclude Poor-quality Trials	Exclude Trials w/ Duration <18 months	Exclude Open-label Trials
ALE	**0.29 (0.22-0.36)**	**0.23 (0.11-0.41)**	**0.33 (0.25-0.42)**	**0.30 (0.24-0.37)**	N/A	**0.27 (0.20-0.37)**	**0.33 (0.24-0.44)**	**0.28 (0.20-0.36)**	**0.22 (0.13-0.33)**
NAT	**0.31 (0.25-0.40)**	N/A	**0.32 (0.26-0.38)**	**0.31 (0.26-0.38)**	N/A	**0.32 (0.25-0.40)**	**0.32 (0.23-0.42)**	**0.31 (0.23-0.43)**	**0.31 (0.25-0.39)**
RIT	0.42 (0.18-1.00)	N/A	**0.42 (0.19-0.92)**	N/A	N/A	**0.46 (0.18-0.92)**	N/A	N/A	**0.44 (0.19-0.14)**
OCR	**0.43 (0.34-0.54)**	N/A	**0.41 (0.32-0.51)**	**0.44 (0.36-0.55)**	N/A	**0.41 (0.32-0.53)**	**0.42 (0.31-0.54)**	N/A	**0.43 (0.33-0.55)**
DAC	**0.47 (0.38-0.58)**	N/A	**0.45 (0.37-0.54)**	**0.46 (0.38-0.56)**	N/A	**0.45 (0.36-0.56)**	**0.45 (0.29-0.69)**	**0.47 (0.34-0.66)**	**0.46 (0.37-0.58)**
FIN	**0.47 (0.39-0.55)**	N/A	**0.46 (0.39-0.54)**	**0.46 (0.40-0.54)**	N/A	**0.46 (0.39-0.55)**	**0.43 (0.33-0.55)**	**0.49 (0.38-0.61)**	**0.46 (0.40-0.55)**
DMF	**0.50 (0.41-0.61)**	N/A	**0.52 (0.43-0.61)**	**0.51 (0.42-0.60)**	N/A	**0.50 (0.40-0.60)**	N/A	**0.49 (0.39-0.62)**	**0.47 (0.35-0.61)**
PEG	**0.63 (0.47-0.86)**	N/A	**0.63 (0.48-0.83)**	**0.64 (0.48-0.84)**	N/A	**0.64 (0.46-0.86)**	**0.64 (0.45-0.91)**	N/A	**0.65 (0.48-0.86)**
GA 20 mg	**0.65 (0.57-0.72)**	**0.50 (0.31-0.72)**	**0.74 (0.65-0.85)**	**0.68 (0.60-0.76)**	**0.58 (0.34-0.86)**	**0.62 (0.51-0.74)**	**0.62 (0.50-0.72)**	**0.63 (0.53-0.72)**	**0.76 (0.60-0.94)**
IFN β-1b 250 mcg	**0.65 (0.55-0.76)**	**0.58 (0.37-0.84)**	N/A	**0.69 (0.59-0.80)**	0.65 (0.39-1.09)	**0.66 (0.50-0.86)**	**0.64 (0.48-0.80)**	**0.65 (0.52-0.77)**	**0.65 (0.51-0.83)**
IFN β-1a 44 mcg	**0.66 (0.57-0.74)**	**0.59 (0.35-0.88)**	**0.65 (0.56-0.74)**	**0.67 (0.59-0.77)**	0.69 (0.44-1.05)	**0.62 (0.46-0.79)**	**0.68 (0.57-0.80)**	**0.64 (0.50-0.76)**	**0.70 (0.59-0.83)**
TER 14 mg	**0.66 (0.57-0.79)**	N/A	**0.67 (0.58-0.77)**	**0.67 (0.58-0.78)**	0.68 (0.27-1.67)	**0.66 (0.56-0.79)**	0.66 (0.35-1.24)	**0.67 (0.53-0.83)**	**0.66 (0.57-0.78)**
GA 40mg	**0.67 (0.52-0.87)**	N/A	**0.67 (0.54-0.84)**	**0.67 (0.53-0.83)**	N/A	**0.68 (0.52-0.86)**	**0.67 (0.49-0.91)**	N/A	**0.67 (0.53-0.84)**
IFN β-1a 22 mcg	**0.75 (0.63-0.91)**	0.85 (0.45-1.54)	**0.70 (0.58-0.82)**	**0.71 (0.59-0.84)**	0.80 (0.49-1.33)	N/A	**0.77 (0.63-0.97)**	**0.69 (0.51-0.90)**	**0.77 (0.65-0.93)**

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 (0.66-0.92)**	N/A	**0.77 (0.67-0.89)**	**0.77 (0.68-0.90)**	0.73 (0.30-1.78)	**0.77 (0.66-0.93)**	0.73 (0.39-1.34)	**0.74 (0.59-0.92)**	**0.74 (0.63-0.86)**
IFN β-1a 30 mcg	**0.83 (0.74-0.94)**	0.84 (0.55-1.25)	**0.79 (0.69-0.90)**	**0.83 (0.74-0.94)**	0.91 (0.58-1.50)	**0.79 (0.68-0.93)**	**0.82 (0.69-0.94)**	**0.84 (0.71-0.99)**	**0.83 (0.69-0.98)**

Table D2. 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	**0.29 (0.22-0.36)**	N/A	**0.30 (0.26-0.36)**	**0.30 (0.21-0.40)**	**0.28 (0.21-0.37)**	**0.30 (0.23-0.37)**
NAT	**0.31 (0.25-0.40)**	**0.32 (0.27-0.37)**	**0.31 (0.27-0.37)**	**0.30 (0.23-0.40)**	**0.31 (0.24-0.42)**	**0.29 (0.22-0.38)**
RIT	0.42 (0.18-1.00)	**0.43 (0.19-0.96)**	**0.43 (0.19-0.98)**	**0.36 (0.14-0.88)**	0.37 (0.15-1.05)	0.43 (0.20-1.02)
OCR	**0.43 (0.34-0.54)**	**0.18 (0.05-0.63)**	**0.44 (0.36-0.52)**	**0.41 (0.30-0.54)**	**0.42 (0.31-0.57)**	**0.45 (0.35-0.57)**
DAC	**0.47 (0.38-0.58)**	**0.46 (0.32-0.65)**	**0.47 (0.41-0.54)**	**0.45 (0.34-0.58)**	**0.44 (0.34-0.59)**	**0.48 (0.39-0.61)**
FIN	**0.47 (0.39-0.55)**	**0.48 (0.42-0.56)**	**0.47 (0.41-0.53)**	**0.41 (0.28-0.63)**	**0.47 (0.38-0.56)**	**0.49 (0.41-0.58)**
DMF	**0.50 (0.41-0.61)**	**0.51 (0.44-0.60)**	**0.50 (0.43-0.58)**	**0.47 (0.37-0.61)**	**0.48 (0.38-0.61)**	**0.50 (0.41-0.61)**
PEG	**0.63 (0.47-0.86)**	**0.64 (0.50-0.82)**	**0.64 (0.50-0.82)**	**0.59 (0.40-0.88)**	**0.66 (0.46-0.94)**	N/A
GA 20 mg	**0.65 (0.57-0.72)**	**0.59 (0.43-0.80)**	**0.65 (0.59-0.71)**	**0.60 (0.47-0.75)**	**0.63 (0.53-0.73)**	**0.65 (0.58-0.74)**
IFN β-1b 250 mcg	**0.65 (0.55-0.76)**	**0.65 (0.54-0.79)**	**0.66 (0.59-0.74)**	**0.61 (0.46-0.80)**	**0.62 (0.51-0.77)**	**0.65 (0.55-0.76)**
IFN β-1a 44 mcg	**0.66 (0.57-0.74)**	**0.70 (0.61-0.79)**	**0.67 (0.61-0.73)**	**0.61 (0.48-0.77)**	**0.63 (0.52-0.75)**	**0.67 (0.58-0.76)**
TER 14 mg	**0.66 (0.57-0.79)**	**0.67 (0.59-0.75)**	**0.67 (0.59-0.75)**	**0.59 (0.41-0.86)**	**0.64 (0.53-0.80)**	**0.71 (0.60-0.86)**
GA 40mg	**0.67 (0.52-0.87)**	**0.66 (0.55-0.78)**	**0.67 (0.56-0.80)**	**0.59 (0.41-0.89)**	**0.63 (0.46-0.88)**	0.75 (0.55-1.03)
IFN β-1a 22 mcg	**0.75 (0.63-0.91)**	0.83 (0.59-1.14)	**0.74 (0.66-0.84)**	**0.71 (0.55-0.93)**	**0.73 (0.59-0.93)**	**0.77 (0.65-0.94)**
TER 7 mg	**0.77 (0.66-0.92)**	**0.74 (0.65-0.82)**	**0.76 (0.68-0.85)**	0.68 (0.48-1.01)	**0.75 (0.62-0.94)**	0.82 (0.70-1.01)
IFN β-1a 30 mcg	**0.83 (0.74-0.94)**	**0.78 (0.69-0.90)**	**0.83 (0.76-0.91)**	**0.78 (0.62-0.98)**	**0.79 (0.67-0.95)**	**0.85 (0.75-0.96)**

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.[163]

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

ALE														
0.74 (0.31–1.67)	OCR													
0.47 (0.18–1.12)	0.63 (0.35 – 1.19)	DAC												
0.46 (0.17 – 1.23)	0.63 (0.29 – 1.33)	0.98 (0.50 – 1.97)	PEG											
0.44 (0.20 – 0.91)	**0.60 (0.42 – 0.85)**	0.94 (0.57 – 1.51)	0.95 (0.49 – 1.85)	IFN β-1a 44 mcg										
0.43 (0.16 – 1.12)	0.59 (0.29 – 1.22)	0.92 (0.49 – 1.74)	0.93 (0.45 – 1.86)	0.98 (0.54 – 1.80)	DMF									
0.41 (0.16 – 0.98)	0.56 (0.29 – 1.01)	0.87 (0.51 – 1.44)	0.87 (0.47 – 1.64)	0.92 (0.55 – 1.51)	0.94 (0.54 – 1.69)	TER 14 mg								
0.39 (0.16 – 0.92)	**0.53 (0.30 – 0.96)**	0.83 (0.52 – 1.32)	0.84 (0.47 – 1.53)	0.89 (0.56 – 1.39)	0.90 (0.53 – 1.57)	0.96 (0.64 – 1.48)	FIN							
0.37 (0.15 – 0.89)	**0.50 (0.27 – 0.90)**	0.79 (0.43 – 1.41)	0.80 (0.40 – 1.59)	0.84 (0.51 – 1.34)	0.85 (0.44 – 1.64)	0.90 (0.52 – 1.60)	0.94 (0.56 – 1.60)	IFN β-1a 22 mcg						
0.37 (0.15 – 0.83)	**0.50 (0.29 – 0.84)**	0.78 (0.55 – 1.07)	0.79 (0.42 – 1.49)	0.84 (0.56 – 1.21)	0.84 (0.47 – 1.49)	0.90 (0.57 – 1.41)	0.94 (0.64 – 1.33)	0.99 (0.58 – 1.70)	IFN β-1a 30 mcg					
0.33 (0.13 – 0.78)	**0.45 (0.24 – 0.83)**	0.70 (0.41 – 1.15)	0.70 (0.38 – 1.28)	0.75 (0.45 – 1.22)	0.76 (0.43 – 1.34)	0.80 (0.58 – 1.12)	0.84 (0.55 – 1.25)	0.89 (0.51 – 1.54)	0.89 (0.58 – 1.40)	TER 7 mg				
0.31 (0.11 – 0.81)	**0.43 (0.21 – 0.86)**	0.66 (0.36 – 1.25)	0.68 (0.34 – 1.32)	0.71 (0.39 – 1.33)	0.72 (0.40 – 1.30)	0.76 (0.45 – 1.38)	0.80 (0.48 – 1.38)	0.85 (0.45 – 1.64)	0.85 (0.50 – 1.49)	0.96 (0.56 – 1.69)	GA 20 mg			
0.30 (0.10 – 0.83)	**0.40 (0.18 – 0.89)**	0.63 (0.30 – 1.31)	0.64 (0.28 – 1.39)	0.67 (0.32 – 1.39)	0.67 (0.34 – 1.39)	0.72 (0.37 – 1.45)	0.76 (0.39 – 1.46)	0.80 (0.37 – 1.73)	0.80 (0.41 – 1.59)	0.90 (0.46 – 1.78)	0.95 (0.64 – 1.37)	IFN β-1b 250		
0.22 (0.07 – 0.60)	**0.30 (0.12 – 0.66)**	0.47 (0.22 – 1.00)	0.47 (0.21 – 1.09)	0.50 (0.23 – 1.00)	0.51 (0.23 – 1.12)	0.54 (0.26 – 1.09)	0.56 (0.28 – 1.11)	0.60 (0.27 – 1.29)	0.60 (0.29 – 1.23)	0.67 (0.33 – 1.36)	0.70 (0.33 – 1.54)	0.73 (0.32 – 1.83)	GA 40 mg	
0.27 (0.11 – 0.62)	**0.37 (0.22 – 0.62)**	**0.58 (0.38 – 0.86)**	0.58 (0.35 – 1.00)	**0.62 (0.41 – 0.92)**	0.63 (0.39 – 1.02)	**0.67 (0.48 – 0.93)**	**0.70 (0.53 – 0.90)**	0.73 (0.46 – 1.16)	0.74 (0.54 – 1.02)	0.82 (0.61 – 1.13)	0.87 (0.54 – 1.33)	0.92 (0.50 – 1.67)	1.23 (0.65 – 2.27)	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								
0.90 (0.32 – 1.92)	**IFN β-1b 250 mcg**							
0.90 (0.39 – 1.87)	1.01 (0.32 – 2.85)	**OCR**						
0.80 (0.22 – 2.25)	0.89 (0.32 – 2.08)	0.88 (0.24 – 2.47)	**NAT**					
0.61 (0.18 – 1.76)	0.70 (0.28 – 1.56)	0.69 (0.21 – 1.98)	0.79 (0.30 – 1.88)	FIN				
0.60 (0.24 – 1.28)	0.68 (0.25 – 1.59)	0.67 (0.27 – 1.49)	0.76 (0.23 – 2.06)	0.96 (0.36 – 2.21)	**GA 20 mg**			
0.57 (0.32 – 0.92)	0.64 (0.23 – 1.59)	0.63 (0.35 – 1.12)	0.73 (0.21 – 2.11)	0.93 (0.33 – 2.30)	0.97 (0.49 – 1.81)	**IFN β-1a 44 mcg**		
0.56 (0.21 – 1.22)	0.64 (0.30 – 1.18)	0.63 (0.25 – 1.41)	0.72 (0.26 – 1.67)	0.90 (0.41 – 1.76)	0.95 (0.49 – 1.70)	0.98 (0.50 – 1.78)	**IFNβ 1-a 30 mcg**	
0.45 (0.16 – 1.10)	**0.50 (0.25 – 0.94)**	0.50 (0.17 – 1.26)	0.57 (0.25 – 1.14)	0.71 (0.42 – 1.18)	0.74 (0.33 – 1.53)	0.77 (0.34 – 1.59)	0.78 (0.48 – 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 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	**0.40 (0.24-0.66)**	0.43 (0.52 -2.15)	**0.44 (0.24-0.79)**	**0.40 (0.25-0.64)**	N/A	0.69 (0.34-1.44)	**0.45 (0.23-0.89)**	**0.44 (0.25-0.79)**	**0.19 (0.06-0.54)**
OCR	**0.44 (0.27-0.74)**	N/A	**0.45 (0.27-0.75)**	**0.44 (0.27-0.71)**	N/A	0.77 (0.36-1.60)	**0.42 (0.21-0.82)**	N/A	0.41 (0.21-0.77)
NAT	**0.55 (0.36-0.84)**	N/A	**0.55 (0.37-0.82)**	**0.55 (0.38-0.80)**	N/A	**0.54 (0.36-0.80)**	0.56 (0.30-1.00)	**0.56 (0.35-0.90)**	**0.56 (0.36-0.86)**
DAC	**0.61 (0.40-0.88)**	N/A	**0.64 (0.41-0.92)**	**0.58 (0.40-0.82)**	N/A	**0.61 (0.39-0.89)**	**0.45 (0.18-0.98)**	0.64 (0.37-1.11)	**0.55 (0.34-0.84)**
PEG	0.62 (0.36-1.02)	N/A	0.62 (0.36-1.01)	**0.62 (0.38-0.99)**	N/A	**0.61 (0.36-0.99)**	0.63 (0.31-1.18)	N/A	0.62 (0.36-1.02)
DMF	**0.63 (0.44-0.87)**	N/A	0.65 (0.42-1.02)	**0.65 (0.41-0.98)**	N/A	0.67 (0.43-1.07)	N/A	0.65 (0.40-1.04)	0.62 (0.31-1.13)
IFN β-1b 250 mcg	0.64 (0.40-1.00)	0.62 (0.14-1.53)	N/A	0.74 (0.53-1.02)	0.57 (0.14-1.49)	0.94 (0.55-1.55)	**0.56 (0.28-0.93)**	**0.63 (0.42-0.91)**	0.69 (0.39-1.16)
FIN	**0.67 (0.50-0.89)**	N/A	**0.67 (0.50-0.90)**	**0.66 (0.51-0.85)**	N/A	**0.66 (0.50-0.87)**	**0.61 (0.36-0.98)**	**0.72 (0.49-1.02)**	**0.65 (0.48-0.87)**
IFN β-1a 44 mcg	**0.70 (0.50-0.98)**	0.89 (0.07-2.27)	**0.71 (0.51-0.98)**	**0.70 (0.52-0.94)**	0.68 (0.18-1.68)	0.99 (0.42-2.12)	0.67 (0.43-1.03)	0.76 (0.51-1.16)	0.64 (0.38-1.03)
GA 20 mg	**0.70 (0.54-0.93)**	0.71 (0.13-1.90)	0.71 (0.49-1.03)	**0.73 (0.56-0.95)**	0.89 (0.16-2.15)	0.90 (0.60-1.33)	**0.64 (0.41-0.98)**	**0.72 (0.52-0.98)**	0.88 (0.45-1.50)
TER 14mg	**0.71 (0.51-0.97)**	N/A	**0.71 (0.52-0.96)**	**0.71 (0.53-0.94)**	N/A	**0.71 (0.51-0.94)**	N/A	0.72 (0.49-1.02)	**0.72 (0.52-0.99)**
IFN β-1a 30 mcg	**0.76 (0.60-0.97)**	0.67 (0.21-1.76)	0.79 (0.58-1.01)	**0.71 (0.56-0.90)**	0.85 (0.28-1.80)	0.76 (0.56-1.02)	0.75 (0.53-1.07)	0.74 (0.54-1.02)	**0.67 (0.45-0.95)**
IFN β-1a 22 mcg	0.80 (0.51-1.23)	N/A	0.80 (0.52-1.23)	0.80 (0.53-1.17)	0.80 (0.16-1.99)	N/A	0.79 (0.42-1.07)	0.84 (0.50-1.35)	0.77 (0.47-1.21)
TER 7 mg	0.85 (0.62-1.16)	N/A	**0.85 (0.64-1.14)**	0.85 (0.65-1.11)	N/A	0.84 (0.64-1.12)	N/A	0.86 (0.60-1.19)	0.86 (0.63-1.16)
GA 40mg	1.18 (0.69-1.97)	N/A	N/A	1.20 (0.71-1.95)	N/A	1.17 (0.69-1.97)	1.22 (0.56-2.14)	N/A	1.17 (0.68-1.96)

Table D6. 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	**0.40 (0.24-0.66)**	N/A	**0.41 (0.27-0.61)**	**0.32 (0.19-0.53)**	**0.40 (0.20-0.80)**	**0.41 (0.15-0.91)**	**0.35 (0.20-0.61)**
OCR	**0.44 (0.27-0.74)**	N/A	**0.44 (0.29-0.74)**	**0.35 (0.22-0.56)**	**0.38 (0.19-0.74)**	0.46 (0.17-1.02)	0.39 (0.22-0.69)
NAT	**0.55 (0.36-0.84)**	**0.59 (0.46 - 0.75)**	**0.55 (0.41-0.74)**	**0.58 (0.40-0.83)**	**0.49 (0.28-0.86)**	**0.56 (0.29-0.98)**	**0.55 (0.35-0.84)**
DAC	**0.61 (0.40-0.88)**	**0.43 (0.22 - 0.85)**	**0.62 (0.46-0.82)**	**0.54 (0.34-0.85)**	**0.53 (0.31-0.87)**	0.62 (0.23-1.30)	**0.65 (0.40-0.99)**
PEG	0.62 (0.36-1.02)	**0.60 (0.39 - 0.93)**	**0.62 (0.40-0.93)**	0.62 (0.38-1.01)	0.52 (0.23-1.07)	N/A	0.60 (0.35-1.00)
DMF	**0.63 (0.44-0.87)**	0.66 (0.42 - 1.05)	**0.65 (0.42-0.95)**	**0.62 (0.45-0.87)**	0.57 (0.30-1.00)	0.65 (0.27-1.33)	0.68 (0.41-1.10)
IFN β-1b 250 mcg	0.64 (0.40-1.00)	0.77 (0.56 - 1.05)	**0.65 (0.50-0.85)**	**0.32 (0.16-0.66)**	**0.51 (0.26-0.90)**	0.64 (0.27-1.20)	0.70 (0.45-1.01)
FIN	**0.67 (0.50-0.89)**	**0.71 (0.56 - 0.90)**	**0.67 (0.54-0.84)**	**0.67 (0.49-0.91)**	0.51 (0.20-1.16)	0.69 0.25-1.46)	**0.67 (0.50-0.90)**
IFN β-1a 44 mcg	**0.70 (0.50-0.98)**	0.96 (0.52 - 1.77)	**0.70 (0.55-0.87)**	**0.58 (0.40-0.86)**	0.61 (0.36-1.01)	0.72 (0.31-1.39)	**0.62 (0.41-0.93)**
GA 20 mg	**0.70 (0.54-0.93)**	0.91 (0.62 - 1.32)	**0.70 0.55-0.87)**	0.87 (0.53-1.44)	**0.59 (0.35-0.98)**	0.72 (0.31-1.38)	0.80 (0.56-1.13)
TER 14 mg	**0.71 (0.51-0.97)**	**0.72 (0.58 - 0.91)**	0.71 (0.56-1.11)	0.69 (0.51-0.92)	0.54 (0.23-1.17)	0.73 (0.24-1.67)	0.73 (0.51-1.03)
IFN β-1a 30 mcg	**0.76 (0.60-0.97)**	**0.69 (0.52 - 0.91)**	**0.75 (0.61-0.92)**	0.72 (0.49-1.06)	0.65 (0.40-1.05)	0.78 (0.35-1.47)	0.81 (0.58-1.13)
IFN β-1a 22 mcg	0.80 (0.51-1.23)	0.82 (0.63 - 1.07)	0.80 (0.56-1.11)	0.68 (0.44-1.03)	0.70 (0.38-1.25)	0.81 (0.33-1.63)	0.76 (0.47-1.17)
TER 7 mg	0.85 (0.62-1.16)	0.86 (0.70 - 1.06)	0.85 (0.68-1.06)	0.84 (0.64-1.11)	0.66 (0.29-1.38)	0.88 (0.30-1.94)	0.88 (0.63-1.21)
GA 40 mg	1.18 (0.69-1.97)	1.20 (0.70 – 2.10)	1.19 (0.74-1.88)	N/A	0.95 (0.39-2.12)	1.22 (0.34-2.92)	1.24 (0.67-2.13)

Appendix E. Comparative Value Supplemental Information

Table E1. DMT administration costs

Product Name	Administration instructions	Annual administration cost*	
		Year 1	Subsequent years
Lemtrada	Infusion over 4 hours; 5 infusions year 1, 3 infusions subsequent years	$634	$380
Ocrevus (PPMS)	Infusion of 300 mg given over 150 minutes (4.35 infusions per year)	$427	$427
Ocrevus (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
Tysabri	Infusion over 1 hour, 13.04 infusions per year	$910	$910

*Varied ±20% in sensitivity analysis

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[164]
Infusion cost/hr (2+ hours), CPT 96366	$19		Source: physician fee schedule 2016[164]
Complete blood count, CPT 85025	$14	c_blood	Source: lab fee schedule 2016[165]
Serum Creatinine, CPT 80053	$19	c_creatinine	Source: lab fee schedule 2016[165]
Urinanlysis, CPT 81000	$6	c_urine	Source: lab fee schedule 2016[165]
Thyroid, CPT 84436+84479	$25	c_thyroid	Source: lab fee schedule 2016[165]
Liver, CPT 80076	$15	c_liver	Source: lab fee schedule 2016[165]
MRI, CPT 70543	$495	c_MRI	Source: physician fee schedule 2016[164]
ECG, CPT 93000	$17	c_ecg	Source: physician fee schedule 2016[164]
ALT, CPT 84460	$10	c_ALT	Source: lab fee schedule 2016[165]
CD4 lymphocyte, CPT 86360	$87	c_cd4	Source: lab fee schedule 2016[165]
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 [166]
Hospital stay for disorders of the biliary without complications, DRG 446	$4,477		Source: physician fee schedule 2016[164]
Inpatient stay for depression, DRG 881	$3,884		Source: physician fee schedule 2016[164]
Hospital stay for influenza/pneumonia, DRG 194	$5,687		Source: physician fee schedule 2016[164]
Serious infection, DRG 177	$11,177		Source: physician fee schedule 2016[164]
Cranial nerve disorder, DRG 073	$7,829		Source: physician fee schedule 2016[164]
Specialist visit, CPT 99215	$112	c_office	Source: physician fee schedule 2016[164]

*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
Aubagio	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
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
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
Copaxone	None	N/A	$0	$0	N/A
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
Gilenya	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
Glatopa	None	N/A	$0	$0	N/A

Product Name	Monitoring instructions	Implemented as (annual)	Annual monitoring cost**		
			Year 1	Subsequent years	After discontinuation
Lemtrada	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*
Ocrevus (PPMS)	None	N/A	$0	$0	N/A
Ocrevus (RRMS)	None	N/A	$0	$0	N/A
Plegridy	CBC and liver function every 6 months	2*(c_blood+c_liver)	$59	$59	N/A
Rebif	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
Tecfidera	Obtain a complete blood cell count (CBC) including lymphocyte count before initiation of therapy; CBC every 6 months	6*c_blood	$29	$29	N/A
Tysabri	MRI every 6 months CBC+ LFT every month	2*c_MRI +12*c_liver	$1,171	$1,171	N/A
Zinbryta	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

*All monitoring costs paid by manufacturer

**Varied ±20% in sensitivity analysis

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)**	**GA_C 20mg**	**GA_C 40mg**	**IFN β-1a 22mcg**	**IFN β-1a 44mcg**	**PEG**	**FIN**	**TER 7mg**	**TER 14mg**	**DMF**	**NAT**	**ALE**	**DAC**	**OCR**
Lymphopenia*					0.01										
ALT increased*									0.01	0.01					
Cholelithiasis*					0.01										
Influenza*					0.01										
Serious infection*											0.01				
Trigeminal neuralgia*					0.01										
Depression*					0.01										
PML†												0.0003			
Total Cost	$0	$0	$0	$0	$154	$0	$0	$0	$4	$3	$3	$0	$0	$0	$0
Total Disutility	0	0	0	0	0.01075	0	0	0	0	0	0.00007	0.00012	0	0	0

*Rate source: trial aggregate >1%

†Rate source: NAT package insert

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)	0.40	0.24-0.66	0.29	0.22-0.36
Daclizumab (Zinbryta)	0.61	0.40-0.88	0.47	0.38-0.58
Dimethyl Fumarate (Tecfidera)	0.64	0.40-1.00	0.50	0.41-0.61
Fingolimod (Gilenya)	0.67	0.50-0.89	0.47	0.39-0.55
Glatiramer acetate 20 mg (Glatopa)	0.70	0.54-0.93	0.65	0.57-0.72
Glatiramer acetate 20 mg (Copaxone)	0.70	0.54-0.93	0.65	0.57-0.72
Glatiramer acetate 40 mg (Copaxone)	1.18	0.69-1.97	0.67	0.52-0.87
Interferon β-1a 30 mcg (Avonex)	0.76	0.60-0.97	0.83	0.74-0.94
Interferon β-1a 22 mcg (Rebif)	0.80	0.51-1.23	0.75	0.63-0.91
Interferon β-1a 44 mcg (Rebif)	0.70	0.50-0.98	0.66	0.57-0.74
Interferon β-1b 250 mcg (Betaseron)	0.63	0.44-0.87	0.65	0.55-0.76
Interferon β-1b 250 mcg (Extavia)	0.63	0.44-0.87	0.65	0.55-0.76
Natalizumab (Tysabri)	0.55	0.36-0.84	0.31	0.25-0.40
Ocrelizumab (Ocrevus) (RRMS)	0.44	0.27-0.74	0.43	0.34-0.54
Ocrelizumab (Ocrevus) (PPMS)*	0.75	0.58-0.98	N/A	
Peginterferon β-1a (Plegridy)	0.62	0.36-1.02	0.63	0.47-0.86
Teriflunomide 7 mg (Aubagio)	0.85	0.62-1.16	0.77	0.66-0.92
Teriflunomide 14mg (Aubagio)	0.71	0.51-0.97	0.66	0.57-0.79

*Source: ORATORIO trial slide deck

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

EDSS State	RRMS												PPMS
	CONFIRM[67] (n)				DEFINE[83] (n)			OPERA I & II[117] (n)	TOWER & TEMSO[118] (% of n)	CARE II[119] (% of n)	TOTAL		ORATORIO[117] 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[116]*		Scenario SA[138]	
	Base case[116,124]	Range for One-Way SA	Base case[116,124]	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[14,67,83,116]									
		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 RRMS EDSS+1 in SPMS[14,116]	Range for SA
0	0.003	0.002-0.004
1	0.032	0.026-0.038
2	0.117	0.094-0.140
3	0.210	0.168-0.252
4	0.299	0.239-0.359
5	0.237	0.190-0.284
6	0.254	0.203-0.305
7	0.153	0.122-0.184
8	1.000	0.900-1.000

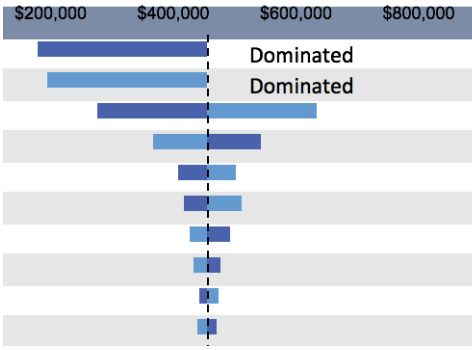
Table E10. Annual Probability of Moving Between EDSS States for Patients with Primary Progressive or Secondary Progressive Multiple Sclerosis

		EDSS State at End of Year[14,116]								
		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

Cost per additional QALY

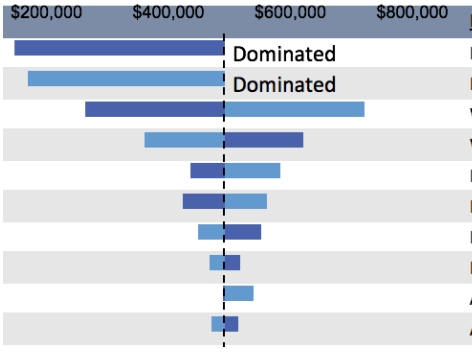
RRMS DAC vs GA 20 mg (Glatopa)



Parameter	Low Value	High Value
Relative Risk, Progression, DAC	0.400	0.880
Relative Risk, Progression, GA 20 mg (Glatopa)	0.540	0.930
WAC, DAC	5466.664	8199.996
WAC, GA 20 mg (Glatopa)	4155.136	6232.704
Discount from WAC, GA 20 mg (Glatopa)	0.280	0.420
Rate Ratio, Relapse, DAC	0.380	0.580
Rate Ratio, Relapse, GA 20 mg (Glatopa)	0.570	0.720
Annual Utiity, RRMS, EDSS 2	0.624	0.936
Age at beginning treatment, RRMS	23	35
Annual Utiity, RRMS, EDSS 0	0.700	1.050

Cost per additional QALY

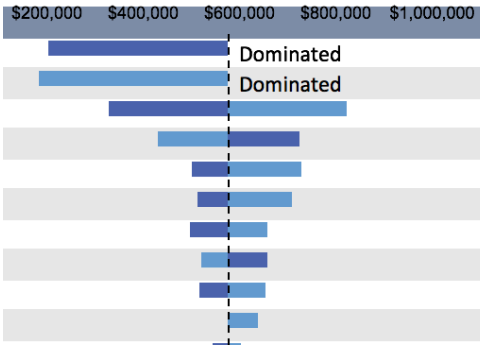
RRMS DMF vs GA 20 mg (Glatopa)



Parameter	Low Value	High Value
Relative Risk, Progression, DMF	0.400	1.000
Relative Risk, Progression, GA 20 mg (Glatopa)	0.540	0.930
WAC, DMF	5052.000	7578.000
WAC, GA 20 mg (Glatopa)	4155.136	6232.704
Rate Ratio, Relapse, DMF	0.410	0.610
Discount from WAC, GA 20 mg (Glatopa)	0.280	0.420
Rate Ratio, Relapse, GA 20 mg (Glatopa)	0.570	0.720
Discount from WAC, DMF	0.080	0.120
AE Disutility, DMF	0.000	0.050
Annual Utiity, RRMS, EDSS 2	0.624	0.936

Cost per Additional QALY

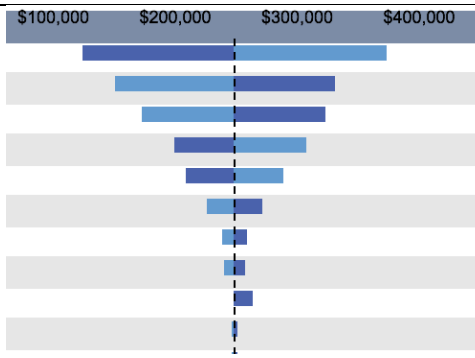
RRMS FIN vs GA 20 mg (Glatopa)



Parameter	Low Value	High Value
Relative Risk, Progression, FIN	0.500	0.890
Relative Risk, Progression, GA 20 mg (Glatopa)	0.540	0.930
WAC, FIN	5394.608	8091.912
WAC, GA 20 mg (Glatopa)	4155.136	6232.704
Relative Risk, Progression, NAT	0.360	0.840
Relative Risk, Progression, ALE	0.240	0.660
Discount from WAC, GA 20 mg (Glatopa)	0.280	0.420
Rate Ratio, Relapse, GA 20 mg (Glatopa)	0.570	0.720
Rate Ratio, Relapse, FIN	0.390	0.550
AE Disutility, FIN	0.000	0.050

Incremental costs

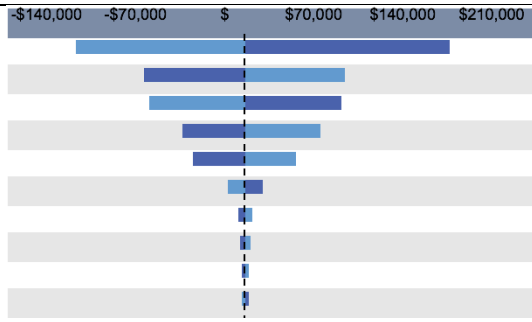
RRMS GA 20 mg vs GA 20 mg (Glatopa)



Parameter	Low Value	High Value
WAC, GA 20 mg (Copaxone)	5274.400	7911.600
Relative Risk, Progression, GA 20 mg (Copaxone)	0.540	0.930
WAC, GA 20 mg (Glatopa)	4155.136	6232.704
Relative Risk, Progression, GA 20 mg (Glatopa)	0.540	0.930
Discount from WAC, GA 20 mg (Glatopa)	0.280	0.420
Discount from WAC, GA 20 mg (Copaxone)	0.120	0.180
Discontinuation Rate, First Line, Year 1-X	0.080	0.120
Discontinuation Rate, First Line, Year >X	0.024	0.036
Discontinuation Switch Year (X), First-Line	1.600	2.400
Probability: RRMS to SPMS, EDSS 3	0.168	0.252

Incremental costs

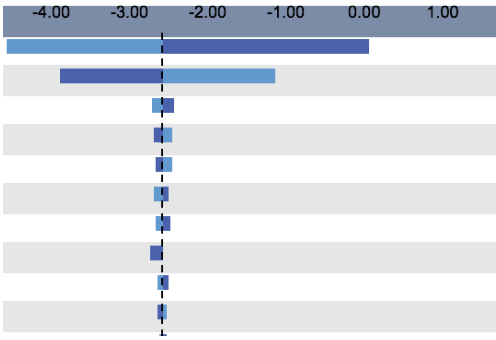
RRMS GA 40 mg vs GA 20 mg (Glatopa)



Parameter	Low Value	High Value
Relative Risk, Progression, GA 40 mg	0.690	1.970
WAC, GA 40 mg	4323.200	6484.800
WAC, GA 20 mg (Glatopa)	4155.136	6232.704
Relative Risk, Progression, GA 20 mg (Glatopa)	0.540	0.930
Discount from WAC, GA 20 mg (Glatopa)	0.280	0.420
Discount from WAC, GA 40 mg	0.120	0.180
Direct Costs, EDSS 9	16881.774	25322.661
Direct Costs, EDSS 8	15257.131	22885.696
Discontinuation Rate, Second Line	0.080	0.120
WAC, FIN	5394.608	8091.912

Incremental QALYs

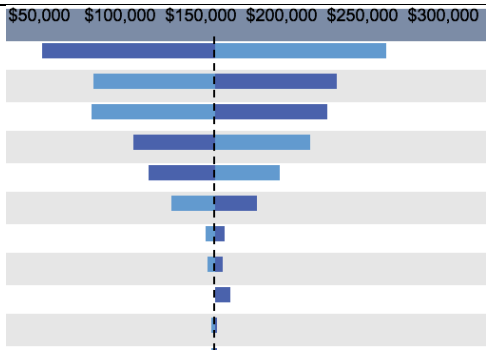
RRMS GA 40 mg vs GA 20 mg (Glatopa)



Parameter	Low Value	High Value
Relative Risk, Progression, GA 40 mg	0.690	1.970
Relative Risk, Progression, GA 20 mg (Glatopa)	0.540	0.930
Annual Utility, RRMS, EDSS 2	0.624	0.936
Discontinuation Rate, First Line, Year 1-X	0.080	0.120
Age at beginning treatment, RRMS	23	35
Rate Ratio, Relapse, GA 40 mg	0.520	0.870
Annual Utility, RRMS, EDSS 1	0.667	1.001
Discontinuation Switch Year (X), First-Line	1.600	2.400
Annual Utility, RRMS, EDSS 0	0.700	1.050
Rate Ratio, Relapse, GA 20 mg (Glatopa)	0.570	0.720

Incremental costs

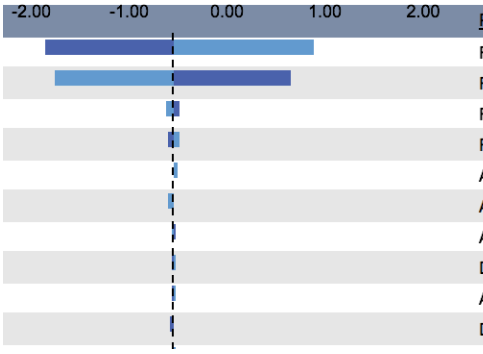
RRMS IFN β-1a 30 mcg vs GA 20 mg (Glatopa)



Parameter	Low Value	High Value
WAC, IFN β-1a 30 mcg	4656.800	6985.200
WAC, GA 20 mg (Glatopa)	4155.136	6232.704
Relative Risk, Progression, IFN β-1a 30 mcg	0.600	0.970
Relative Risk, Progression, GA 20 mg (Glatopa)	0.540	0.930
Discount from WAC, GA 20 mg (Glatopa)	0.280	0.420
Discount from WAC, IFN β-1a 30 mcg	0.160	0.240
Discontinuation Rate, First Line, Year 1-X	0.080	0.120
Discontinuation Rate, First Line, Year >X	0.024	0.036
Discontinuation Switch Year (X), First-Line	1.600	2.400
Probability: RRMS to SPMS, EDSS 3	0.168	0.252

Incremental QALYs

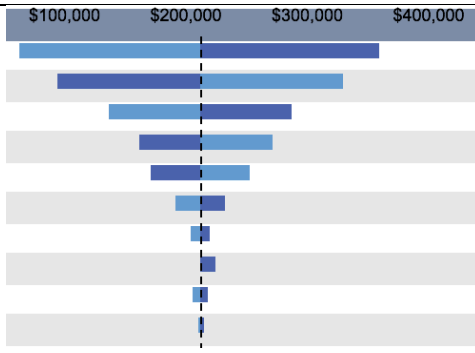
RRMS IFN β-1a 30 mcg vs GA 20 mg (Glatopa)



Parameter	Low Value	High Value
Relative Risk, Progression, GA 20 mg (Glatopa)	0.540	0.930
Relative Risk, Progression, IFN β-1a 30 mcg	0.600	0.970
Rate Ratio, Relapse, IFN β-1a 30 mcg	0.740	0.940
Rate Ratio, Relapse, GA 20 mg (Glatopa)	0.570	0.720
AE Disutility, GA 20 mg (Glatopa)	0.000	0.050
AE Disutility, IFN β-1a 30 mcg	0.000	0.050
Annual Utility, RRMS, EDSS 2	0.624	0.936
Discontinuation Rate, First Line, Year 1-X	0.080	0.120
Age at beginning treatment, RRMS	23	35
Discontinuation Switch Year (X), First-Line	1.600	2.400

Incremental costs

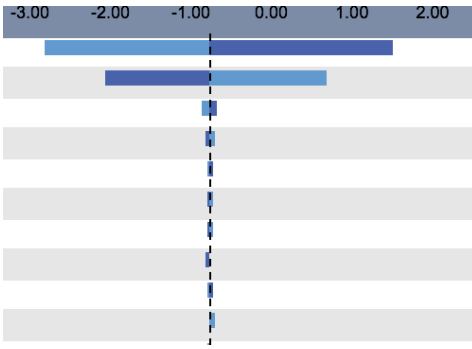
RRMS IFN β-1a 22 mcg vs GA 20 mg (Glatopa)



Parameter	Low Value	High Value
Relative Risk, Progression, IFN β-1a 22 mcg	0.510	1.230
WAC, IFN β-1a 22 mcg	5026.856	7540.284
WAC, GA 20 mg (Glatopa)	4155.136	6232.704
Relative Risk, Progression, GA 20 mg (Glatopa)	0.540	0.930
Discount from WAC, GA 20 mg (Glatopa)	0.280	0.420
Discount from WAC, IFN β-1a 22 mcg	0.120	0.180
Discontinuation Rate, First Line, Year 1-X	0.080	0.120
Discontinuation Switch Year (X), First-Line	1.600	2.400
Discontinuation Rate, First Line, Year >X	0.024	0.036
Probability: RRMS to SPMS, EDSS 3	0.168	0.252

Incremental QALYs

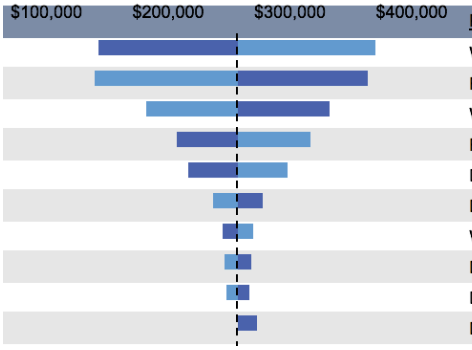
RRMS IFN β-1a 22 mcg vs GA 20 mg (Glatopa)



Parameter	Low Value	High Value
Relative Risk, Progression, IFN β-1a 22 mcg	0.510	1.230
Relative Risk, Progression, GA 20 mg (Glatopa)	0.540	0.930
Rate Ratio, Relapse, IFN β-1a 22 mcg	0.630	0.910
Rate Ratio, Relapse, GA 20 mg (Glatopa)	0.570	0.720
Annual Utiity, RRMS, EDSS 2	0.624	0.936
Age at beginning treatment, RRMS	23	35
Discontinuation Rate, First Line, Year 1-X	0.080	0.120
Discontinuation Switch Year (X), First-Line	1.600	2.400
Annual Utiity, RRMS, EDSS 1	0.667	1.001
AE Disutility, GA 20 mg (Glatopa)	0.000	0.050

Incremental costs

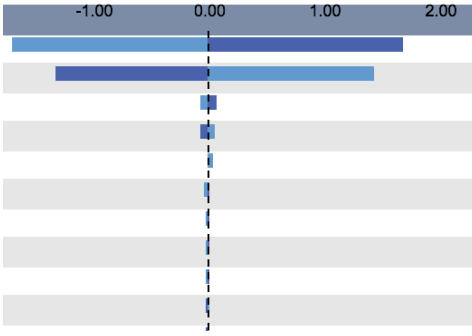
RRMS IFN β-1a 44 mcg vs GA 20 mg (Glatopa)



Parameter	Low Value	High Value
WAC, IFN β-1a 22 mcg	5026.856	7540.284
Relative Risk, Progression, IFN β-1a 44 mcg	0.500	0.980
WAC, GA 20 mg (Glatopa)	4155.136	6232.704
Relative Risk, Progression, GA 20 mg (Glatopa)	0.540	0.930
Discount from WAC, GA 20 mg (Glatopa)	0.280	0.420
Discount from WAC, IFN β-1a 22 mcg	0.120	0.180
WAC, IFN β-1a 44 mcg	5026.856	7540.284
Discontinuation Rate, First Line, Year 1-X	0.080	0.120
Discontinuation Rate, First Line, Year >X	0.024	0.036
Discontinuation Switch Year (X), First-Line	1.600	2.400

Incremental QALYs

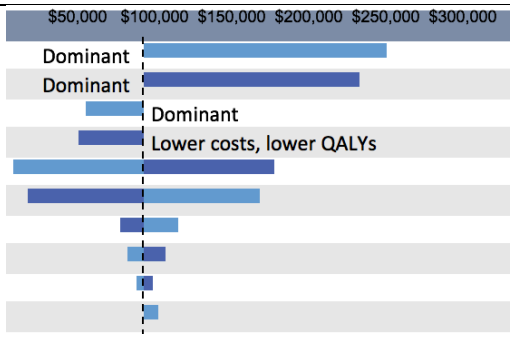
RRMS IFN β-1a 44 mcg vs GA 20 mg (Glatopa)



Parameter	Low Value	High Value
Relative Risk, Progression, IFN β-1a 44 mcg	0.500	0.980
Relative Risk, Progression, GA 20 mg (Glatopa)	0.540	0.930
Rate Ratio, Relapse, IFN β-1a 44 mcg	0.570	0.740
Rate Ratio, Relapse, GA 20 mg (Glatopa)	0.570	0.720
AE Disutility, GA 20 mg (Glatopa)	0.000	0.050
AE Disutility, IFN β-1a 44 mcg	0.000	0.050
Relapse Disutiity	0.073	0.109
Relapse Disutiity	0.242	0.362
Annual Relapse Rate, RRMS, EDSS 2	0.544	0.816
Discontinuation Rate, First Line, Year 1-X	0.080	0.120

Cost per additional QALY

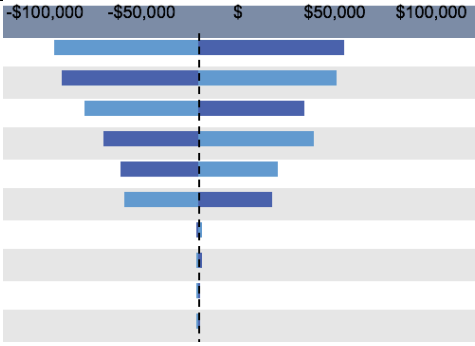
RRMS IFN β-1b 250 mcg (Betaseron) vs GA 20 mg (Glatopa)



Parameter	Low Value	High Value
WAC, IFN β-1b 250 mcg (Betaseron)	4974.968	7462.452
WAC, GA 20 mg (Glatopa)	4155.136	6232.704
Relative Risk, Progression, GA 20 mg (Glatopa)	0.540	0.930
Relative Risk, Progression, IFN β-1b 250 mcg (Betaseron)	0.440	0.870
Discount from WAC, IFN β-1b 250 mcg (Betaseron)	0.280	0.420
Discount from WAC, GA 20 mg (Glatopa)	0.280	0.420
Rate Ratio, Relapse, IFN β-1b 250 mcg (Betaseron)	0.550	0.760
Rate Ratio, Relapse, GA 20 mg (Glatopa)	0.570	0.720
Annual Utiity, RRMS, EDSS 2	0.624	0.936
AE Disutility, IFN β-1b 250 mcg (Betaseron)	0.000	0.050

Incremental costs

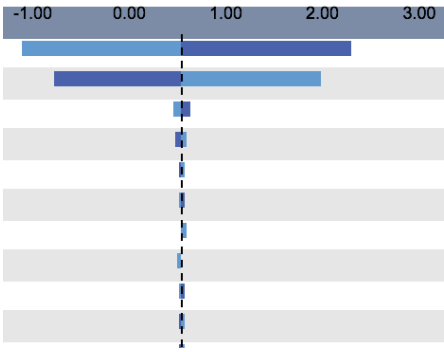
RRMS) vs GA 20 mg (Glatopa)



Parameter	Low Value	High Value
WAC, GA 20 mg (Glatopa)	4155.136	6232.704
WAC, IFN β-1b 250 mcg (Extavia)	4446.568	6669.852
Relative Risk, Progression, IFN β-1b 250 mcg (Extavia)	0.440	0.870
Relative Risk, Progression, GA 20 mg (Glatopa)	0.540	0.930
Discount from WAC, GA 20 mg (Glatopa)	0.280	0.420
Discount from WAC, IFN β-1b 250 mcg (Extavia)	0.280	0.420
Rate Ratio, Relapse, IFN β-1b 250 mcg (Extavia)	0.550	0.760
Rate Ratio, Relapse, GA 20 mg (Glatopa)	0.570	0.720
Direct Costs, EDSS 9	16881.774	25322.661
Direct Costs, EDSS 8	15257.131	22885.696

Incremental QALYs

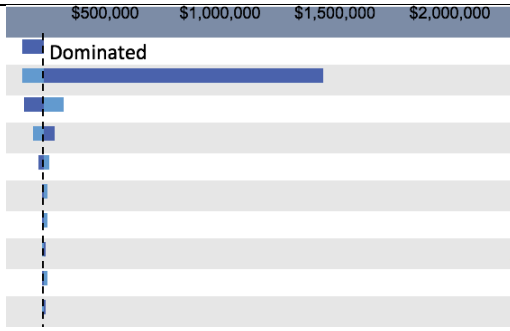
RRMS IFN β-1b 250 mcg (Extavia) vs GA 20 mg (Glatopa)



Parameter	Low Value	High Value
Relative Risk, Progression, IFN β-1b 250 mcg (Extavia)	0.440	0.870
Relative Risk, Progression, GA 20 mg (Glatopa)	0.540	0.930
Rate Ratio, Relapse, IFN β-1b 250 mcg (Extavia)	0.550	0.760
Rate Ratio, Relapse, GA 20 mg (Glatopa)	0.570	0.720
Annual Utiity, RRMS, EDSS 2	0.624	0.936
Age at beginning treatment, RRMS	23	35
AE Disutility, GA 20 mg (Glatopa)	0.000	0.050
AE Disutility, IFN β-1b 250 mcg (Extavia)	0.000	0.050
Discontinuation Rate, First Line, Year 1-X	0.080	0.120
Annual Utiity, RRMS, EDSS 0	0.700	1.050

Cost per additional QALY

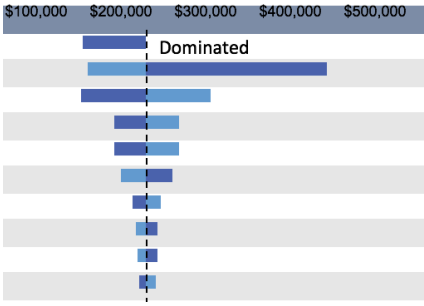
RRMS NAT vs GA 20 mg (Glatopa)



Parameter	Low Value	High Value
Relative Risk, Progression, NAT	0.360	0.840
Relative Risk, Progression, GA 20 mg (Glatopa)	0.540	0.930
WAC, NAT	4637.600	6956.400
WAC, GA 20 mg (Glatopa)	4155.136	6232.704
Discount from WAC, GA 20 mg (Glatopa)	0.280	0.420
Relative Risk, Progression, ALE	0.240	0.660
Relative Risk, Progression, FIN	0.500	0.890
Annual Utiity, RRMS, EDSS 2	0.624	0.936
Rate Ratio, Relapse, NAT	0.250	0.400
Rate Ratio, Relapse, GA 20 mg (Glatopa)	0.570	0.720

Cost per additional QALY

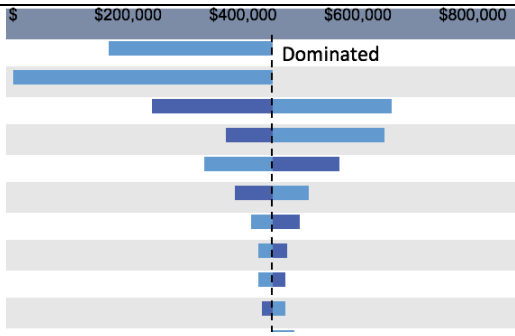
RRMS OCR vs GA 20 mg (Glatopa)



Parameter	Low Value	High Value	Low Result
Relative Risk, Progression, OCR	0.270	0.740	$154,901
Relative Risk, Progression, GA 20 mg (Glatopa)	0.540	0.930	$442,981
Annual Cost, OCR	68123.533	102185.300	$153,638
WAC, DAC	5466.664	8199.996	$191,501
WAC, ALE	16195.000	24292.500	$191,734
WAC, GA 20 mg (Glatopa)	4155.136	6232.704	$259,929
Discount from WAC, GA 20 mg (Glatopa)	0.280	0.420	$213,641
Annual Utiity, RRMS, EDSS 2	0.624	0.936	$243,058
Annual Utiity, RRMS, EDSS 0	0.700	1.050	$241,900
Rate Ratio, Relapse, OCR	0.340	0.540	$221,487

Cost per additional QALY

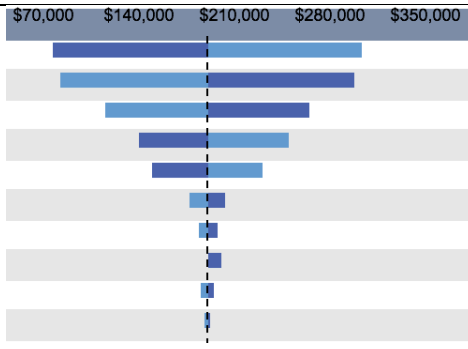
RRMS PEG vs GA 20 mg (Glatopa)



Parameter	Low Value	High Value
Relative Risk, Progression, GA 20 mg (Glatopa)	0.540	0.930
Relative Risk, Progression, PEG	0.360	1.020
WAC, PEG	4656.800	6985.200
Rate Ratio, Relapse, PEG	0.470	0.860
WAC, GA 20 mg (Glatopa)	4155.136	6232.704
Discount from WAC, GA 20 mg (Glatopa)	0.280	0.420
Rate Ratio, Relapse, GA 20 mg (Glatopa)	0.570	0.720
Annual Utiity, RRMS, EDSS 2	0.624	0.936
Discount from WAC, PEG	0.080	0.120
Age at beginning treatment, RRMS	23	35

Incremental costs

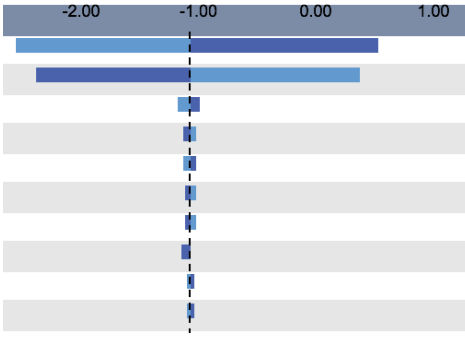
RRMS TER 7 mg vs GA 20 mg (Glatopa)



Parameter	Low Value	High Value
WAC, TER 7 mg	4701.664	7052.496
Relative Risk, Progression, TER 7 mg	0.620	1.160
WAC, GA 20 mg (Glatopa)	4155.136	6232.704
Relative Risk, Progression, GA 20 mg (Glatopa)	0.540	0.930
Discount from WAC, GA 20 mg (Glatopa)	0.280	0.420
Discount from WAC, TER 7 mg	0.080	0.120
Discontinuation Rate, First Line, Year 1-X	0.080	0.120
Discontinuation Switch Year (X), First-Line	1.600	2.400
Discontinuation Rate, First Line, Year >X	0.024	0.036
Probability: RRMS to SPMS, EDSS 3	0.168	0.252

Incremental QALYs

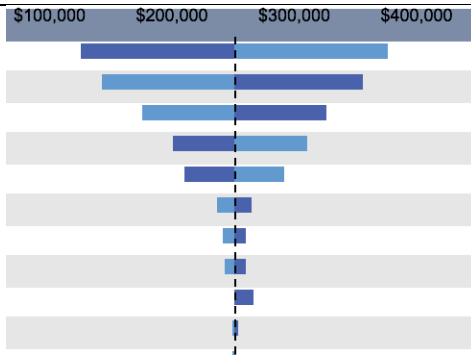
RRMS TER 7 mg vs GA 20 mg (Glatopa)



Parameter	Low Value	High Value
Relative Risk, Progression, TER 7 mg	0.620	1.160
Relative Risk, Progression, GA 20 mg (Glatopa)	0.540	0.930
Rate Ratio, Relapse, TER 7 mg	0.660	0.920
Rate Ratio, Relapse, GA 20 mg (Glatopa)	0.570	0.720
Annual Utiity, RRMS, EDSS 2	0.624	0.936
Age at beginning treatment, RRMS	23	35
Discontinuation Rate, First Line, Year 1-X	0.080	0.120
Discontinuation Switch Year (X), First-Line	1.600	2.400
Annual Utiity, RRMS, EDSS 1	0.667	1.001
Annual Utiity, RRMS, EDSS 0	0.700	1.050

Incremental costs

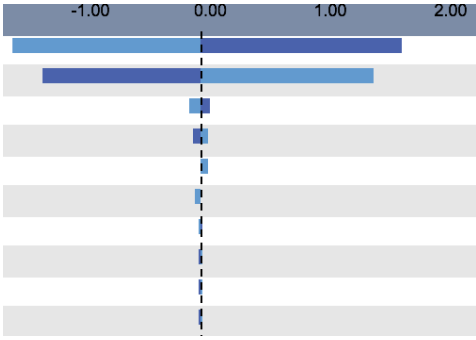
RRMS TER 14 mg vs GA 20 mg (Glatopa)



Parameter	Low Value	High Value
WAC, TER 14 mg	4701.664	7052.496
Relative Risk, Progression, TER 14 mg	0.510	0.970
WAC, GA 20 mg (Glatopa)	4155.136	6232.704
Relative Risk, Progression, GA 20 mg (Glatopa)	0.540	0.930
Discount from WAC, GA 20 mg (Glatopa)	0.280	0.420
Discount from WAC, TER 14 mg	0.080	0.120
Discontinuation Rate, First Line, Year 1-X	0.080	0.120
Discontinuation Rate, First Line, Year >X	0.024	0.036
Discontinuation Switch Year (X), First-Line	1.600	2.400
Probability: RRMS to SPMS, EDSS 3	0.168	0.252

Incremental QALYs

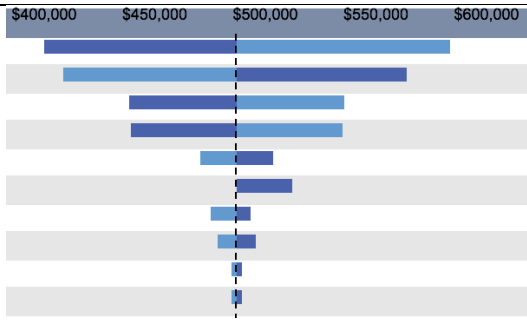
RRMS TER 14 mg vs GA 20 mg (Glatopa)



Parameter	Low Value	High Value
Relative Risk, Progression, TER 14 mg	0.510	0.970
Relative Risk, Progression, GA 20 mg (Glatopa)	0.540	0.930
Rate Ratio, Relapse, TER 14 mg	0.570	0.790
Rate Ratio, Relapse, GA 20 mg (Glatopa)	0.570	0.720
AE Disutility, GA 20 mg (Glatopa)	0.000	0.050
AE Disutility, TER 14 mg	0.000	0.050
Annual Utility, RRMS, EDSS 2	0.624	0.936
Age at beginning treatment, RRMS	23	35
Discontinuation Rate, First Line, Year 1-X	0.080	0.120
Discontinuation Rate, First Line, Year >X	0.024	0.036

Cost per additional QALY

PPMS OCR vs Supportive care



Parameter	Low Value	High Value
Annual Cost, OCR	68123.533	102185.300
Relative Risk, Progression, OCR	0.580	0.980
WAC, DAC	5466.664	8199.996
WAC, ALE	16195.000	24292.500
Discontinuation Rate, First Line, Year 1-X	0.080	0.120
Discontinuation Switch Year (X), First-Line	1.600	2.400
Age at beginning treatment, PPMS	33	50
Discontinuation Rate, First Line, Year >X	0.024	0.036
Discount from WAC, DAC	0.040	0.060
Discount from WAC, ALE	0.040	0.060

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	$344,438	$302,688	-	$388,821	$652,695	$585,008	-	$722,173	$1,251,258	$1,034,204	-	$1,482,829
Drug Costs	$0	$0	-	$0	$378,662	$314,961	-	$446,983	$952,280	$722,040	-	$1,191,475
Healthcare Costs	$344,438	$302,688	-	$388,821	$274,033	$235,454	-	$318,537	$298,978	$259,267	-	$343,862
Adverse Event Costs	$0	$0	-	$0	$0	$0	-	$0	$0	$0	-	$0
Total QALYs	4.9	4.30	-	5.54	10.5	7.93	-	12.78	8.5	6.26	-	10.64
Relapses	15.1	13.33	-	17.02	10.9	9.18	-	12.79	12.3	10.36	-	14.34
Life-Years	21.1	19.53	-	22.62	22.5	20.93	-	23.91	22.0	20.40	-	23.49
	Dimethyl fumarate				Fingolimod				Glatiramer acetate 20 mg (Glatopa)			
	Mean	Credible Range			Mean	Credible Range			Mean	Credible Range		
Total Costs	$1,131,483	$929,560	-	$1,351,462	$1,144,051	$964,529	-	$1,335,515	$836,217	$723,025	-	$955,791
Drug Costs	$827,301	$613,643	-	$1,059,202	$839,260	$655,143	-	$1,039,158	$524,441	$409,039	-	$647,462
Healthcare Costs	$304,175	$261,381	-	$351,349	$304,791	$266,706	-	$345,265	$311,777	$273,224	-	$353,093
Adverse Event Costs	$6	$0	-	$40	$0	$0	-	$0	$0	$0	-	$0
Total QALYs	8.0	5.55	-	10.63	7.9	6.24	-	9.71	7.4	5.86	-	9.12
Relapses	12.4	10.43	-	14.50	12.0	10.28	-	13.98	13.4	11.59	-	15.44
Life-Years	21.9	20.26	-	23.39	21.8	20.32	-	23.31	21.7	20.20	-	23.19
	Glatiramer acetate 20 mg (Copaxone)				Glatiramer acetate 40 mg (Copaxone)				Interferon β-1a 30 mcg (Avonex)			
	Mean	Credible Range			Mean	Credible Range			Mean	Credible Range		
Total Costs	$1,111,426	$946,519	-	$1,284,201	$859,615	$697,051	-	$1,059,588	$1,011,796	$872,605	-	$1,166,466
Drug Costs	$802,621	$634,079	-	$983,273	$521,222	$344,049	-	$744,772	$694,388	$555,435	-	$851,170
Healthcare Costs	$308,805	$271,532	-	$349,971	$338,394	$290,465	-	$390,960	$317,408	$279,039	-	$358,687
Adverse Event Costs	$0	$0	-	$0	$0	$0	-	$0	$0	$0	-	$0
Total QALYs	7.7	6.13	-	9.34	5.1	2.50	-	7.55	7.0	5.63	-	8.54
Relapses	13.5	11.61	-	15.48	13.0	10.50	-	14.97	14.6	12.62	-	16.73
Life-Years	21.8	20.26	-	23.25	21.1	19.42	-	22.76	21.7	20.15	-	23.11

Continued on next page

	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	$1,060,949	$863,032	-	$1,274,177	$1,108,590	$939,430	-	$1,293,550	$890,375	$768,577	-	$1,026,679
Drug Costs	$740,830	$532,625	-	$968,406	$797,211	$616,804	-	$988,714	$585,183	$457,177	-	$731,263
Healthcare Costs	$320,109	$276,102	-	$366,663	$311,368	$270,613	-	$354,265	$305,192	$266,127	-	$347,815
Adverse Event Costs	$10	$0	-	$41	$11	$0	-	$42	$0	$0	-	$0
Total QALYs	6.7	4.45	-	9.18	7.5	5.64	-	9.43	8.1	6.10	-	9.96
Relapses	13.9	11.69	-	16.34	13.5	11.60	-	15.58	13.7	11.71	-	15.93
Life-Years	21.6	19.99	-	23.14	21.8	20.22	-	23.20	21.9	20.34	-	23.38
	Interferon β-1b 250 mcg (Extavia)				Natalizumab				Ocrelizumab			
	Mean	Credible Range			Mean	Credible Range			Mean	Credible Range		
Total Costs	$819,958	$710,087	-	$938,319	$1,216,360	$1,016,401	-	$1,424,438	$1,424,807	$1,144,099	-	$1,746,212
Drug Costs	$515,450	$401,612	-	$640,304	$926,992	$712,534	-	$1,147,759	$1,143,057	$848,035	-	$1,476,283
Healthcare Costs	$304,508	$265,720	-	$346,821	$289,367	$248,723	-	$333,819	$281,750	$240,917	-	$327,447
Adverse Event Costs	$0	$0	-	$0	$0	$0	-	$0	$0	$0	-	$0
Total QALYs	8.1	6.18	-	10.07	9.2	6.88	-	11.44	9.9	7.27	-	12.39
Relapses	13.7	11.67	-	15.89	11.0	9.27	-	12.81	12.2	10.29	-	14.38
Life-Years	21.9	20.38	-	23.41	22.1	20.61	-	23.59	22.4	20.77	-	23.85
	Peginterferon β-1a				Teriflunomide 7 mg				Teriflunomide 14 mg			
	Mean	Credible Range			Mean	Credible Range			Mean	Credible Range		
Total Costs	$1,131,616	$912,860	-	$1,358,479	$1,037,965	$869,333	-	$1,222,109	$1,090,012	$918,508	-	$1,282,010
Drug Costs	$827,244	$587,317	-	$1,073,482	$714,200	$538,346	-	$903,708	$776,054	$594,379	-	$977,016
Healthcare Costs	$304,372	$261,838	-	$353,096	$323,764	$283,515	-	$368,453	$313,958	$274,443	-	$358,002
Adverse Event Costs	$0	$0	-	$0	$0	$0	-	$0	$0	$0	-	$0
Total QALYs	8.1	5.26	-	10.81	6.4	4.60	-	8.18	7.2	5.45	-	9.05
Relapses	13.6	11.14	-	16.45	13.8	11.74	-	16.06	13.4	11.46	-	15.55
Life-Years	21.9	20.23	-	23.46	21.5	19.90	-	22.96	21.7	20.15	-	23.18

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

	Supportive Care				Ocrelizumab			
	Mean	Credible Range			Mean	Credible Range		
Total Costs	$265,915	$246,537	-	$265,711	$787,821	$730,310	-	$783,679
Drug Costs	$0	$0	-	$0	$519,703	$465,920	-	$515,079
Healthcare Costs	$265,915	$246,537	-	$265,711	$268,118	$249,025	-	$267,897
Adverse Event Costs	$0	$0	-	$0	$0	$0	-	$0
Total QALYs	2.7	2.58	-	2.74	3.5	3.21	-	3.47
Life-Years	15.7	14.78	-	15.69	16.2	15.35	-	16.29

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	$55,685	$36,609	-	$99,687	$255,879	$174,472	-	$544,389	$254,810	$158,433	-	$874,926
$ per Relapse	$73,671	$53,115	-	$108,454	$320,003	$200,591	-	$672,076	$293,755	$177,277	-	$660,872
$ per Life-Year	$223,224	$142,502	-	$430,351	$1,023,398	$659,497	-	$2,330,022	$1,017,047	$605,680	-	$3,666,807
Total Costs	$308,851	$325,654	-	$372,987	$913,550	$832,694	-	$1,146,272	$785,508	$663,354	-	$987,717
Drug Costs	$379,379	$314,712	-	$402,189	$959,636	$732,841	-	$933,188	$826,279	$613,772	-	$924,318
Healthcare Costs	-$70,528	-$101,834	-	-$80,840	-$46,085	-$72,080	-	-$74,351	-$40,778	-$71,294	-	-$47,371
Adverse Event Costs	$0	$0	-	$0	$0	$0	-	$0	$7	$0	-	$0
Total QALYs	5.54	3.11	-	4.33	3.60	1.60	-	4.12	3.13	0.76	-	3.82
Relapses	-4.17	-5.19	-	-3.72	-2.81	-3.76	-	-1.10	-2.67	-3.70	-	-2.32
Life-Years	1.38	0.71	-	1.37	0.90	0.37	-	0.57	0.78	0.18	-	0.43
	Fingolimod				Glatiramer acetate 20 mg (Glatopa)				Glatiramer acetate 20 mg (Copaxone)			
	Mean	Credible Range			Mean	Credible Range			Mean	Credible Range		
$ per QALY	$265,248	$180,579	-	$506,969	$195,982	$128,509	-	$418,883	$275,587	$189,704	-	$502,036
$ per Relapse	$261,026	$178,922	-	$412,019	$292,682	$170,333	-	$838,750	$472,797	$268,808	-	$1,359,413
$ per Life-Year	$1,078,300	$695,271	-	$2,221,958	$758,358	$477,307	-	$1,606,869	$1,065,859	$701,022	-	$2,017,597
Total Costs	$797,766	$863,009	-	$979,358	$493,964	$418,302	-	$604,955	$767,679	$777,920	-	$937,860
Drug Costs	$837,343	$655,072	-	$782,856	$527,133	$416,504	-	$570,416	$803,609	$636,931	-	$665,279
Healthcare Costs	-$39,577	-$61,129	-	-$45,399	-$33,169	-$52,271	-	-$32,539	-$35,930	-$55,281	-	-$46,011
Adverse Event Costs	$0	$0	-	$0	$0	$0	-	$0	$0	$0	-	$0
Total QALYs	3.00	1.34	-	1.85	2.55	1.18	-	1.57	2.80	1.40	-	2.00
Relapses	-3.05	-3.82	-	-3.36	-1.66	-2.43	-	-1.87	-1.63	-2.49	-	-1.51
Life-Years	0.74	0.31	-	0.23	0.66	0.31	-	0.46	0.72	0.34	-	0.90

Continued on next page

	Glatiramer acetate 40 mg (Copaxone)				Interferon β-1a 30 mcg (Avonex)				Interferon β-1a 22 mcg (Rebif)			
	Mean	Credible Range			Mean	Credible Range			Mean	Credible Range		
$ per QALY	$4,038,894	$264,013	-	Dominated	$316,603	$204,893	-	$707,072	$405,994	$202,785	-	Dominated
$ per Relapse	$240,876	$106,694	-	$662,440	$1,356,857	$387,971	-	Dominated	$584,419	$224,870	-	Dominated
$ per Life-Year	Dominated	$989,181	-	Dominated	$1,151,617	$725,288	-	$2,518,060	$1,485,181	$736,674	-	Dominated
Total Costs	$518,071	$484,479	-	$725,879	$663,450	$792,616	-	$810,126	$719,556	$797,676	-	$920,181
Drug Costs	$524,630	$348,821	-	$515,693	$690,059	$552,309	-	$632,027	$744,027	$528,417	-	$792,265
Healthcare Costs	-$6,560	-$32,283	-	-$15,201	-$26,609	-$43,461	-	-$32,075	-$24,481	-$52,535	-	-$23,703
Adverse Event Costs	$0	$0	-	$0	$0	$0	-	$0	$11	$0	-	$8
Total QALYs	-0.04	-2.20	-	0.36	2.07	0.89	-	2.13	1.78	-0.44	-	1.73
Relapses	-2.48	-3.59	-	-2.52	-0.51	-1.51	-	-1.29	-1.22	-2.54	-	-1.43
Life-Years	0.02	-0.52	-	-0.06	0.57	0.25	-	0.61	0.49	-0.06	-	0.00
	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		
$ per QALY	$300,581	$192,255	-	$817,897	$175,021	$116,871	-	$368,023	$149,476	$99,278	-	$306,729
$ per Relapse	$484,449	$251,678	-	$2,404,611	$390,386	$185,956	-	Dominated	$339,799	$161,629	-	Dominated
$ per Life-Year	$1,149,916	$707,951	-	$3,037,695	$672,277	$430,738	-	$1,444,137	$574,137	$365,365	-	$1,244,131
Total Costs	$769,266	$719,512	-	$949,367	$546,817	$639,520	-	$685,639	$476,786	$504,899	-	$594,275
Drug Costs	$802,794	$617,338	-	$765,338	$586,130	$461,727	-	$555,283	$516,664	$405,781	-	$578,328
Healthcare Costs	-$33,539	-$56,037	-	-$36,297	-$39,312	-$62,658	-	-$54,516	-$39,879	-$64,289	-	-$36,821
Adverse Event Costs	$11	$0	-	$4	$0	$0	-	$0	$0	$0	-	$0
Total QALYs	2.58	0.94	-	2.57	3.12	1.18	-	3.95	3.17	1.42	-	2.17
Relapses	-1.55	-2.49	-	-0.80	-1.40	-2.52	-	-1.94	-1.42	-2.54	-	-2.37
Life-Years	0.68	0.24	-	0.59	0.81	0.32	-	0.89	0.83	0.35	-	0.78

Continued on next page

	Natalizumab				Ocrelizumab				Peginterferon β-1a			
	Mean	Credible Range			Mean	Credible Range			Mean	Credible Range		
$ per QALY	$203,847	$142,109	-	$368,172	$216,252	$149,975	-	$386,465	$249,258	$152,625	-	$1,319,411
$ per Relapse	$211,814	$153,083	-	$304,847	$379,140	$226,394	-	$872,201	$523,805	$201,389	-	Dominated
$ per Life-Year	$833,755	$549,480	-	$1,685,235	$851,028	$564,237	-	$1,638,723	$956,299	$559,079	-	$4,958,445
Total Costs	$876,422	$953,488	-	$1,096,731	$1,083,562	$1,112,440	-	$1,412,183	$786,889	$580,572	-	$1,011,471
Drug Costs	$932,308	$716,171	-	$850,208	$1,146,799	$859,251	-	$1,255,527	$827,355	$575,961	-	$832,237
Healthcare Costs	-$55,887	-$86,482	-	-$77,210	-$63,238	-$96,439	-	-$85,974	-$40,467	-$75,232	-	-$43,461
Adverse Event Costs	$0	$0	-	$0	$0	$0	-	$0	$0	$0	-	$0
Total QALYs	4.34	2.08	-	3.51	5.03	2.52	-	5.84	3.20	0.55	-	1.61
Relapses	-4.10	-4.94	-	-4.11	-2.82	-3.98	-	-1.46	-1.50	-3.23	-	-1.10
Life-Years	1.06	0.44	-	1.15	1.28	0.58	-	0.56	0.83	0.13	-	1.29

	Teriflunomide 7 mg				Teriflunomide 14 mg			
	Mean	Credible Range			Mean	Credible Range		
$ per QALY	$481,402	$246,255	-	Dominated	$322,785	$201,895	-	$1,011,723
$ per Relapse	$536,359	$242,896	-	Dominated	$449,988	$236,394	-	$2,484,901
$ per Life-Year	$1,750,604	$905,207	-	Dominated	$1,240,470	$749,436	-	$3,859,511
Total Costs	$693,105	$598,972	-	$871,445	$744,265	$761,889	-	$926,959
Drug Costs	$714,256	$533,316	-	$502,438	$774,739	$599,275	-	$770,861
Healthcare Costs	-$21,152	-$41,219	-	-$17,154	-$30,474	-$51,984	-	-$27,144
Adverse Event Costs	$0	$0	-	$0	$0	$0	-	$0
Total QALYs	1.48	-0.20	-	2.17	2.30	0.63	-	1.32
Relapses	-1.28	-2.39	-	-1.49	-1.66	-2.69	-	-1.35
Life-Years	0.41	-0.01	-	0.20	0.60	0.17	-	0.63

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

	Ocrelizumab			
	Mean	Credible Range		
$ per QALY	$702,243	$411,165	-	$2,257,499
$ per Life-Year	$880,075	$545,912	-	$2,557,427
Total Costs	$522,482	$485,861	-	$669,703
Drug Costs	$520,291	$380,242	-	$527,527
Healthcare Costs	$2,191	-$919	-	$1,658
Adverse Event Costs	$0	$0	-	$0
Total QALYs	0.75	0.20	-	0.80
Life-Years	0.59	0.17	-	0.66

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	$401,146	$139,624	-	Dominated	$509,563	$109,667	-	Dominated
$ per Life-Year	Dominant	Dominant	-	Dominant	$359,801	$95,654	-	Dominated	$295,562	$44,356	-	Dominated
$ per Relapse	Dominant	Dominant	-	Dominant	$1,746,742	$536,017	-	Dominated	$2,355,077	$427,607	-	Dominated
Total Costs	-$185,113	-$302,206	-	-$71,729	$419,586	$193,864	-	$662,606	$291,544	$59,807	-	$517,330
Drug Costs	-$147,754	-$273,321	-	-$29,344	$432,503	$188,115	-	$686,680	$299,147	$51,558	-	$542,483
Healthcare Costs	-$37,359	-$68,231	-	-$7,279	-$12,917	-$40,812	-	$14,728	-$7,609	-$38,282	-	$21,769
Adverse Event Costs	$0	$0	-	$0	$0	$0	-	$0	$7	$0	-	$40
Total QALYs	2.99	0.41	-	5.42	1.04	-1.59	-	3.53	0.57	-2.12	-	3.35
Relapses	-2.51	-3.72	-	-1.28	-1.15	-2.51	-	0.24	-1.02	-2.43	-	0.57
Life-Years	0.72	0.03	-	1.36	0.24	-0.44	-	0.92	0.12	-0.60	-	0.88
	Fingolimod				Glatiramer acetate 20 mg (Copaxone)				Glatiramer acetate 40 mg (Copaxone)			
	Mean	Credible Range			Mean	Credible Range			Mean	Credible Range		
Total Costs	$609,223	$133,765	-	Dominated	N/A	N/A	-	N/A	Dominated	$542,973	-	Dominated
$ per Life-Year	$222,569	$60,701	-	$1,447,046	N/A	N/A	-	N/A	$51,031	Dominant	-	Dominated
$ per Relapse	$3,307,509	$552,531	-	Dominated	N/A	N/A	-	N/A	Dominated	$2,164,017	-	Dominated
Total Costs	$303,802	$96,935	-	$504,227	$273,715	$82,820	-	$471,389	$24,107	-$157,551	-	$235,307
Drug Costs	$310,210	$92,898	-	$525,113	$276,477	$72,925	-	$482,762	-$2,502	-$209,365	-	$232,505
Healthcare Costs	-$6,408	-$28,424	-	$16,050	-$2,761	-$24,025	-	$19,631	$26,609	-$4,094	-	$57,963
Adverse Event Costs	$0	$0	-	$0	$0	$0	-	$0	$0	$0	-	$0
Total QALYs	0.45	-1.64	-	2.48	N/A	N/A	-	N/A	-2.59	-5.31	-	0.45
Relapses	-1.39	-2.55	-	-0.31	N/A	N/A	-	N/A	-0.82	-2.38	-	0.97
Life-Years	0.08	-0.46	-	0.58	N/A	N/A	-	N/A	-0.64	-1.32	-	0.10

Continued on next page

	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		
Total Costs	Dominated	$144,319	-	Dominated	Dominated	$182,732	-	Dominated	$8,267,164	$152,127	-	Dominated
$ per Life-Year	Dominated	$413,011	-	Dominated	Dominated	$15,305	-	Dominated	Dominated	$96,118	-	Dominated
$ per Relapse	Dominated	$469,160	-	Dominated	Dominated	$636,870	-	Dominated	$16,970,490	$555,451	-	Dominated
Total Costs	$169,486	$5,140	-	$339,039	$225,592	$5,052	-	$445,026	$275,302	$86,962	-	$461,044
Drug Costs	$162,926	-$15,153	-	$347,768	$216,894	-$18,678	-	$452,198	$275,661	$67,819	-	$476,747
Healthcare Costs	$6,560	-$13,289	-	$27,087	$8,688	-$18,662	-	$37,802	-$370	-$24,500	-	$21,888
Adverse Event Costs	$0	$0	-	$0	$11	$0	-	$43	$11	$0	-	$42
Total QALYs	-0.48	-2.41	-	1.31	-0.77	-3.42	-	1.86	0.03	-2.09	-	2.18
Relapses	1.15	-0.23	-	2.57	0.44	-1.17	-	2.43	0.11	-1.26	-	1.50
Life-Years	-0.09	-0.61	-	0.39	-0.17	-0.84	-	0.52	0.02	-0.55	-	0.60
	Interferon β-1b 250 mcg (Betaseron)				Interferon β-1b 250 mcg (Extavia)				Natalizumab			
	Mean	Credible Range			Mean	Credible Range			Mean	Credible Range		
Total Costs	$88,788	Dominant	-	Dominated	Dominant	Dominant	-	Dominated	$215,008	$95,938	-	Dominated
$ per Life-Year	Dominated	Dominant	-	Dominated	Lower cost, more relapses	Dominant	-	Dominated	$156,039	$60,330	-	$372,739
$ per Relapse	$331,052	Dominant	-	Dominated	Dominant	Dominant	-	Dominated	$956,820	$387,725	-	Dominated
Total Costs	$52,853	-$114,939	-	$216,660	-$17,178	-$158,112	-	$145,655	$382,458	$155,459	-	$617,959
Drug Costs	$58,997	-$128,849	-	$238,197	-$10,468	-$174,021	-	$167,777	$405,176	$164,248	-	$660,731
Healthcare Costs	-$6,144	-$31,326	-	$17,084	-$6,710	-$32,809	-	$16,071	-$22,718	-$52,227	-	$5,300
Adverse Event Costs	$0	$0	-	$0	$0	$0	-	$0	$0	$0	-	$0
Total QALYs	0.57	-1.55	-	2.84	0.62	-1.52	-	2.94	1.79	-0.75	-	4.24
Relapses	0.26	-1.20	-	1.82	0.24	-1.27	-	1.78	-2.44	-3.68	-	-1.32
Life-Years	0.15	-0.44	-	0.74	0.16	-0.42	-	0.79	0.40	-0.24	-	1.07

Continued on next page

	Ocrelizumab				Peginterferon β-1a				Teriflunomide 7 mg			
	Mean	Credible Range			Mean	Credible Range			Mean	Credible Range		
Total Costs	$236,708	$113,802	-	Dominated	$455,309	$103,808	-	Dominated	Dominated	$284,138	-	Dominated
$ per Life-Year	$503,380	$142,066	-	Dominated	Dominated	$54,137	-	Dominated	Dominated	$23,713	-	Dominated
$ per Relapse	$947,797	$433,964	-	Dominated	$1,691,162	$383,234	-	Dominated	Dominated	$982,602	-	Dominated
Total Costs	$589,598	$293,786	-	$912,480	$292,925	$64,493	-	$524,374	$199,141	-$1,349	-	$396,772
Drug Costs	$619,667	$302,564	-	$962,209	$300,223	$45,500	-	$561,153	$187,124	-$30,760	-	$396,840
Healthcare Costs	-$30,069	-$61,341	-	$1,748	-$7,298	-$38,021	-	$23,731	$12,017	-$8,227	-	$35,722
Adverse Event Costs	$0	$0	-	$0	$0	$0	-	$0	$0	$0	-	$0
Total QALYs	2.48	-0.36	-	5.10	0.65	-2.25	-	3.38	-1.07	-3.20	-	0.91
Relapses	-1.17	-2.51	-	0.42	0.16	-1.89	-	2.75	0.38	-1.04	-	1.90
Life-Years	0.62	-0.13	-	1.32	0.17	-0.60	-	0.95	-0.25	-0.81	-	0.26

	Teriflunomide 14 mg			
	Mean	Credible Range		
Total Costs	Dominated	$164,208	-	Dominated
$ per Life-Year	Dominated	$63,904	-	Dominated
$ per Relapse	Dominated	$599,428	-	Dominated
Total Costs	$250,301	$58,613	-	$459,325
Drug Costs	$247,606	$34,954	-	$467,209
Healthcare Costs	$2,695	-$21,550	-	$26,302
Adverse Event Costs	$0	$0	-	$0
Total QALYs	-0.25	-2.47	-	1.98
Relapses	-0.01	-1.51	-	1.46
Life-Years	-0.06	-0.67	-	0.51

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. Projected relapses were higher compared to the base case, as were total projected costs, while projected life-year 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 and generic glatiramer acetate 20 mg all decreased. The decreases in cost per relapse avoided were particularly large. The exception to this decrease was the cost per additional QALY and cost per additional life-year for interferon β-1b 250 mcg (Betaseron) compared to generic glatiramer acetate 20 mg, which both slightly increased.

In the second scenario, we used alternative untreated ARR rates by EDSS state that were lower than the base case rates. This had the opposite effect, decreasing projected relapses and costs and increasing QALYs compared to the base case, which in turn increases the costs per additional QALY, costs per additional life-year, and costs per relapse avoided compared to supportive care and generic glatiramer acetate 20 mg, with an exception for interferon β-1b 250 mcg (Betaseron). Again, the changes in cost per relapse avoided were particularly notable.

In scenario three, we used results from the NMA including only studies with 12-week progression results. Natalizumab did not have any trials with 12-week results. The cost per relapse avoided for glatiramer acetate 40 mg compared to generic glatiramer acetate 20 mg which increased from $17,988 for base line to $134,452. Costs per additional QALY and costs per additional life-year for teriflunomide 7/14 mg and interferon β-1a (22, 30, and 44 mcg) compared to generic glatiramer acetate 20 mg changed from dominated in the base case to increased incremental costs and outcomes, albeit with high ratios. Cost per additional life-year for interferon β-1b 250 mcg (Betaseron) compared to generic glatiramer acetate 20 mg became dominated, while the cost per relapse avoided was dominated in the base case, and changed to $175,935. The cost per additional QALY compared to supportive care for interferon β-1b 250 mcg (Extavia) increased from $159,412 in the base case to $389,854, and compared to generic glatiramer acetate 20 mg the cost per additional QALY and cost per additional life-year changed from dominant in the base case to lower costs and lower QALYs/life-years, while cost per relapse avoided changed from lower costs and more relapses in the base case to dominant.

In scenario four, we used results from the NMA including only studies with 24-week progression results. Those DMTs without results did not have any trials with 24-week results. Results varied by DMT, with projected costs, relapses, life-years, and QALYs increasing compared to the base case for four DMTs (interferon β-1a 22 mcg, interferon β-1b 250 mcg [Betaseron, Extavia])and decreasing for eight DMTs (interferon β-1a 30 mcg, interferon β-1a 44 mcg, glatiramer acetate 20 mg [branded and generic], fingolimod, natalizumab, ocrelizumab, and alemtuzumab). For interferon β-1a 22 mcg

the cost per additional QALY and cost per additional life-year compared to supportive care and generic glatiramer acetate 20 mg dramatically decreased compared to the base case (going from dominated to calculated cost per additional QALY values compared to generic glatiramer acetate 20 mg), and both costs per relapse avoided became dominated. For interferon β-1b (Extavia) compared to generic glatiramer acetate 20 mg, the cost per additional QALY and cost per additional life-year changed from dominant in the base case to $13,962 and $52,333, respectively, while cost per relapse avoided changed from lower costs and more relapses in the base case to dominated. For all other pairwise results this scenario resulted in quantitative but non-influential changes from base case.

In scenario five, we included indirect costs. This increased the projected costs for all DMTs and supportive care without changing health outcomes from the base case (Table 23). This resulted in quantitative but non-influential changes from base case for all pairwise results, with the exception of cost per relapse avoided for glatiramer acetate 40 mg compared to generic glatiramer acetate 20 mg which increased from $17,988 for base line to $101,557.

In scenario six, we removed the stopping rule for EDSS 7 and modeled all patients to continue DMTs beyond EDSS 7. This resulted in higher projected costs, fewer relapses, more life-years, and more QALYs compared to base case. The cost per relapse avoided for glatiramer acetate 40 mg increased from $17,988 for base line to $170,746, and pairwise results for ocrelizumab for PPMS notably increased compared to the base case. All other pairwise results had quantitative but non-influential changes from base case.

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. This resulted in minimal increases in projected costs, minimal decreases in projected QALYs, and insubstantial changes to pairwise results from base case (Table 25).

Table E17. Scenario 1 Results: Higher Untreated ARR by EDSS States Data Source[116] (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					
GA 40 mg	$873,207	28.5	21.2	3.5	$5,123,081	DOMINATED	$91,891	DOMINATED	DOMINATED	$13,647
Supportive Care	$378,333	33.9	21.2	3.4	--	--	--	--	--	--
TER 7 mg	$1,048,828	30.7	21.5	4.9	$439,394	$1,907,457	$206,153	DOMINATED	DOMINATED	DOMINATED
IFN β-1a 22mcg	$1,070,373	30.6	21.6	5.2	$375,401	$1,615,545	$211,446	DOMINATED	DOMINATED	DOMINATED
IIFN β-1a 30mcg	$1,018,129	32.0	21.7	5.4	$320,887	$1,293,223	$329,387	DOMINATED	DOMINATED	DOMINATED
TER 14 mg	$1,108,116	29.8	21.8	6.0	$281,789	$1,248,761	$177,505	DOMINATED	DOMINATED	DOMINATED
IFN β-1a 44mcg	$1,114,259	29.8	21.8	6.0	$277,544	$1,219,842	$181,050	DOMINATED	DOMINATED	DOMINATED
GA 20 mg	$1,105,503	29.7	21.8	6.0	$271,572	$1,205,328	$172,548	--	--	--
GA 20 mg (Glatopa)	$857,224	29.7	21.8	6.0	$178,849	$793,791	$113,635	--	--	--
FIN	$1,148,156	26.9	21.9	6.7	$230,485	$1,105,783	$109,769	$439,224	$3,132,245	$103,949
IFN β-1b 250 mcg (Betaseron)	$907,296	30.0	21.9	6.6	$164,489	$709,883	$136,747	$93,043	$353,005	DOMINATED
IFN β-1b 250 mcg (Extavia)	$836,749	30.0	21.9	6.6	$142,552	$615,207	$118,509	DOMINANT	DOMINANT	Lower costs, more relapses
DMF	$1,139,700	27.6	21.9	6.7	$225,484	$1,051,891	$120,534	$404,136	$2,343,970	$134,363
PEG	$1,143,755	29.8	22.0	6.7	$229,874	$998,147	$184,860	$439,388	$1,751,976	DOMINATED
DAC	$1,241,633	27.2	22.0	7.0	$234,860	$1,094,279	$128,248	$385,110	$2,070,885	$152,713
NAT	$1,205,495	24.6	22.1	7.9	$184,397	$887,231	$89,082	$192,614	$1,058,574	$68,678
OCR	$1,427,946	26.9	22.4	8.7	$195,246	$857,200	$149,575	$211,519	$918,784	$203,612
ALE	$683,141	24.1	22.5	9.3	$51,579	$234,308	$31,130	DOMINANT	DOMINANT	DOMINANT

Table E18. Scenario 2 Results: Lower Untreated ARR by EDSS States Data Source[138]

					Compared to Supportive Care			Compared to GA_G20mg		
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**					
GA 40 mg	$835,309	5.0	21.2	5.3	DOMINATED	DOMINATED	$340,278	DOMINATED	DOMINATED	$18,867
Supportive Care	$331,790	6.5	21.2	5.6	--	--	--	--	--	--
TER 7 mg	$1,008,829	5.9	21.5	6.8	$560,291	$1,926,074	$1,153,168	DOMINATED	DOMINATED	DOMINATED
IFN β-1a 22 mcg	$1,030,693	6.0	21.6	7.1	$462,719	$1,631,567	$1,319,626	DOMINATED	DOMINATED	DOMINATED
IFN β-1a 30 mcg	$976,644	6.4	21.7	7.4	$368,850	$1,303,446	$6,052,519	DOMINATED	DOMINATED	DOMINATED
TER 14 mg	$1,070,276	5.9	21.8	7.8	$340,689	$1,263,653	$1,164,648	DOMINATED	DOMINATED	DOMINATED
IFN β-1a 44 mcg	$1,076,411	5.9	21.8	7.9	$333,954	$1,234,256	$1,229,254	DOMINATED	DOMINATED	DOMINATED
GA 20 mg	$1,067,881	5.9	21.8	7.9	$327,907	$1,220,117	$1,137,238	--	--	--
GA 20 mg (Glatopa)	$819,603	5.9	21.8	7.9	$217,306	$808,580	$753,656	--	--	--
FIN	$1,115,020	5.2	21.9	8.3	$291,182	$1,125,042	$580,923	$663,837	$3,180,538	$421,429
IFN β-1b 250 mcg (Betaseron)	$869,626	6.1	21.9	8.4	$193,096	$721,792	$1,234,656	$92,549	$352,663	DOMINATED
IFN β-1b 250 mcg (Extavia)	$799,079	6.1	21.9	8.4	$167,768	$627,116	$1,072,709	DOMINANT	DOMINANT	Lower costs, more relapses
DMF	$1,105,594	5.4	21.9	8.4	$279,006	$1,069,075	$682,213	$541,023	$2,373,141	$587,259
PEG	$1,106,558	6.0	22.0	8.5	$269,357	$1,010,335	$1,568,824	$454,368	$1,754,571	DOMINATED
DAC	$1,208,314	5.3	22.0	8.7	$288,850	$1,111,041	$731,759	$492,218	$2,094,061	$706,018
NAT	$1,176,231	4.7	22.1	9.3	$231,483	$905,765	$469,461	$254,163	$1,083,977	$309,712
OCR	$1,396,104	5.6	22.4	10.3	$228,246	$869,206	$1,133,479	$238,401	$928,086	$1,976,233
ALE	$655,199	4.9	22.5	10.6	$64,582	$248,607	$194,326	DOMINANT	DOMINANT	DOMINANT
	Results for PPMS				**Pairwise Results for PPMS**					
Supportive Care	$264,334	--	15.6	2.7	--	--	--	--	--	--
OCR	$751,097	--	16.1	3.3	$854,020	$1,012,599	--	--	--	--

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

					Compared to Supportive Care			Compared to GA_G20mg		
Drug	Cost	Relapses	Life-Years	QALYs	ICER	Cost per Additional Life-Year	Cost per Relapse Avoided	ICER	Cost per Additional Life-Year	Cost per Relapse Avoided
	Results for RRMS				Pairwise Results for RRMS					
GA 40 mg	$820,893	12.5	21.1	4.6	DOMINATED	DOMINATED	$180,869	DOMINATED	DOMINATED	$134,452
Supportive Care	$346,212	15.1	21.2	4.9	--	--	--	--	--	--
TER 7 mg	$1,005,477	13.8	21.6	6.3	$475,649	$1,766,012	$503,604	$1,166,166	$3,378,243	DOMINATED
IFN β-1a 22 mcg	$1,040,250	14.0	21.7	6.8	$366,422	$1,382,494	$593,774	$388,194	$1,385,932	DOMINATED
IFN β-1a 30 mcg	$964,801	14.5	21.7	6.7	$347,346	$1,275,571	$939,909	$336,002	$1,104,029	DOMINATED
TER 14 mg	$1,060,649	13.5	21.8	7.2	$308,047	$1,206,951	$437,447	$261,540	$1,027,437	DOMINATED
IFN β-1a 44mcg	$1,086,123	13.7	21.9	7.6	$275,738	$1,072,303	$508,124	$215,222	$833,756	DOMINATED
GA 20 mg	$977,879	13.0	21.5	6.1	$536,577	$2,097,004	$288,942	--	--	--
GA 20 mg (Glatopa)	$761,961	13.0	21.5	6.1	$353,163	$1,380,201	$190,175	--	--	--
FIN	$991,727	11.9	21.9	8.0	$208,520	$868,696	$200,384	$119,764	$519,996	$221,940
IFN β-1b 250 mcg (Betaseron)	$776,635	12.9	21.4	5.9	$448,849	$1,738,055	$189,652	DOMINATED	DOMINATED	$175,935
IFN β-1b 250 mcg (Extavia)	$720,062	12.9	21.4	5.9	$389,854	$1,509,615	$164,725	Lower costs, lower QALYs	Lower costs, lower LYs	DOMINANT
DMF	$1,079,178	12.4	21.9	7.7	$267,293	$1,094,445	$269,899	$202,698	$860,853	$599,012
PEG	$1,095,561	13.6	22.0	8.0	$246,638	$967,091	$486,098	$179,255	$704,354	DOMINATED
DAC	$1,190,246	12.3	22.0	8.1	$266,339	$1,089,288	$297,390	$215,024	$904,269	$656,874
NAT	--	--	--	--	--	--	--	--	--	--
OCR	$1,401,062	12.5	22.5	10.2	$201,884	$797,694	$406,091	$157,888	$625,863	$1,553,358
ALE	$654,909	11.2	22.7	10.9	$51,469	$205,016	$79,167	DOMINANT	DOMINANT	DOMINANT

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

					Compared to Supportive Care			Compared to GA_G20mg		
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					
GA 40 mg	--	--	--	--	--	--	--	--	--	--
Supportive Care	$346,212	15.1	21.2	4.9	--	--	--	--	--	--
TER 7 mg	--	--	--	--	--	--	--	--	--	--
IFN β-1a 22 mcg	$1,371,287	19.5	23.8	14.2	$110,341	$397,430	DOMINATED	$76,621	$269,449	DOMINATED
IFN β-1a 30 mcg	$975,956	14.3	21.6	6.6	$387,795	$1,419,060	$791,271	DOMINATED	DOMINATED	DOMINATED
TER 14 mg	--	--	--	--	--	--	--	--	--	--
IFN β-1a 44 mcg	$1,049,542	13.2	21.6	6.7	$390,729	$1,527,660	$366,817	DOMINATED	DOMINATED	$13,693,093
GA 20 mg	$1,055,145	13.2	21.7	6.9	$350,899	$1,384,582	$373,082	--	--	--
GA 20 mg (Glatopa)	$814,272	13.2	21.7	6.9	$231,675	$914,145	$246,321	--	--	--
FIN	$1,097,507	12.0	21.8	7.4	$299,410	$1,253,079	$236,207	$579,315	$3,235,517	$221,198
IFN β-1b 250 mcg (Betaseron)	$919,745	14.2	22.2	8.9	$143,855	$553,235	$609,405	$53,634	$201,027	DOMINATED
IFN β-1b 250 mcg (Extavia)	$841,730	14.2	22.2	8.9	$124,287	$477,981	$526,511	$13,962	$52,333	DOMINATED
DMF	--	--	--	--	--	--	--	--	--	--
PEG	--	--	--	--	--	--	--	--	--	--
DAC	--	--	--	--	--	--	--	--	--	--
NAT	$1,165,856	11.0	22.0	8.6	$226,204	$953,692	$197,177	$219,310	$1,011,975	$155,797
OCR	$1,357,951	12.1	22.2	9.1	$241,648	$975,933	$336,155	$250,948	$1,036,233	$490,007
ALE	$661,156	10.9	22.3	9.6	$67,298	$276,754	$73,948	DOMINANT	DOMINANT	DOMINANT

Table E21. Scenario 5 Results: Inclusion of Indirect Costs

					Compared to Supportive Care			Compared to GA_G20mg		
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					
GA 40 mg	$1,552,946	12.5	21.2	4.7	DOMINATED	DOMINATED	$190,083	DOMINATED	DOMINATED	$101,557
Supportive Care	$1,054,479	15.1	21.2	4.9	--	--	--	--	--	--
TER 7 mg	$1,684,087	13.7	21.5	6.2	$482,895	$1,791,140	$449,633	DOMINATED	DOMINATED	DOMINATED
IFN β-1a 22mcg	$1,696,698	13.8	21.6	6.5	$398,724	$1,499,240	$468,747	DOMINATED	DOMINATED	DOMINATED
IFN β-1a 30 mcg	$1,636,531	14.5	21.7	6.7	$319,335	$1,176,505	$856,074	DOMINATED	DOMINATED	DOMINATED
TER 14 mg	$1,716,424	13.4	21.8	7.2	$288,480	$1,132,681	$389,494	DOMINATED	DOMINATED	DOMINATED
IFN β-1a 44mcg	$1,720,362	13.5	21.8	7.3	$282,562	$1,103,742	$399,615	DOMINATED	DOMINATED	DOMINATED
GA 20 mg	$1,711,628	13.4	21.8	7.3	$276,698	$1,089,265	$377,643	--	--	--
GA 20 mg (Glatopa)	$1,463,349	13.4	21.8	7.3	$172,158	$677,727	$234,965	--	--	--
FIN	$1,743,730	12.1	21.9	7.8	$238,890	$990,050	$224,150	$549,495	$3,018,654	$210,051
IFN β-1b 250mcg (Betaseron)	$1,496,849	13.7	21.9	7.8	$151,777	$593,674	$296,805	$62,079	$236,177	DOMINATED
IFN β-1b 250mcg (Extavia)	$1,426,303	13.7	21.9	7.8	$127,573	$498,998	$249,472	DOMINANT	DOMINANT	Lower costs, more relapses
DMF	$1,732,076	12.4	21.9	7.9	$229,334	$936,157	$249,510	$463,596	$2,229,882	$275,454
PEG	$1,730,813	13.5	22.0	7.9	$224,510	$881,971	$419,235	$419,542	$1,635,388	DOMINATED
DAC	$1,826,453	12.3	22.0	8.2	$239,207	$978,518	$267,374	$426,055	$1,956,107	$316,537
NAT	$1,773,783	11.1	22.1	8.8	$184,429	$771,541	$176,082	$203,536	$943,568	$132,386
OCR	$1,961,120	12.4	22.4	9.8	$185,947	$740,437	$325,184	$199,042	$801,342	$474,993
ALE	$1,207,020	11.0	22.5	10.2	$28,898	$117,260	$36,791	DOMINANT	DOMINANT	DOMINANT
	Results for PPMS				Pairwise Results for PPMS					
Supportive Care	$858,690	--	15.6	2.7	--	--	--	--	--	--
OCR	$1,352,191	--	16.1	3.3	$865,841	$1,026,614	--	--	--	--

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

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_G20mg: Cost per Additional QALY	Compared to GA_G20mg: Cost per Additional Life-Year	Compared to GA_G20mg: Cost per Relapse Avoided
	Results for RRMS				**Pairwise Results for RRMS**					
GA 40 mg	$1,281,962	10.8	21.3	4.8	DOMINATED	DOMINATED	$208,871	DOMINATED	DOMINATED	$170,746
Supportive Care	$349,630	15.2	21.4	4.9	--	--	--	--	--	--
TER 7 mg	$1,397,979	12.7	21.8	6.5	$668,298	$2,629,115	$405,744	DOMINATED	DOMINATED	DOMINATED
IFN β-1a 22 mcg	$1,401,778	12.7	21.8	6.8	$553,068	$2,195,886	$412,338	DOMINATED	DOMINATED	DOMINATED
IFN β-1a 30 mcg	$1,294,806	13.6	21.9	7.0	$446,763	$1,725,964	$591,751	DOMINATED	DOMINATED	DOMINATED
TER 14 mg	$1,396,559	12.3	22.0	7.5	$397,491	$1,639,018	$350,237	DOMINATED	DOMINATED	DOMINATED
IFN β-1a 44 mcg	$1,400,614	12.3	22.0	7.6	$389,491	$1,597,850	$357,573	DOMINATED	DOMINATED	DOMINATED
GA 20 mg	$1,386,465	12.2	22.0	7.6	$381,413	$1,576,339	$341,309	--	--	--
GA 20 mg (Glatopa)	$1,038,503	12.2	22.0	7.6	$253,411	$1,047,320	$226,766	--	--	--
FIN	$1,418,759	10.5	22.1	8.2	$326,812	$1,420,302	$224,616	$687,634	$4,002,717	$220,825
IFN β-1b 250 mcg (Betaseron)	$1,075,352	12.6	22.2	8.2	$221,943	$909,184	$272,555	$66,821	$262,337	DOMINATED
IFN β-1b 250 mcg (Extavia)	$981,221	12.6	22.2	8.2	$193,156	$791,256	$237,203	DOMINANT	DOMINANT	Lower costs, more relapses
DMF	$1,396,570	11.0	22.1	8.2	$314,257	$1,346,847	$246,500	$584,048	$2,994,414	$296,068
PEG	$1,385,956	12.4	22.2	8.3	$307,383	$1,264,773	$368,702	$532,044	$2,149,697	DOMINATED
DAC	$1,511,175	10.8	22.2	8.5	$321,803	$1,381,441	$263,341	$530,445	$2,581,878	$344,268
NAT	$1,416,291	9.5	22.3	9.2	$248,255	$1,090,265	$185,924	$239,373	$1,178,370	$139,959
OCR	$1,608,536	11.3	22.6	10.1	$241,103	$1,008,715	$323,143	$227,736	$965,698	$664,378
ALE	$728,279	9.9	22.7	10.5	$67,509	$288,995	$71,165	DOMINANT	DOMINANT	DOMINANT
	Results for PPMS				**Pairwise Results for PPMS**					
Supportive Care	**$288,810**	--	**16.8**	**2.7**	--	--	--	--	--	--
OCR	$1,235,066	--	17.1	3.4	$1,239,809	$3,188,764	--	--	--	--

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

					Compared to Supportive Care			Compared to GA_G20mg		
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					
GA 40 mg	$847,421	12.5	21.2	4.7	DOMINATED	DOMINATED	$191,129	DOMINATED	DOMINATED	$17,988
Supportive Care	$346,212	15.1	21.2	4.9	--	--	--	--	--	--
TER 7 mg	$1,021,494	13.7	21.5	6.2	$529,047	$1,921,076	$482,251	DOMINATED	DOMINATED	DOMINATED
IFN β-1a 22mcg	$1,043,249	13.8	21.6	6.5	$437,281	$1,627,210	$508,758	DOMINATED	DOMINATED	DOMINATED
IFN β-1a 30mcg	$989,743	14.5	21.7	6.7	$358,455	$1,300,773	$946,497	DOMINATED	DOMINATED	DOMINATED
TER 14 mg	$1,082,291	13.4	21.8	7.2	$324,665	$1,259,533	$433,114	DOMINATED	DOMINATED	DOMINATED
IFN β-1a 44mcg	$1,088,418	13.5	21.8	7.3	$317,191	$1,230,252	$445,419	DOMINATED	DOMINATED	DOMINATED
GA 20 mg	$1,079,831	13.4	21.8	7.3	$312,502	$1,216,018	$421,588	--	--	--
GA 20 mg (Glatopa)	$831,552	13.4	21.8	7.3	$206,742	$804,481	$278,910	--	--	--
FIN	$1,125,623	12.1	21.9	7.8	$272,730	$1,119,556	$253,471	$576,324	$3,166,043	$220,307
IFN β-1b 250mcg (Betaseron)	$881,593	13.7	21.9	7.8	$185,433	$718,497	$359,210	$92,731	$352,790	DOMINATED
IFN β-1b 250mcg (Extavia)	$811,046	13.7	21.9	7.8	$160,998	$623,822	$311,877	DOMINANT	DOMINANT	Lower costs, more relapses
DMF	$1,116,484	12.4	21.9	7.9	$263,135	$1,064,194	$283,635	$491,497	$2,364,347	$292,064
PEG	$1,118,385	13.5	22.0	7.9	$258,678	$1,006,950	$478,642	$449,924	$1,753,818	DOMINATED
DAC	$1,218,973	12.3	22.0	8.1	$272,754	$1,106,271	$302,282	$454,588	$2,087,109	$337,736
NAT	$1,185,661	11.1	22.1	8.8	$216,751	$900,411	$205,493	$232,155	$1,076,321	$151,011
OCR	$1,406,348	12.4	22.4	9.8	$218,657	$865,793	$380,238	$229,842	$925,341	$548,493
ALE	$664,243	11.0	22.5	10.2	$60,563	$244,473	$76,705	DOMINANT	DOMINANT	DOMINANT
	Results for PPMS				Pairwise Results for PPMS					
Supportive Care	$264,334	--	15.6	2.7	--	--	--	--	--	--
OCR	$751,099	--	16.1	3.3	$893,201	$1,012,603	--	--	--	--

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 restrictionsRisk 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)