Disease-Modifying Therapies for Multiple Sclerosis: Update

Washington P&T Committee Meeting

April 17, 2024

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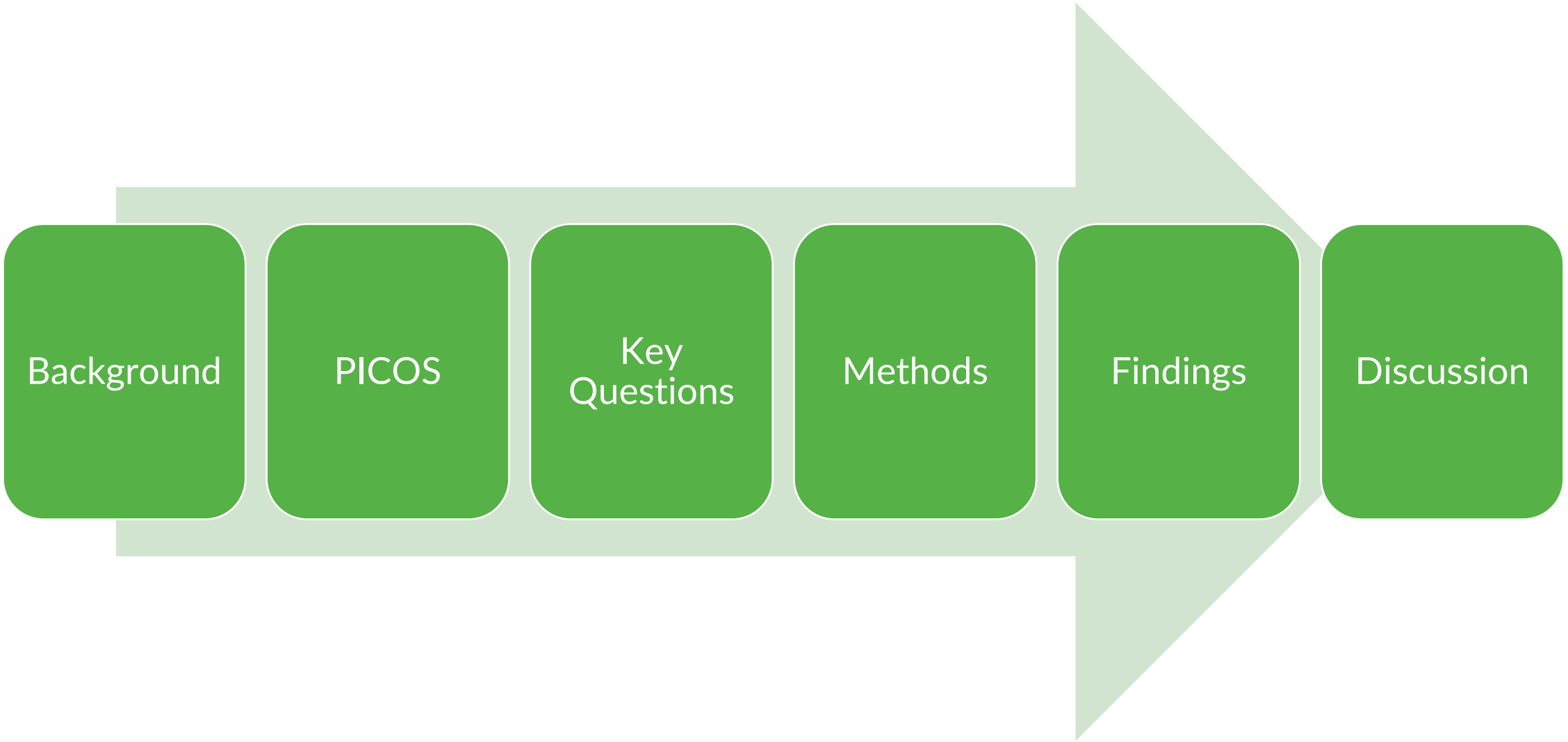
OHSU

Overview


Background
PICOS
Key Questions
Methods
Findings
Discussion

Abbreviations

- **AE**: adverse event
- **ARR**: annualized relapse rate
- **CI**: confidence interval
- **CIS:** clinically isolated syndrome
- **CoE**: certainty of evidence
- **DMT:** disease-modifying therapy
- **EDSS**: Expanded Disability Scale Score
- **FDA:** US Food and Drug Administration
- **GRADE**: Grading of Recommendations Assessment, Development and Evaluation approach
- **MS**: multiple sclerosis
- **MSFC**: Multiple Sclerosis Functional Composite score
- **NRS**: nonrandomized study
- **PPMS:** primary progressive MS
- **QoL:** quality of life
- **RCT**: randomized controlled trial
- **RR**: risk ratio
- **RRMS:** relapsing remitting MS
- **SAE**: serious adverse event
- **SPMS:** secondary progressive MS

Topic History

Shaw B, Chapman S, Kelly R, Vintro A, Anderson R, C H. *Disease-modifying drugs for multiple sclerosis*. Portland, OR: Center for Evidence-based Policy, Oregon Health & Science University; 2020.

Selph S, Holmes R, Thakurta S, Griffin J, McDonagh M. *Drug class review: disease-modifying drugs for multiple sclerosis: final update 3 report*. Portland, OR: Center for Evidence-based Policy, Oregon Health & Science University; 2016.

Selph S, Thakurta S, McDonagh M. *Drug class review: disease-modifying drugs for multiple sclerosis: final update 2 report*. Portland, OR: Center for Evidence-based Policy, Oregon Health & Science University; 2013.

McDonagh M. *Drug class review: disease-modifying drugs for multiple sclerosis: single drug addendum: fingolimod*. Portland, OR: Center for Evidence-based Policy, Oregon Health & Science University; 2011.

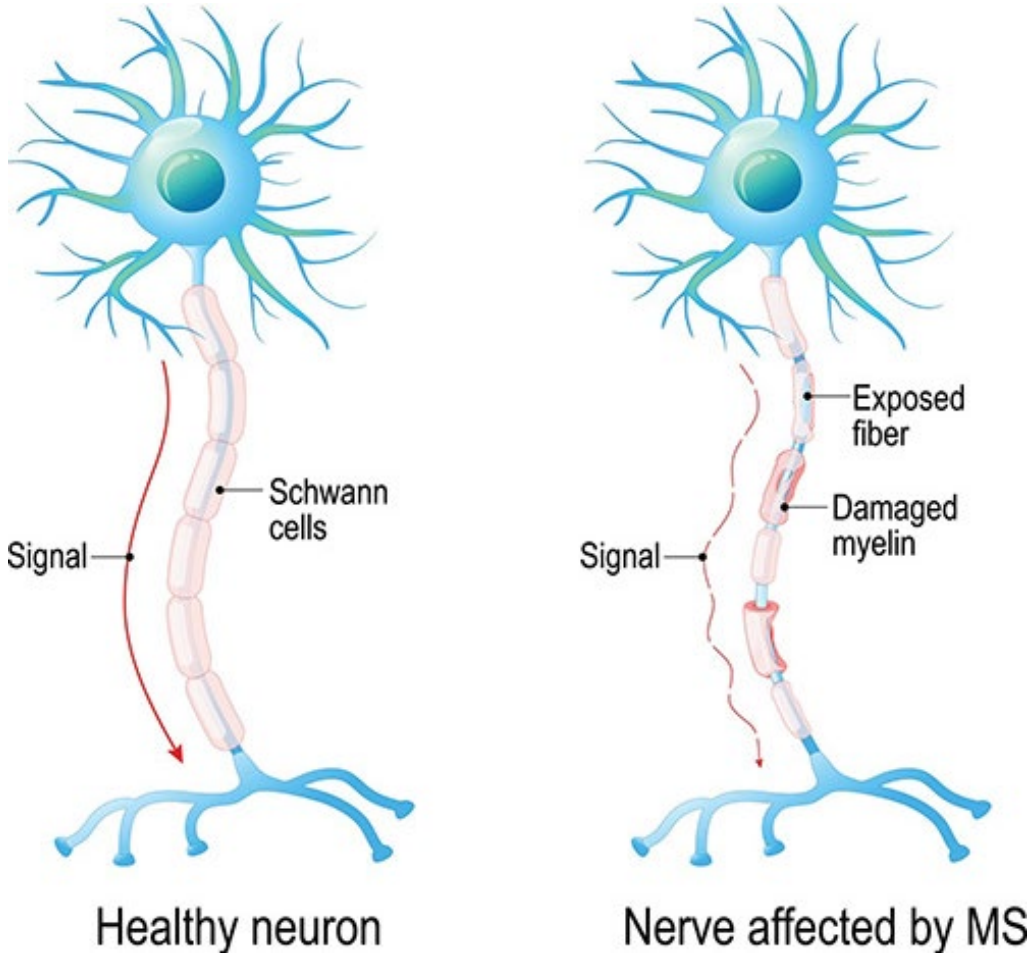
Smith B, Carson S, Fu R, et al. *Drug class review: disease-modifying drugs for multiple sclerosis: final update 1 report*. Portland, OR: Center for Evidence-based Policy, Oregon Health & Science University; 2010.

McDonagh M, Dana T, Chan BKS, Thakurta S, Gibler A. *Drug class review: disease-modifying drugs for multiple sclerosis: final report*. Portland, OR: Center for Evidence-based Policy, Oregon Health & Science University; 2007.

Background

Background (1 of 2)

- Myelin surrounds and insulates neurons and allows efficient transmission of nerve impulses.
- In MS, the body's immune system attacks the myelin, leading to neurologic dysfunction.
- Symptoms of MS include sensory issues such as numbness, muscle weakness or spasms, vision problems, dizziness, and trouble walking or speaking.



Source. OHSU Brain Institute. *Understanding Multiple Sclerosis.*

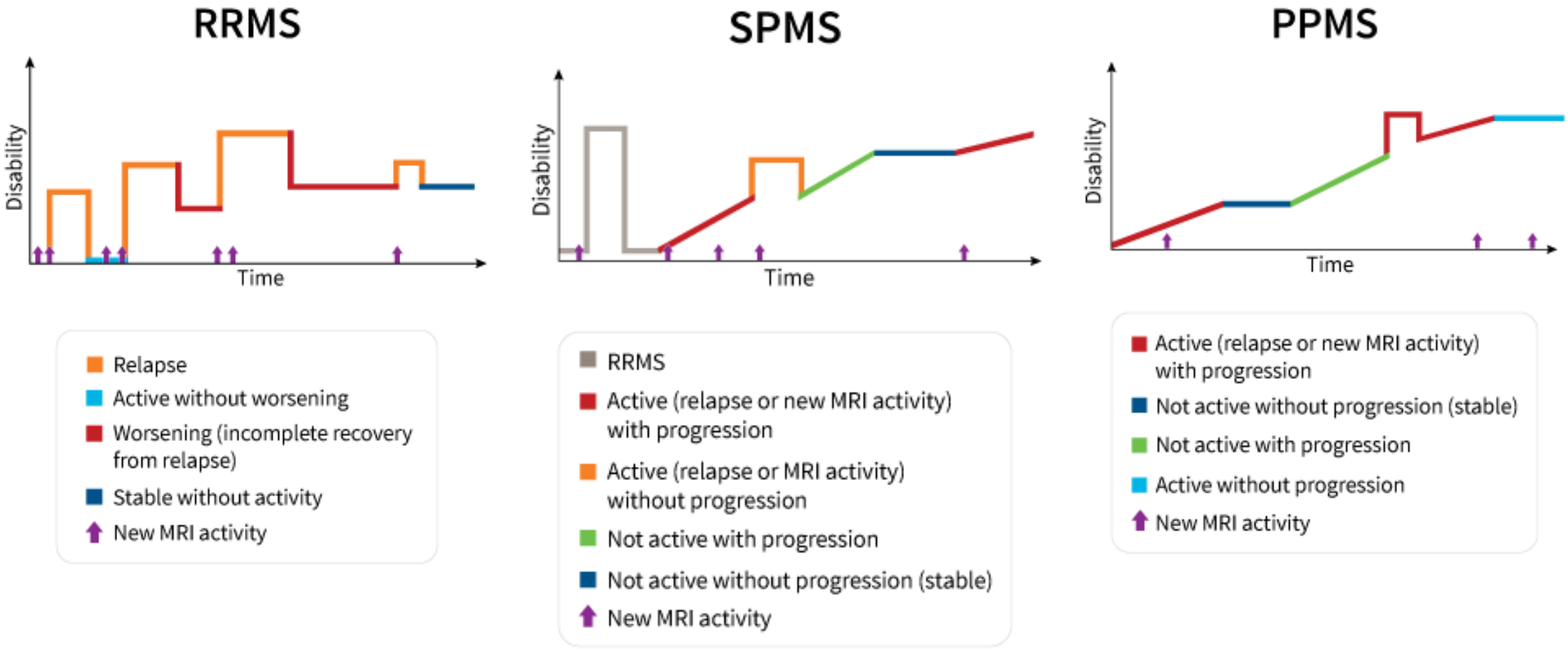
Background (2 of 2)

- MS is the most common immune-mediated inflammatory demyelinating disease of the central nervous system.
  - The prevalence of MS has been increasing over the past 5 decades.
  - A 2019 population-based estimate found 1 million adults were estimated to be living with MS in the US.
- MS is the most common disabling neurological disease of young adults, with symptom onset typically occuring between the ages of 20 and 40 years.

Types of MS

Clinical Type	Definition
Clinically isolated syndrome (CIS)	First episode of neurologic symptoms caused by inflammation and demyelination in the central nervous system.
Relapsing-remitting MS (RRMS)	Clearly defined attacks of new or increasing neurologic symptoms, followed by periods of partial or complete recovery (remission). RRMS can be further characterized as either **active** (with relapses, evidence of new magnetic resonance imaging (MRI) activity over a specified period of time, or both) or **not active**.
Secondary progressive MS (SPMS)	Progressive worsening of neurological function, or disability accumulation, from RRMS; with or without occasional relapses, minor remissions, and plateaus in severity.
Primary progressive MS (PPMS)	Neurologic function worsens, or disability accumulates, from disease onset with occasional plateaus in severity, temporary minor improvements, or acute relapses.

Types of MS



Source. National Multiple Sclerosis Society. *Types of MS.*

Disease-Modifying Therapies

- At the time of this report, FDA has approved 19 DMTs for MS and CIS.
  - Aim is to reduce the number of relapses, delay progression of disability, and limit new MS disease activity (as seen on MRI).

Disease-Modifying Therapies (1 of 3)

Generic Name	Brand Name(s)	Indication	Route of Administration	Frequency	First FDA Approval Date	FDA Approved Dose(s)
Ublituximab	Briumvy	Relapsing forms of MS in adults	Injectable, intravenous infusion	Every 6 months	12/28/2022	450 mg
Ponesimod	Ponvory	Relapsing forms of MS in adults	Oral	Daily	3/18/2021	20 mg
Ofatumumab	Kesimpta	Relapsing forms of MS in adults	Injectable, subcutaneous	Monthly	8/20/2020	20 mg
Monomethyl Fumarate	Bafiertam	Relapsing forms of MS in adults	Oral	Twice daily	4/28/2020	190 mg
Ozanimod	Zeposia	Relapsing forms of MS in adults	Oral	Daily	3/25/2020	0.92 mg
Diroximel Fumarate	Vumerity	Relapsing forms of MS in adults	Oral	Twice daily	10/30/2019	462 mg (maintenance)

Disease-Modifying Therapies (2 of 3)

Generic Name	Brand Name(s)	Indication	Route of Administration	Frequency	First FDA Approval Date	FDA Approved Dose(s)
Cladribine	Mavenclad	RRMS and active SPMS in adults	Oral	Yearly (for 2 years)	3/29/2019	3.5 mg/kg (cumulative dose in 2 treatment courses)
Siponimod	Mayzent	Relapsing forms of MS in adults	Oral	Daily	3/27/2019	2 mg (maintenance) 1 mg for people with cytochrome P450 2C9 *1/*3 or *2/*3 genotype (maintenance)
Ocrelizumab	Ocrevus	Relapsing forms of MS and PPMS, in adults	Injectable, intravenous infusion	Every 6 months	3/28/2017	600 mg (maintenance)
Alemtuzumab	Lemtrada	RRMS and active SPMS in adults	Injectable, intravenous infusion	Daily for 5 days, then daily for 3 days 12 months after the first course	11/14/2014	12 mg
Peginterferon Beta-1a	Plegridy	Relapsing forms of MS in adults	Injectable, subcutaneous	Every 14 days	8/15/2014	125 µg

Disease-Modifying Therapies (3 of 3)

Generic Name	Brand Name(s)	Indication	Route of Administration	Frequency	First FDA Approval Date	FDA Approved Dose(s)
Dimethyl Fumarate	Tecfidera	Relapsing forms of MS in adults	Oral	Twice daily	3/27/2013	240 mg (maintenance)
Teriflunomide	Aubagio	Relapsing forms of MS in adults	Oral	Daily	9/12/2012	7 mg or 14 mg
Fingolimod	Tascenso ODT, Gilenya	Relapsing forms of MS in people aged ≥ 10 years	Oral	Daily	9/21/2010	0.5 mg (adults)
Interferon Beta-1a	Rebif	Relapsing forms of MS in adults	Injectable, subcutaneous	Three times per week	3/7/2002	22 µg or 44 µg
Glatiramer Acetate	Glatopa, Copaxone	Relapsing forms of MS in adults	Injectable, subcutaneous	Daily or 3 times per week	12/20/1996	20 mg (daily) or 40 mg (3x per week)
Interferon Beta-1a	Avonex	Relapsing forms of MS in adults	Injectable, intramuscular	Weekly	5/17/1996	30 µg
Interferon Beta-1b	Extavia, Betaseron	Relapsing forms of MS in adults	Injectable, subcutaneous	Every other day	7/23/1993	0.25 mg

PICOS

- Populations:
  - Adult outpatients (aged 18 years and older) with MS
    - RRMS
    - SPMS
    - PPMS
  - Adult outpatients with CIS (also known as a “first demyelinating event,” the first clinical attack suggestive of MS, or monosymptomatic presentation)
- Interventions:
  - Listed DMTs with FDA approval for the treatment of MS and CIS

PICOS

- Comparators:
  - Another listed intervention (head-to-head comparison)
  - Placebo (for CIS only)
- Outcomes:
  - Relapse
  - Disability
  - Quality of life (QoL)
  - Functional outcomes
  - Persistence
  - Conversion to MS diagnosis (for CIS)
  - Adverse events
    - Overall adverse events
    - Serious adverse events (SAEs)
    - Withdrawals due to adverse events
    - Specific adverse events (e.g., hepatotoxicity)

PICOS

- Study Designs:
  - Randomized controlled trials (RCTs)
    - 12 weeks study duration or longer
  - Placebo-controlled trials for CIS only
    - 12 weeks study duration or longer
  - Retrospective and prospective cohort (nonrandomized) studies comparing an intervention type with another for outcomes on harms
    - 12 weeks study duration or longer
    - Minimum total sample size of 1,000

Key Questions

1. Comparative effectiveness for MS
2. Comparative effectiveness for CIS
3. Variations in harms by indications (MS or CIS)
4. Variations in effectiveness and harms by subgroup
5. Characteristics of ongoing studies

Methods

Methods

- Searched clinical evidence sources (e.g., Ovid MEDLINE ALL, Cochrane Library)
- Checked studies from previous reports against our inclusion criteria
- Assessed the risk of bias of individual studies
- Combined studies using Review Manager for major outcomes
- Used GRADE approach for major outcomes
- Searched ClinicalTrials.gov for ongoing studies through December 31, 2023

DERP Risk of Bias Assessment

- **Low**

  Clear reporting of methods and mitigation of potential biases and conflicts of interest

- **Moderate**

  Incomplete information about methods that might mask important limitations or a meaningful conflict of interest

- **High**

  Clear flaws that might introduce serious bias

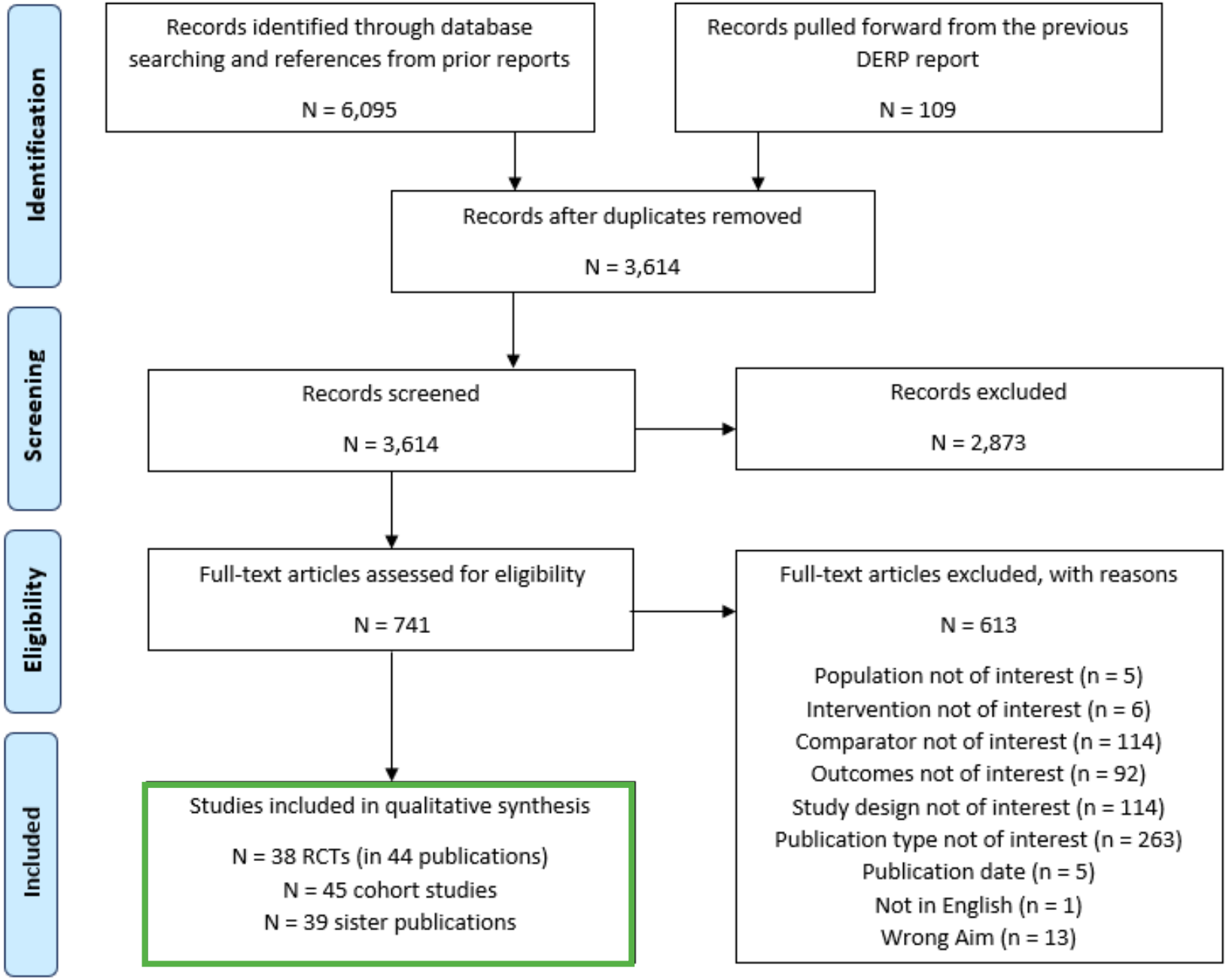
GRADE Certainty of Evidence

Outcomes Rated: *Relapse, Disability Progression, Change in Disability (EDSS), Change in Function (MSFC), Persistence, SAEs*

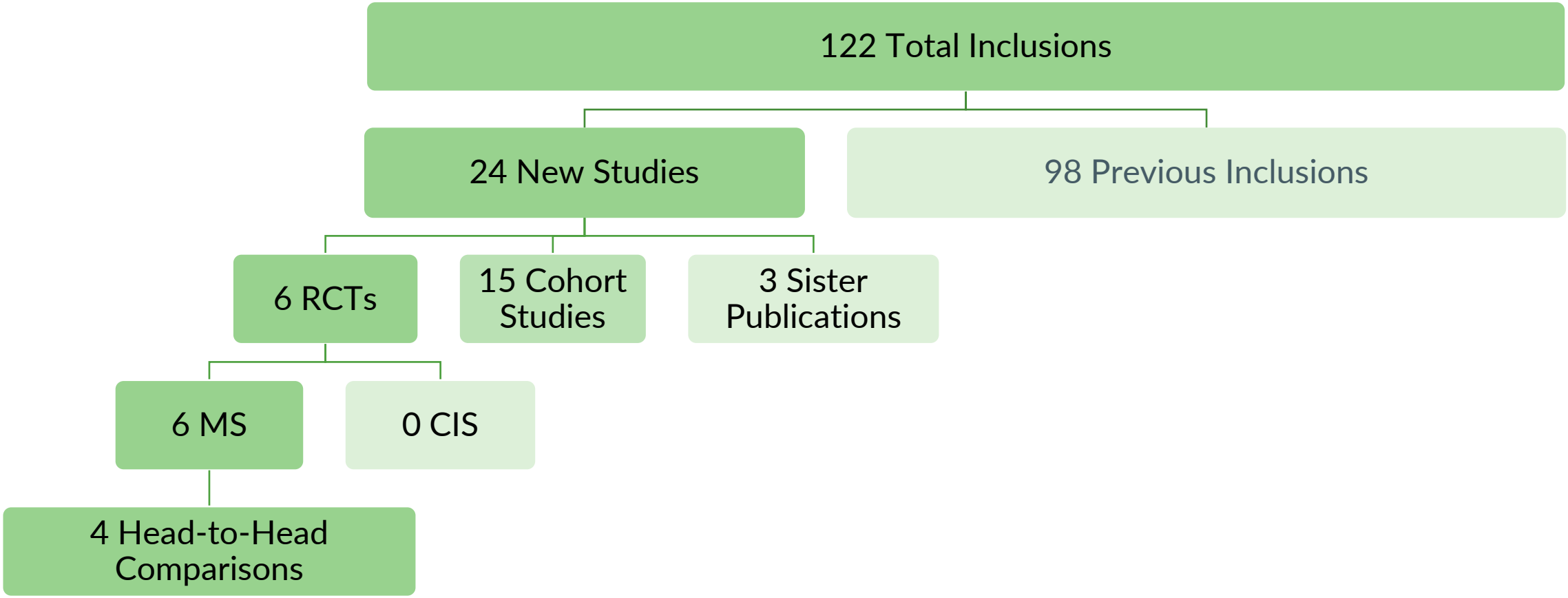
- **High** *(RCTs start here)*
  Very confident that the estimate of effect of intervention on outcome lies close to the true effect
- **Moderate**
  Moderately confident in estimate of effect of intervention on outcome; true effect is likely close to estimate, but possibly different
- **Low** *(Nonrandomized studies start here)*
  Little confidence in estimate of effect of intervention on outcome; true effect may be substantially different from estimate
- **Very Low**
  No confidence in estimate of effect of intervention on outcome; true effect is likely substantially different from estimate

Findings

Study Flow Diagram

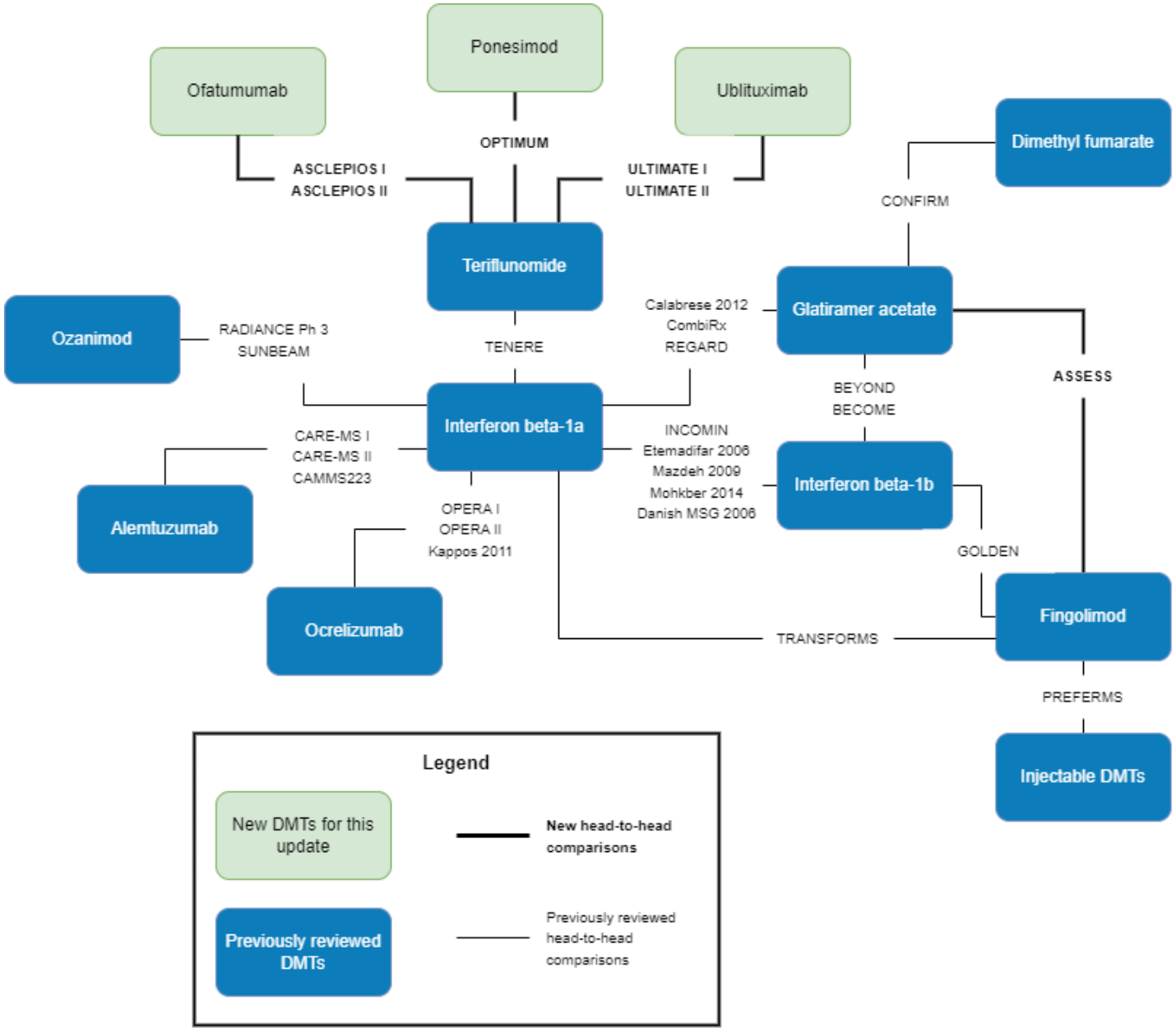


Findings: Study Characteristics



Findings

Key Questions 1 and 3:
Comparative Effectiveness and Harms for MS



No Published RCTs

- Cladribine
- Diroximel fumarate
- Monomethyl fumarate
- Peginterferon beta-1a
- Siponimod

Combinations

CombiRx
(GA or IFNB-1a vs. GA+INFB-1a)

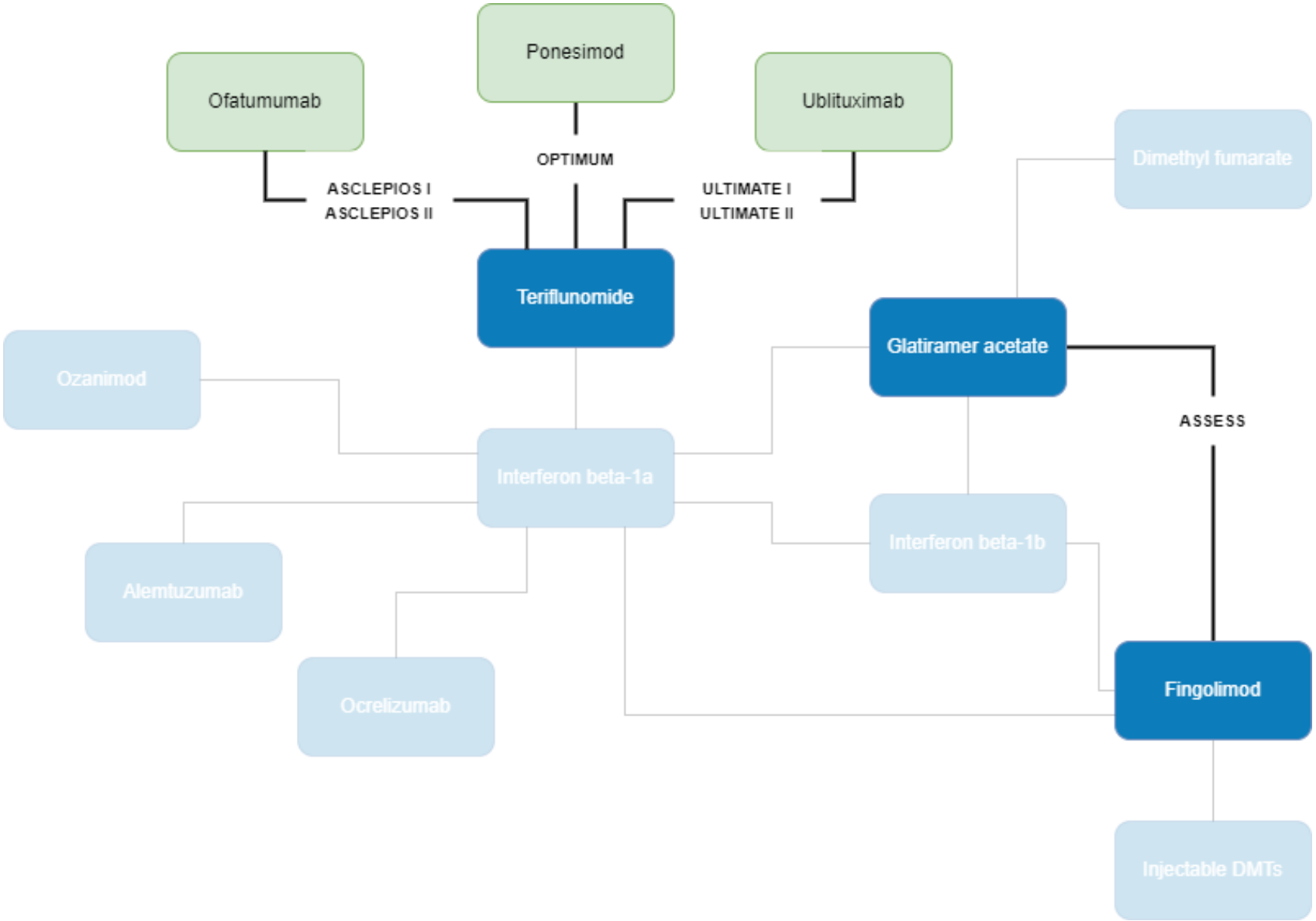
Different Dosing Schedules

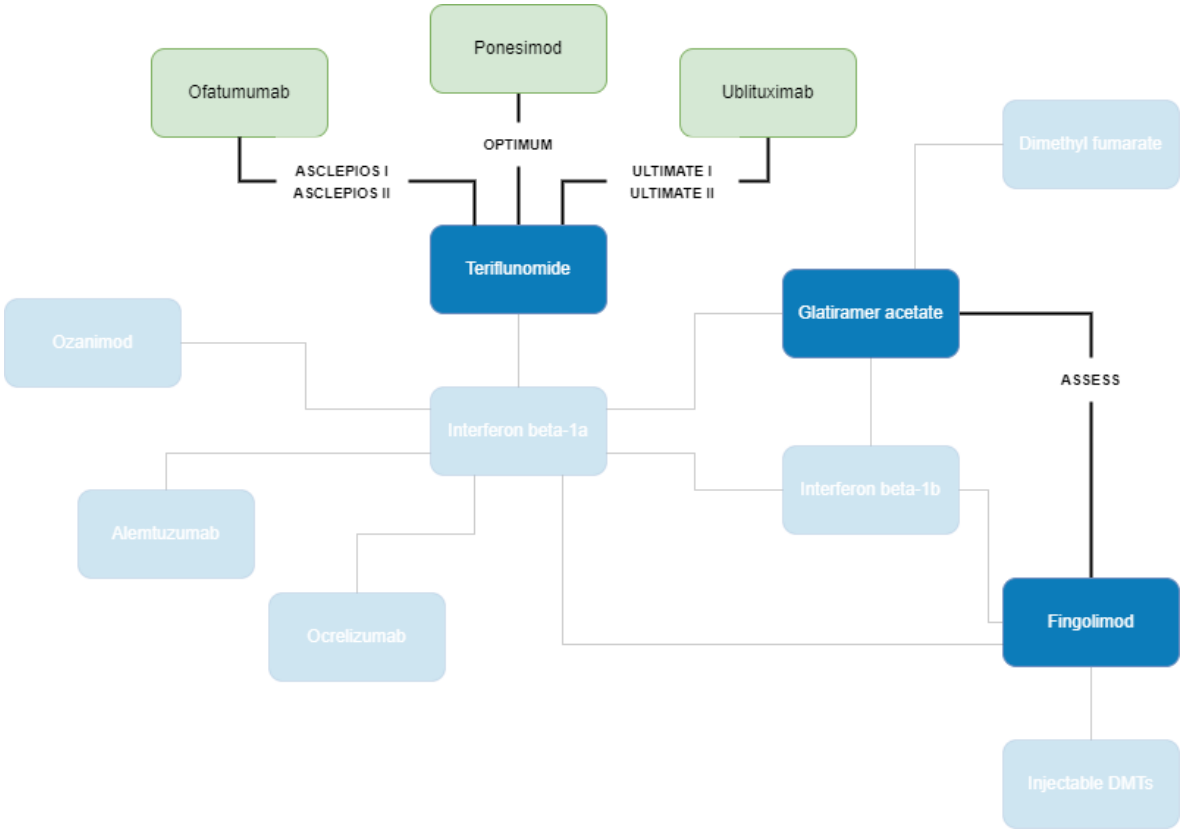
Glatiramer Acetate
CONFIDENCE
GLACIER

IFNB-1a
Calabrese 2012
Etemadifar 2006
EVIDENCE 2002
Mazdeh 2009
Mohkber 2014

PegIFNB-1a
ADVANCE

Dimethyl fumarate
BG-12 Phase IIb
CONFIRM
DEFINE


Ponesimod
Ofatumumab
Ublituximab
OPTIMUM
ASCLEPIOS I
ASCLEPIOS II
ULTIMATE I
ULTIMATE II
Dimethyl fumarate
Teriflunomide
Glatiramer acetate
Ozanimod
ASSESS
Interferon beta-1a
Interferon beta-1b
Alemtuzumab
Ocrelizumab
Fingolimod
Injectable DMTs



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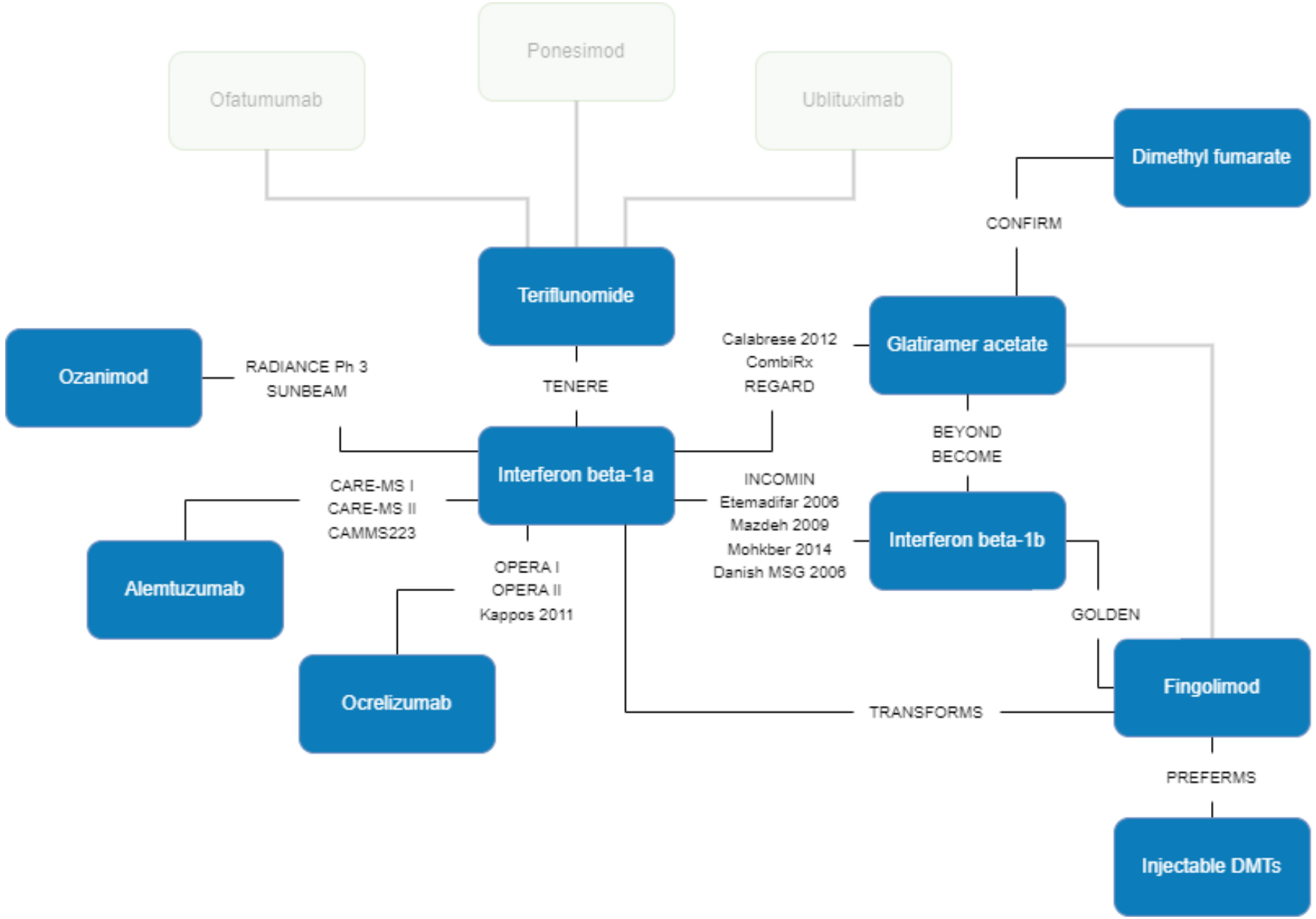

Combinations

CombiRx
(GA or IFNB-1a vs. GA+INFB-1a)

Different Dosing Schedules

Glatiramer Acetate
CONFIDENCE
GLACIER

IFNB-1a
Calabrese 2012
Etemadifar 2006
EVIDENCE 2002
Mazdeh 2009
Mohkber 2014

PegIFNB-1a
ADVANCE

Dimethyl fumarate
BG-12 Phase IIb
CONFIRM
DEFINE

Findings

- The previous report included 11 head-to-head comparisons (23 RCTs) and 4 different dosing schedules comparisons.
  - We did not identify any new evidence for these previously reviewed comparisons.
  - **The findings from the 11 previously reviewed head-to-head comparisons have not changed since the previous report and we will not be discussing the specific studies in this presentation.**
    - The findings from specific studies remain included in your report.
    - The slides from the 2020 presentation with the findings from specific studies can be found at the end of this presentation.

Study Characteristics

Comparators	Number of RCTs	Population[a]	Total N	Study Duration
Ofatumumab vs. teriflunomide	2	RRMS or SPMS	1,882	30 months
Ponesimod vs. teriflunomide	1	RRMS or SPMS	1,133	108 weeks (approx. 25 months)
Ublituximab vs. teriflunomide	2	Relapsing MS	1,094	96 weeks (approx. 22 months)
Fingolimod vs. glatiramer acetate	1	RRMS	1,064	12 months

Note. [a]*Populations include adults only.*

Ofatumumab 20 mg vs. Teriflunomide 14 mg

- We identified 2 RCTs, with a total sample size of 1,882, evaluating the efficacy and safety of subcutaneous ofatumumab compared with oral teriflunomide in patients with RRMS or SPMS.
  - ASCLEPIOS I and ASCLEPIOS II were identically designed, conducted concurrently, and reported together in 1 publication.
    - Each trial was powered for the primary end point (ARR) and the combined trials provided the sample size and power for the preplanned meta-analysis of disability worsening.
    - Participants in the subcutaneous ofatumumab groups also received oral placebo and participants in the oral teriflunomide groups also received subcutaneous placebo corresponding to the active drug in the other group.
  - ASCLEPIOS trials both at moderate risk of bias because of concerns around author conflicts of interest and sponsor involvement in the study design and analysis.

Ofatumumab 20 mg vs. Teriflunomide 14 mg

Relapse

- Ofatumumab significantly reduced annualized relapse rates at 30 months (MD, −0.13; 95% CI, −0.16 to −0.09; *P* < .001)
- Moderate CoE; meta-analysis of 2 RCTs; 1,882 participants

Change in Disability (EDSS)

- Ofatumumab significantly reduced the risk of disability worsening at 6 months (8.1% vs. 12%; *P* = .01)
- No significant difference in confirmed disability improvement at 6 months was observed (11% vs. 8.1%; *P* = .09)
- Moderate CoE; pooled analysis of 2 RCTs; 1,882 participants

ASCLEPIOS I and II

Ofatumumab 20 mg vs. Teriflunomide 14 mg

Persistence

- Significantly higher for participants in the ofatumumab groups (85.9% vs. 81.7%; *P* = .01)
- Moderate CoE; meta-analysis of 2 RCTs; 1,882 participants

SAEs

- No significant difference
- Low CoE; pooled analysis of 2 RCTs; 1,882 participants

ASCLEPIOS I and II

Ponesimod 20 mg vs. Teriflunomide 14 mg

- We identified 1 RCT, with a total sample size of 1,133, evaluating the efficacy and safety of oral ponesimod compared with oral teriflunomide in patients with RRMS or SPMS.
  - OPTIMUM trial at moderate risk of bias because of concerns around attrition, author conflicts of interest and sponsor involvement in all aspects of the study.

Ponesimod 20 mg vs. Teriflunomide 14 mg

Relapse

- Ponesimod significantly reduced relapse rates at 108 weeks (mean ARR, 0.20 vs. 0.29; rate ratio, 0.70; 99% CI, 0.54 to 0.90; *P* < .001)
- Moderate CoE; 1 RCT; 1,133 participants

Change in Disability (EDSS)

- No significant difference at 12 weeks
- Very Low CoE; 1 RCT; 1,133 participants

OPTIMUM

Ponesimod 20 mg vs. Teriflunomide 14 mg

Persistence

- No significant difference
- Low CoE; 1 RCT; 1,133 participants

SAEs

- No significant difference
- Low CoE; 1 RCT; 1,133 participants

OPTIMUM

Ublituximab 450 mg vs. Teriflunomide 14 mg

- We identified 2 RCTs, total sample size of 1,094, evaluating the efficacy and safety of intravenous infusions of ublituximab compared with oral teriflunomide, in patients with relapsing MS.
  - ULTIMATE I and ULTIMATE II were identically designed, conducted concurrently, and reported together in 1 publication.
    - Authors analyzed results separately for primary outcomes in 2 trials, but conducted prespecified pooled analyses for selected secondary and tertiary outcomes.
    - Participants in intravenous ublituximab group received oral placebo, and participants in oral teriflunomide group received intravenous placebo, corresponding to the active drug in the other group.
  - ULTIMATE trials both at high risk of bias because of author financial conflict of interest and a high level of sponsor involvement in study design, analysis, and publication.

Ublituximab 450 mg vs. Teriflunomide 14 mg

Relapse

- Ublituximab significantly reduced relapse rates at 96 weeks (MD, −0.10; 95% CI, −0.17 to −0.03; *P* = .005)
- Moderate CoE; meta-analysis of 2 RCTs; 1,094 participants

Change in Disability (EDSS)

- No significant difference at 12 weeks
- Low CoE; pooled analysis of 2 RCTs; 1,094 participants

ULTIMATE I and II

Ublituximab 450 mg vs. Teriflunomide 14 mg

Persistence

- No significant difference
- Very Low CoE; meta-analysis of 2 RCTs; 1,094 participants

SAEs

- Ublituximab was associated with a significantly higher number of reported SAEs at 96 weeks (10.8% vs. 7.3%; *P* = .04)
- Low CoE; meta-analysis of 2 RCTs; 1,094 participants

ULTIMATE I and II

Fingolimod 0.25 mg and 0.5 mg vs. Glatiramer Acetate 20 mg

- We identified 1 RCT, with a total sample size of 1,064, evaluating the efficacy and safety of oral fingolimod 0.25 mg and oral fingolimod 0.5 mg, each compared with subcutaneous injections of glatiramer acetate in patients with RRMS.
  - ASSESS trial at moderate risk of bias because of concerns around the number of enrolled participants, lack of participant blinding, and author conflicts of interest.
    - Enrolled fewer than half the planned number of participants, which affected the power calculations, and randomization ratios requested by the FDA were not possible.
    - Although the trial was rater blinded, a double-blind design was not used for this trial.

Fingolimod 0.25 mg and 0.5 mg vs. Glatiramer Acetate 20 mg

Relapse

- Fingolimod 0.5 mg significantly reduced relapse rates at 12 months (ARR, 0.15 vs. 0.26; *P* = .01)
- No significant difference with fingolimod 0.25 mg and glatiramer acetate at 12 months
- Moderate CoE; 1 RCT; 1,064 participants

Change in Function (MSFC)

- Fingolimod 0.5 mg significantly improved functional disability at 12 months (MD, 0.09 vs. 0.03; *P* = .05)
- No significant difference with fingolimod 0.25 mg and glatiramer acetate at 12 months
- Moderate CoE; 1 RCT; 1,064 participants

ASSESS

Fingolimod 0.25 mg and 0.5 mg vs. Glatiramer Acetate 20 mg

Persistence

- Significantly higher for fingolimod groups (85.2% fingolimod 0.5 mg, vs. 84.1% fingolimod 0.25 mg, vs. 74.3% glatiramer acetate; $P < .001$ all)
- Higher proportions of the fingolimod groups received the study drug until completion (94.6% fingolimod 0.5 mg, vs. 95.4% fingolimod 0.25 mg, vs. 89.2% glatiramer acetate)
- Moderate CoE; 1 RCT; 1,064 participants

SAEs

- No significant difference
- Low CoE; 1 RCT; 1,064 participants

Findings

Key Questions 2 and 3:
Comparative Effectiveness and Harms for CIS

Findings: Comparative Effectiveness and Harms for CIS

- The previous report identified 5 placebo-controlled comparisons (8 RCTs) and 1 dosing schedule comparison for people diagnosed with CIS.
- We did not identify any new evidence for these previously reviewed comparisons.
  - **The findings from the previously reviewed comparisons have not changed since the previous report and we will not be discussing the specific studies in this presentation.**
    - Findings from specific studies remain included in your report.
    - Slides from the 2020 presentation with the findings from specific studies can be found at the end of this presentation.

Findings

Key Question 4: Variation by Subgroup

Findings: Variation by Subgroup

- Across all 43 RCTs reviewed (6 new):
  - As anticipated, RCTs do not consistently assess variation in effectiveness or harms by subgroup.
  - Some information on age, previous treatment, baseline disease severity, neutralizing antibody status, body mass, number of prior relapses, sex, disease activity, subtype of MS, type of initial event for CIS.
  - Difficult to draw robust conclusions.

Findings

Key Question 3:
Comparative Harms for MS and CIS From Cohort Studies

Findings: Comparative Harms

- We identified 45 cohort studies (15 new):
  - Majority of studies were moderate risk of bias because of concerns about author conflicts of interest and industry funding.
  - Rest were high risk of bias because of additional concerns about adjustment for confounding.
- 35[a] cohort studies (11 new) reported on treatment discontinuation or switch.
- 12[a] cohort studies (6 new) reported on SAEs.
- No direct comparison of harms by indication.

Note. [a]2 cohort studies reported on both treatment discontinuation or switch and SAEs.

Findings: Comparative Harms (Discontinuation or Switch)

- 35 cohort studies (11 new) reported on discontinuation or switch.
  - Treatment discontinuations or switches appear to be significantly lower with fingolimod and dimethyl fumarate.
  - Uncertainty remains regarding the risk of treatment discontinuation or switch for oral DMTs compared with injectable DMTs as not every FDA-approved DMT was included in the reviewed studies, and the reported outcomes are not generalizable to all categorically oral or injectable DMTs.

Findings: Comparative Harms (Serious Adverse Events)

- 12 cohort studies (6 new) reported on SAEs, specifically:
  - Risk of liver injury was higher for interferons, alemtuzumab, teriflunomide, and fingolimod.
  - Risk of PML was higher with fingolimod and dimethyl fumarate.
  - Risk of infection was lower with interferon beta and glatiramer acetate.
  - Uncertainty remains regarding the association of cancer risk and DMTs.
    - Although this association was investigated in multiple studies, only 1 study reported a statistically significant association.[a]

Note. [a]*Interferon beta, dimethyl fumarate and fingolimod were significantly associated with cancer reporting.*
Abbreviations. PML: progressive multifocal leukoencephalopathy.

Findings

Key Question 5: Ongoing Studies

Findings: Ongoing Studies

- We identified 12 ongoing studies.
- The ongoing studies identified could fill evidence gaps, particularly where comparative RCT evidence was not identified.[a]
- Ongoing study findings are based on posted eligibility criteria, we will not know for certainty if these studies are relevant for DERP until results are published.

Note. [a]*This is the case for: cladribine, diroximel fumarate, monomethyl fumarate, peginterferon beta-1a, and siponomid.*

Findings: Ongoing Studies (Comparative RCTs)

- 6 ongoing studies are comparative RCTs.
  - All eligible DMTs have ongoing, comparative RCT trials.
  - Groups of DMTs are compared rather than one DMT to another, these groupings are defined by trial investigators:
    - 2 trials comparing ofatumumab versus first line DMTs and ofatumumab versus other approved DMTs
    - 2 trials group DMTs as early aggressive therapy versus traditional therapy and highly effective therapies versus escalation therapies
    - 2 trials comparing several DMTs of interest to DERP to a stem cell treatment not currently FDA approved[a]

Note. [a]*Stem cell treatment: Autologous haematopoietic stem cell transplantation (aHSCT). Trials included given the possibility of subgroup analyses comparing DMTs of interest.*

Ongoing Studies

Comparators	Estimated Completion Date	Trial Number	Population[a]	Estimated Enrollment
Active Comparator RCTs				
Ofatumumab vs. first line DMT[b]	June 2025	NCT04788615	Relapsing MS	186
Ofatumumab vs. other approved DMT[b]	February 2026	NCT05090371	RRMS	150
Early aggressive therapy[b] vs. traditional therapy[b]	August 2025	NCT03500328	RRMS	900
Early highly effective therapies[b] vs. escalation therapies[b]	April 2030	NCT03535298	RRMS	800
Alemtuzumab, cladribine, or ocrelizumab vs. aHSCT	March 2024	NCT03477500	RRMS	100
Alemtuzumab, cladribine, ocrelizumab, or ofatumumab vs. aHSCT	May 2026	ISRCTN88667898	RRMS	198

Note. [a]Populations include adults only. [b]DMT categories as published in the registry and defined by trial investigators.
Abbreviations. aHSCT: autologous hematopoietic stem cell transplantation; ISRCTN: International Standard Randomised Controlled Trials Number; NCT: US National Clinical Trial number.

Findings: Ongoing Studies (Comparative RCTs)

- Additionally, there is 1 ongoing comparative RCT trial (identified in the 2020 report) that has yet to publish results:
  - Trial completed October 2020
  - Comparing interferon beta-1a/1b against peginterferon beta-1a, a DMT for which we lack reviewed, comparative RCT evidence
  - Study population: 80 participants

Findings: Ongoing Studies (Placebo-Controlled RCTs)

- We identified 2 placebo-controlled RCTs:
  - Both are comparing ocrelizumab against a placebo.
  - 1 includes participants with relapsing MS and has the potential to investigate a population with CIS.
  - The other trial includes individuals with PPMS.
    - Potentially of interest as ocrelizumab is the only DMT currently FDA approved for this population so there is not head-to-head RCT evidence for this population.

Findings: Ongoing Studies (Cohorts)

- We identified 3 prospective cohort studies:
  - Comparative evidence emphasized.
  - These trials could provide evidence on all DMTs of interest.
  - 1 trial that was completed in September 2023 includes 1,250 adults with RRMS and rSPMS and any DMT.
  - Other 2 trials only include pregnant women with MS .
    - Both trials are evaluating diroximel fumarate.

Abbreviations. rSPMS: relapsing secondary progressive multiple sclerosis.

Ongoing Studies

Comparators	Estimated Completion Date	Trial Number	Population	Estimated Enrollment
Placebo-controlled RCTs				
Ocrelizumab[a] vs. PBO	December 2027	NCT04035005	PPMS[b]	1,000
Ocrelizumab[a] vs. PBO	August 2028	NCT05285891	Relapsing MS[b]	175
Prospective Cohort Studies				
Any DMT	September 2023 (actual)	ISRCTN40939838	RRMS; rSPMS[b]	1,250 (actual)
Diroximel fumarate vs. other DMTs[c]	January 2031	NCT05688436	Pregnant women with MS[b]	1,178
Diroximel fumarate vs. interferon beta	July 2032	NCT05658497	Pregnant women with MS	908

Note. [a]Ocrelizumab is the only DMT currently FDA-approved to treat individuals with PPMS. [b]Populations include adults only. [c]DMT categories as published in the registry and defined by trial investigators.
Abbreviations. ISRCTN: International Standard Randomised Controlled Trials Number; NCT: US National Clinical Trial number; PBO: placebo; rSPMS: relapsing secondary progressive multiple sclerosis.

Discussion

Discussion: DMTs for MS

- We identified 38 RCTs (6 new):
  - 15 head-to-head comparisons in MS (4 new) evaluated in 29 RCTs (6 new)
  - 4 comparisons of different dosing schedules in MS (0 new) evaluated in 9 RCTs
  - 1 comparison of different dosing schedules in CIS (0 new) evaluated in 1 RCT
  - 5 placebo-controlled comparisons in CIS (0 new) evaluated in 8 RCTs
- We identified 45 cohort studies (15 new)

Discussion: FDA-Approved DMTs

FDA Approval Date	Generic Name	Indication[a]	Route of Administration; Frequency	Eligible Studies Reviewed: NCT Number Trial Name
12/28/2022	Ublituximab	Relapsing forms of MS	Injectable, IV infusion; Every 6 months	NCT03277261; NCT03277248 ULTIMATE I; ULTIMATE II
3/18/2021	Ponesimod	Relapsing forms of MS	Oral; Daily	NCT02425644 OPTIMUM
8/20/2020	Ofatumumab[b]	Relapsing forms of MS	Injectable, SC; Monthly	NCT02792218; NCT02792231 ASCLEPIOS I; ASCLEPIOS II
4/28/2020	Monomethyl Fumarate	Relapsing forms of MS	Oral; Twice Daily	None.[c]
13 additional DMTs with FDA-approval prior to April 2020[d]				

Note. [a]*Indications include adults only.* [b]*Under further investigation in 2 ongoing RCTs (NCT04788615; NCT05090371).* [c]*FDA-approved based on bioequivalence with dimethyl fumarate.* [d]*Ozanimod, diroximel fumarate, cladribine, siponimod, ocrelizumab, alemtuzumab, peginterferon beta-1a, dimethyl fumarate, teriflunomide, fingolimod, interferon beta-1a, glatiramer acetate, interferon beta-1b.*
Abbreviations. IV: intravenous; NCT: US National Clinical Trial number; SC: subcutaneous.

Discussion: Effectiveness and Harms of DMTs for MS (1 of 2)

- 29 RCTs (6 new) comparing DMTs for MS:
  - When comparing 3 of the new DMTs (i.e., ofatumumab, ponesimod, ublituximab) against teriflunomide, the newer DMTs all significantly reduced relapses.
    - Ublituximab associated with increased SAEs
    - Ofatumumab and ponesimod not associated with increased SAEs
  - When comparing fingolimod against glatiramer acetate, fingolimod significantly reduced relapses.

New in 2024

  - When comparing older DMTs directly, alemtuzumab, fingolimod, ocrelizumab, and teriflunomide significantly reduce relapses and are not associated with increased SAEs, compared with other DMTs.

Discussion: Effectiveness and Harms of DMTs for MS (2 of 2)

- 29 RCTs (6 new) comparing DMTs for MS:
  - We did not identify head-to-head trials for every possible comparison of the relevant interventions.
    - We can't draw conclusions stating definitively that one DMT is more or less effective over all others.
  - We did not identify any eligible head-to-head RCTs for 5 FDA-approved DMTs (diroximel fumarate, cladribine, monomethyl fumarate, siponimod, peginterferon beta-1a).
  - Subgroup analyses are not consistently reported, however:
    - Presence of neutralizing antibodies does not appear to reduce effectiveness.
    - Patient factors such as age and prior treatment may change effectiveness.

Discussion: Effectiveness and Harms of DMTs for CIS

- 5 placebo-controlled comparisons in CIS (0 new) evaluated in 8 RCTs:
  - DMTs reviewed (cladribine, glatiramer acetate, interferon beta-1b, interferon beta-1a, and teriflunomide) significantly reduced conversion to MS, compared with placebo.
  - DMTs (cladribine, glatiramer acetate, interferon beta-1b, interferon beta-1a, and teriflunomide) did not appear to be associated with more SAEs, compared with placebo.
  - Some evidence that women may benefit more than men from glatiramer acetate and interferon beta-1a.

Discussion: Safety of DMTs (1 of 2)

- 45 cohort studies (15 new):
  - Treatment discontinuations or switches appear to be significantly lower with fingolimod and dimethyl fumarate.
  - Uncertainty remains regarding the risk of treatment discontinuation or switch for oral DMTs compared with injectable DMTs.

Discussion: Safety of DMTs (2 of 2)

- 45 cohort studies (15 new):
  - Risk of specific adverse events is higher with some DMTs:
    - Risk of liver injury was higher for interferons, alemtuzumab, teriflunomide, and fingolimod.
    - Risk of PML was higher with fingolimod and dimethyl fumarate.
    - Risk of infection was lower with interferon beta and glatiramer acetate.
    - Uncertainty remains regarding the association of cancer risk and DMTs.
  - Evidence is inconsistent in terms of which DMTs are compared, so our ability to draw conclusions is limited.

Abbreviations. PML: progressive multifocal leukoencephalopathy.

Questions?


CENTER FOR
EVIDENCE-BASED POLICY

Findings Unchanged Since 2020 Report

Findings Unchanged Since 2020 Report

- The following slides contain the findings from individual head-to-head comparisons of DMTs for MS and CIS, and placebo-controlled comparisons of DMTs for CIS.
- During this update, we did not identify any additional studies for any of the previously reviewed comparisons.
- **The findings from these comparisons remain unchanged.**
- These slides are included here for your reference, and further details are available within your report.

Findings Unchanged Since 2020 Report

Key Questions 1 and 3:
Comparative Effectiveness and Harms for MS

Findings: Alemtuzumab 12 mg vs. Interferon Beta-1a 44 µg

Relapse

- Significantly reduced at 24 months (RR, 0.65; 95% CI, 0.48 to 0.88) and at 36 months (RR, 0.52; 95% CI, 0.34 to 0.80)
- Moderate CoE; meta-analysis of 3 RCTs; 1,472 participants

Disability Progression

- Significantly reduced at 24 months (RR, 0.73; 95% CI, 0.54 to 0.99) and at 36 months (RR, 0.33; 95% CI, 0.15 to 0.70)
- Low CoE; meta-analysis of 3 RCTs; 1,472 participants

Disability (EDSS)

- Significantly improved at 36 months (mean difference, -0.07; 95% CI, -1.04 to -0.36), but not at 24 months (mean difference, -0.20; 95% CI, -0.60 to 0.20)
- Low CoE; meta-analysis of 3 RCTs; 1,414 participants
- However, the differences were small and unlikely to be clinically meaningful

CARE MS I, CARE MS II, CAMMS223

Findings: Alemtuzumab 12 mg vs. Interferon Beta-1a 44 µg

Function (MSFC)

- Significantly improved at 24 months (mean difference, 0.10; 95% CI, 0.05 to 0.16)
- Moderate CoE; meta-analysis of 2 RCTs; 1,191 participants
- The clinical importance of the improvement is not clear

Persistence

- Significantly increased at 36 months (RR, 1.37; 95% CI, 1.15 to 1.63) but not at 24 months (RR, 1.16; 95% CI, 0.98 to 1.37
- Low CoE; meta-analysis of 3 RCTs; 1,472 participants

SAEs

- No significant difference at 24 months or 36 months
- Very low CoE; meta-analysis of 3 RCTs; 1,415 participants

CARE MS I, CARE MS II, CAMMS223

Findings: Dimethyl Fumarate 240 mg vs. Glatiramer Acetate 20 mg

Relapse

- No significant difference
- Very low CoE; 1 RCT; 709 participants

Disability Progression

- No significant difference
- Very low CoE; 1 RCT; 709 participants

Persistence

- No significant difference
- Moderate CoE; 1 RCT; 709 participants

SAEs

- No significant difference
- Low CoE; 1 RCT; 709 participants

CONFIRM

Findings: Fingolimod 0.5 mg vs. Interferon Beta-1b 250 µg

Relapse

- Reduced relapse rates numerically, but the statistical significance is not clear (ARR, 0.12 vs. 0.39; *P* value not reported)
- Low CoE; 1 RCT; 157 participants

Disability (EDSS)

- No significant difference (mean increase of 0.12 vs. 0.19; *P* value not reported)
- Low CoE; 1 RCT; 157 participants
- Differences are small and are unlikely to be clinically meaningful

Persistence

- Significantly increased persistence (RR, 1.56; 95% CI, 1.23 to 1.97)
- Moderate CoE; 1 RCT; 157 participants

SAEs

- No significant difference
- Low CoE; 1 RCT; 151 participants

Findings: Fingolimod 0.5 mg vs. Interferon Beta-1a 30 µg

Relapse

- Significantly reduced relapse rates (ARR, 0.16 vs. 0.33; *P* < .001)
- Low CoE; 1 RCT; 860 participants

Disability Progression

- No significant difference
- Low CoE; 1 RCT; 860 participants

Disability (EDSS)

- No significant difference
- Low CoE; 1 RCT; 860 participants

TRANSFORMS

Findings: Fingolimod 0.5 mg vs. Interferon Beta-1a 30 µg

Function (MSFC)

- No significant difference in function as measured by the MSFC
- Low CoE; 1 RCT; 860 participants

Persistence

- No significant difference
- Moderate CoE; 1 RCT; 866 participants

SAEs

- No significant difference in serious adverse events
- Low CoE; 1 RCT; 860 participants

TRANSFORMS

Findings: Fingolimod 0.5 mg vs. Injectable DMTs

Relapse

- No significant difference in relapse
- Low CoE; 1 RCT; 861 participants

Persistence

- Significantly increased persistence (RR, 1.11; 95% CI, 1.04 to 1.18)
- Low CoE; 1 RCT; 875 participants

SAEs

- Significantly increased serious adverse events (RR, 1.91; 95% CI, 1.04 to 3.51)
- Low CoE; 1 RCT; 861 participants

PREFERMS

Findings: Glatiramer Acetate 20 mg vs. Interferon Beta-1b 250 µg

Relapse

- No significant difference
- Low CoE; 2 RCTs; 1,420 participants

Disability Progression

- No significant difference
- Low CoE; 1 RCT; 1,345 participants

Persistence

- No significant difference
- Moderate CoE; meta-analysis of 2 RCTs; 1,420 participants

SAEs

- No significant difference
- Low CoE; 1 RCT; 1,333 participants

BECOME and BEYOND

Findings: Glatiramer Acetate 20 mg vs. Interferon Beta-1a 30 µg or 44 µg

Relapse

- No significant difference at 24 or 36 months, although the proportion was numerically lower with glatiramer acetate at 36 months (20% vs. 26%)
- Low CoE; 2 RCTs; 1,273 participants

Disability Progression

- No significant difference
- Very low CoE; 2 RCTs; 1,273 participants

Disability (EDSS)

- No significant difference
- Low CoE; 1 RCT; 141 participants

Calabrese et al., 2012, CombiRx, REGARD

Findings: Glatiramer Acetate 20 mg vs. Interferon Beta-1a 30 µg or 44 µg

Function (MSFC)

- No significant difference
- Low CoE; 1 RCT; 423 participants

Persistence

- Significantly increased persistence at 24 months (RR, 1.08; 95% CI, 1.02 to 1.15) and at 36 months (RR, 1.08; 95% CI, 1.01 to 1.16)
- Low CoE; meta-analysis of 3 RCTs; ; 1,687 participants

SAEs

- No significant difference
- Very low CoE; meta-analysis of 2 RCTs; 1,265 participants

Calabrese et al., 2012, CombiRx, REGARD

Findings: Interferon Beta-1b 250 µg vs. Interferon Beta-1a (different doses)

Relapse

- No significant difference at 24 months
- Very low CoE; meta-analysis of 3 RCTs; 648 participants

Disability Progression

- No significant difference
- Very low CoE; meta-analysis of 2 RCTs; 489 participants

Disability (EDSS)

- No significant difference at 12 or 24 months
- Moderate CoE; meta-analysis of 4 RCTs; 407 participants

INCOMIN, Danish MSG, Etemadifar et al., 2006, Mazdeh et al, 2010, Mokhber et al., 2014

Findings: Interferon Beta-1b 250 µg vs. Interferon Beta-1a (different doses)

Function (Paced Auditory Serial Addition Test, cognitive component of the MSFC)

- Significantly increased (a difference between groups of 9.04)
- Very low CoE; 1 RCT; 63 participants
- The clinical importance of the difference is unclear

Disability Progression

- No significant difference at 24 months
- Moderate CoE; meta-analysis of 4 RCTs; 648 participants

INCOMIN, Danish MSG, Etemadifar et al., 2006, Mazdeh et al, 2010, Mokhber et al., 2014

Findings: Ocrelizumab 600 mg vs. Interferon Beta-1a 30 µg or 44 µg

Relapse

- Significantly reduced relapse (ARR, 0.13 vs. 0.36, and 0.16 vs. 0.29)
- Low CoE; 3 RCTs; 1,765 participants

Disability Progression

- Significantly reduced (hazard ratio [HR], 0.60; 95% CI, 0.45 to 0.81)
- Low CoE; pooled analysis of 2 RCTs; 1,656 participants

OPERA I, OPERA II, Kappos et al., 2011

Findings: Ocrelizumab 600 mg vs. Interferon Beta-1a 30 µg or 44 µg

Function (MSFC)

- Significantly improved functioning (mean difference, 0.07; 95% CI, 0.02 to 0.13)
- Moderate CoE; meta-analysis of 2 RCTs; ; 1,656 participants
- The clinical importance of the difference is not clear

Persistence

- Significantly increased persistence at 24 months (RR, 1.10; 95% CI, 1.05 to 1.15), but not at 6 months
- Low CoE; meta-analysis of 3 RCTs; 1,767 participants

SAEs

- No significant difference
- Low CoE; meta-analysis of 3 RCTs; 1,760 participants

OPERA I, OPERA II, Kappos et al., 2011

Findings: Ozanimod 0.5 mg and 1 mg vs. Interferon Beta-1a 30 µg

Relapse

- Significantly reduced relapse in the SUNBEAM trial (rate ratio, ozanimod 0.5 mg vs. interferon beta-1a, 0.69; 95% CI, 0.55 to 0.86; rate ratio, ozanimod 1 mg vs. interferon beta-1a, 0.52; 95% CI, 0.41 to 0.66) and in the RADIANCE Phase 3 trial (RR, ozanimod 0.5 mg vs. interferon beta-1a, 0.79; 95% CI, 0.65 to 0.96; RR, ozanimod 1 mg vs. interferon beta-1a, 0.62; 95% CI, 0.51 to 0.77)
- Low CoE; 2 RCTs; 2,659 participants

Disability Progression

- No significant difference
- Low CoE; 2 RCTs; 2,659 participants

RADIANCE Phase 3 and SUNBEAM

Findings: Ozanimod 0.5 mg and 1 mg vs. Interferon Beta-1a 30 µg

Function (MSFC)

- Ozanimod 0.5 mg significantly improved function (mean difference interferon beta-1a, 0.10; 95% CI, 0.01 to 0.19), but no significant difference with ozanimod 1 mg
- Very low CoE; 2 RCTs; 2,659 participants
- The clinical importance of the difference is not clear

Persistence

- No significant difference;
- Moderate CoE; meta-analysis of 2 RCTs; 2,666 participants

SAEs

- No significant difference
- Very low CoE; meta-analysis of 2 RCTs; 2,658 participants

RADIANCE Phase 3 and SUNBEAM

Findings: Teriflunomide 7 mg and 14 mg vs. Interferon Beta-1a

Relapse

- Teriflunomide 7 mg significantly reduced relapse rates (ARR, 0.41 vs. 0.22; *P* = .03), but no significant differences with 14 mg
- Low CoE; 1 RCT; 324 participants

Persistence

- Teriflunomide 7 mg significantly increased persistence (RR, 1.20; 95% CI, 1.02 to 1.40), but the difference is only marginal with 14 mg (RR, 1.17; 95% CI, 1.00 to 1.38)
- Very low CoE; 1 RCT; 324 participants

SAEs

- Teriflunomide 7 mg increased the number of serious adverse events but the difference is not significant (RR, 1.57; 95% CI, 0.64 to 3.84), and no significant differences with 14 mg
- Very low CoE; 1 RCT; 321 participants

TENERE

Findings: Cladribine 3.5 mg/kg + Continued Interferon Beta vs. Placebo + Continued Interferon Beta

Relapse

- Significantly reduced (RR, 0.37; 95% CI, 0.22 to 0.63)
- Moderate CoE; 1 RCT; 172 participants

Disability Progression

- No significant difference
- Low CoE; 1 RCT

Persistence

- Significantly reduced (RR, 0.79; 95% CI, 0.66 to 0.96)
- Low CoE; 1 RCT; 172 participants

SAEs

- No significant difference
- Low CoE; 1 RCT; 172 participants

ONWARD

Findings: Different Dosing Schedules

Dimethyl Fumarate

- No significant difference in relapse, disability progression, persistence, or SAEs
- Low to moderate CoE; 2 RCTs; 1,529 to 1,545 participants

Glatiramer Acetate

- No significant difference in persistence by dose
- Moderate CoE; 2 RCTs; 1,070 participants
- No clear association with dose and SAEs (results were mixed)
- Very low CoE; 2 RCTs; 1,066 participants

CONFIRM and DEFINE
CONFIDENCE and GLACIER

Findings: Different Dosing Schedules

Interferon Beta-1a

- No clear association with relapse by dose
- Very low CoE; 3 RCTs; 860 participants
- No significant difference in disability progression, disability (EDSS), persistence, or SAEs
- Very low CoE; 1 RCT to moderate CoE: 2 RCTs; 103 to 833 participants

Peginterferon Beta-1a

- No significant difference in relapse, disability progression, persistence, or SAEs
- Low to moderate CoE; 1 RCT; 1,012 participants

EVIDENCE, Calabrese et al., 2012, Mazdeh et al., 2010, Mokhber et al., 2014
ADVANCE

Findings: Combination of Glatiramer Acetate 20 mg Plus Interferon Beta-1a 30 µg

Relapse

- Reduced relapse compared with interferon beta-1a alone (ARR, 0.12 vs. 0.16; *P* = .02), but no significant difference with glatiramer acetate 20 mg alone
- Low CoE; 1 RCT; 1,008 participants

Disability Progression

- No significant difference in disability progression, compared with interferon beta-1a or glatiramer acetate alone
- Low CoE; 1 RCT; 1,008 participants

Findings: Combination of Glatiramer Acetate 20 mg Plus Interferon Beta-1a 30 µg

Function (MSFC)

- No significant difference in function (MSFC) compared with interferon beta-1a or glatiramer acetate alone
- Low CoE; 1 RCT; 1,008 participants

Persistence

- Reduced persistence (RR, 0.92; 95% CI, 0.86 to 0.99) compared with glatiramer acetate alone, but not with interferon beta-1a alone
- Low CoE; 1 RCT; 1,008 participants

SAEs

- No significant difference compared with interferon beta-1a alone or glatiramer acetate alone
- Low CoE; 1 RCT; 1,008 participants

Findings From Studies Identified in 2020

Key Questions 2 and 3:
Comparative Effectiveness and Harms for CIS

Findings: Cladribine 3.5 mg/kg vs. Placebo

Conversion to MS

- Significantly reduced conversion to MS (HR, 0.33; 95% CI, 0.21 to 0.51)
- Moderate CoE; 1 RCT; 412 participants

Persistence

- Significantly reduced persistence (RR, 0.90; 95% CI, 0.82 to 0.99)
- Low CoE; 1 RCT; 412 participants

SAEs

- No significant difference
- Low CoE; 1 RCT; 412 participants

ORACLE MS

Findings: Glatiramer Acetate 20 mg vs. Placebo

Conversion to MS

- Reduced conversion to MS (HR, 0.55; 95% CI, 0.40 to 0.77)
- Moderate CoE; 1 RCT; 481 participants

Persistence

- No significant difference
- Low CoE; 1 RCT; 481 participants

SAEs

- No significant difference in serious adverse events
- Low CoE; 1 RCT; 481 participants

PreCISe

Findings: Interferon Beta-1b 250 µg vs. Placebo

Conversion to MS

- Significantly reduced conversion to MS (HR, 0.50; 95% CI, 0.36 to 0.70)
- Moderate CoE; 1 RCT; 468 participants

Persistence

- No significant difference
- Low CoE; 1 RCT; 487 participants

SAEs

- No significant difference
- Very low CoE; 1 RCT; 468 participants

BENEFIT

Findings: Interferon Beta-1a (various doses) vs. Placebo

Conversion to MS

- Significantly reduced conversion to MS at 2 years (RR, 0.80; 95% CI, 0.68 to 0.95) and at 3 years (RR, 0.62; 95% CI, 0.50 to 0.78)
- Low CoE; meta-analysis of 4 RCTs; 1,411 participants

Disability (EDSS)

- No significant difference
- low CoE; 1 RCT; 308 participants

Persistence

- No significant difference
- Moderate CoE; 2 RCTs; 826 participants

SAEs

- No significant difference
- Very low CoE; meta-analysis of 4 RCTs; 1,325 participants

ETOMS, REFLEX, CHAMPS, Pakdaman et al., 2007

Findings: Teriflunomide 7 mg and 14 mg vs. Placebo

Conversion to MS

- Significantly reduced conversion to MS (HR, 0.63; 95% CI, 0.42 to 0.95 for teriflunomide 7 mg; HR, 0.57; 95% CI, 0.38 to 0.87 for teriflunomide 14 mg)
- Low CoE; 1 RCT; 614 participants

Disability Progression

- No significant difference
- Very low CoE; 1 RCT; 614 participants

Disability (EDSS)

- Significantly improved (mean change, -0.25 teriflunomide 7 mg vs. -0.27 teriflunomide 14 mg vs. -0.06 placebo; $P < .05$ for both doses vs. placebo)
- Low CoE; 1 RCT; 614 participants
- However, the differences were small and unlikely to be clinically meaningful

TOPIC

Findings: Teriflunomide 7 mg and 14 mg vs. Placebo

Function (MSFC)

- No significant difference
- Low CoE; 1 RCT; 614 participants

Persistence

- No significant difference
- Low CoE; 1 RCT; 618 participants

SAEs

- No significant difference
- Low CoE; 1 RCT; 614 participants

TOPIC

Findings: Different Dosing Schedule for Interferon Beta-1a

Conversion to MS

- No significant difference
- Very low CoE; 1 RCT; 346 participants

Persistence

- No significant difference
- Moderate CoE; 1 RCT; 346 participants

SAEs

- No significant difference
- Low CoE; 1 RCT; 344 participants

REFLEX