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DERP VI Surveillance:
Disease-modifying Drugs for Multiple Sclerosis

June 2021

Table of Contents

Objectives 1
Topic History and Context 1
PICOS 1
Key Questions 3
Methods 3
Findings 3
New Drugs or Formulations 3
New Indications 4
New Serious Harms or Warnings 4
Randomized Controlled Trials 6
Cohort Studies 7
Ongoing Studies 8
Summary 9
References 11
Appendix A. Abstracts of New Eligible Studies 14
Appendix B. ITS Ratings and Definitions 16

Objectives

The purpose of this Drug Effectiveness Review Project (DERP) surveillance report is to preview the volume and nature of new research and relevant clinical information that has emerged since the most recent systematic review on disease-modifying drugs for multiple sclerosis (MS).[1] The literature search for this report focuses on new randomized controlled trials (RCTs), cohort studies, and actions taken by the US Food and Drug Administration (FDA) since the most recent report,[1] including approval of new drugs, formulations, or indications, and identification of serious harms. Comprehensive searches, quality assessment, and synthesis of evidence would follow only if DERP participants commission an update review or another research product type for this topic. Comprehensive searches might identify additional eligible studies.

Topic History and Context

This report is the first surveillance document on this topic since the completion of the most recent systematic review in May 2020.[1] The search strategy for that systematic review was through October 15, 2019, with an updated Ovid MEDLINE search on February 3, 2020.[1]

Table 1. Topic History and Search Dates

Document Type	Date Presented	Search Dates
Systematic Review Update 4	May 2020	• January 1, 2016 through February 3, 2020 for drugs included in prior DERP reports • Database inception through February 3, 2020 for drugs not included in prior DERP reports
Drug Class Review Update 3	May 2016	• Database inception through January 2016
Drug Class Review Update 2	September 2013	• Database inception through January 2013
Drug Class Review Update 1	August 2010	• Database inception through December 2009
Drug Class Review	July 2007	• Database inception through September 2006

Abbreviation. DERP: Drug Effectiveness Review Project.

PICOS

Population

- Adult outpatients (age ≥ 18 years) with MS
  - Relapsing-remitting MS (RRMS)
  - Secondary progressive MS (SPMS)
  - Primary progressive MS (PPMS)
  - Progressive relapsing MS
- Adult outpatients with clinically isolated syndrome (CIS; also known as a "first demyelinating event," the first clinical attack suggestive of MS, or monosymptomatic presentation)

Interventions

Table 2. Included Interventions

Generic Name	Brand Name	FDA Approval Date
FDA-approved Drugs		
Ozanimod (RPC1063)	Zeposia	March 25, 2020[a]
Diroximel Fumarate	Vumerity	October 30, 2019
Cladribine	Mavenclad	March 29, 2019
Siponimod	Mayzent	March 27, 2019
Ocrelizumab	Ocrevus	March 28, 2017
Glatiramer Acetate	Glatopa (branded generic)	April 16, 2015
Peginterferon Beta-1a	Plegridy	August 15, 2014
Dimethyl Fumarate	Tecfidera	March 27, 2013
Teriflunomide	Aubagio	September 12, 2012
Fingolimod	Gilenya	September 21, 2010
Interferon Beta-1a	Rebif	March 7, 2002
Alemtuzumab	Lemtrada	May 7, 2001
Glatiramer Acetate	Copaxone	December 20, 1996
Interferon Beta-1a	Avonex	May 17, 1996
Interferon Beta-1b	Betaseron Extavia	July 23, 1993

Note. [a] This drug was not approved at the time of writing the previous systematic review, and was considered a pipeline therapy. Abbreviation. FDA: US Food and Drug Administration.

Comparators

- Another listed intervention (head-to-head comparison)
- Placebo (interventions that lack head-to-head comparisons, and for pipeline drugs)

Outcomes

- Health outcomes
  - Disability
  - Clinical exacerbation/relapse
  - Quality of life
  - Functional outcomes (e.g., wheelchair use, time lost from work)
  - Persistence (discontinuation rates)
  - For CIS: progression to MS diagnosis
- Harms
  - Overall adverse events
  - Serious adverse events
  - Withdrawals due to adverse events
  - Specific adverse events (e.g., hepatotoxicity)

Study Designs

- Randomized controlled trials (RCTs)
  - ≥ 12 weeks study duration
- Placebo-controlled trials

- ≥ 12 weeks study duration
- For interventions that do not have head-to-head studies and pipeline drugs

- Retrospective and prospective cohort studies comparing an intervention type to another for outcomes on harms
  - ≥ 12 weeks study duration
  - Minimum total sample size of 1,000

Key Questions

KQ1. What is the effectiveness of disease-modifying treatments for MS?

KQ2. What is the effectiveness of disease-modifying treatments for patients with CIS?

KQ3. Do disease-modifying treatments differ in harms by indication (MS or CIS)?

KQ4. Do the effectiveness and harms vary by subgroup (e.g. patient characteristics, use of prior disease-modifying therapies for MS, subtype of MS, presence of comorbidities, antibody status)?

KQ5. What are the characteristics of ongoing studies of disease-modifying treatments for MS?

Methods

Using the PICOS outlined above, researchers from the Center for Evidence-based Policy (Center) searched for eligible RCTs and cohort studies, in ClinicalTrials.gov, the ISRCTN Registry, and the FDA website. Using relevant clinical trial numbers and other identifiers, we then searched Ovid MEDLINE ALL from February 3, 2020 through March 13, 2021. We used the Google search engine to identify studies published since the implementation of the search strategy in the systematic review (May 2020).[1] We used limits for English language and human participants. We also searched the FDA website to identify newly approved drugs, formulations, indications, and new serious harms (e.g., boxed warnings) or warnings for included interventions. To identify new drugs, we used Google and IPD Analytics and searched CenterWatch, a privately owned database of clinical trials information.

Findings

New Drugs or Formulations

We identified 3 new drugs for MS approved by the FDA since the most recent systematic review.[1]

- Ozanimod, brand name Zeposia, was FDA-approved in March 2020.[2]
  - Approval was based on 2 RCTs comparing ozanimod with interferon beta-1a.[3] Both trials, SUNBEAM (NCT02294058)[4] and RADIANCE Phase 3 (NCT02047734)[5] were included in the most recent systematic review.[1]
- Ofatumumab, brand name Kesimpta, was FDA-approved in August 2020.[2]
  - Approval was based on 2 RCTs, comparing ofatumumab with teriflunomide, ASCLEPIOS I (NCT02792218) and ASCLEPIOS II (NCT02792231).[6]
- Ponesimod, brand name Ponvory, was FDA-approved in March 2021.[2]
  - Approval was based on 1 RCT comparing ponesimod with teriflunomide, OPTIMUM (NCT02425644).[7]

Ozanimod and ponesimod are sphingosine 1-phosphate (S1P) receptor modulators.[3,7] Ofatumumab is a CD20-directed cytolytic antibody.[6] Each of the 3 new drugs were approved for use in the treatment of relapsing forms of MS, to include CIS, RRMS, and active SPMS, in adults.[3,6,7]

In December 2020, the FDA approved a reduction in infusion time for ocrelizumab from 3.5 hours every 6 months to 2 hours every 6 months.[2] In January 2021, the FDA approved the use of peginterferon beta 1a via intramuscular injection, in addition to subcutaneous use.[8]

New Indications

In October 2020, the indications for alemtuzumab were revised, stating that because of its safety profile, alemtuzumab should generally be reserved for patients who have had an inadequate response to 2 or more drugs indicated for the treatment of MS.[9] Similarly, the use of alemtuzumab for people with CIS is not recommended because of safety concerns.[9]

New Serious Harms or Warnings

Alemtuzumab

In May 2020, the prescribing label for alemtuzumab was updated to highlight the association between its use and hemophagocytic lymphohistiocytosis (HLH), a life-threatening syndrome of pathologic immune activation characterized by clinical signs and symptoms of extreme systemic inflammation.[9]

In September 2020, the FDA updated the prescribing label again for alemtuzumab with a series of additional warnings[9]:

- Recommendations on monitoring complete blood counts added to the boxed warning on serious, sometimes fatal, autoimmune conditions associated with alemtuzumab use, such as immune thrombocytopenia and antiglomerular basement membrane disease.
- Recommendations on the administration of alemtuzumab added because of the potential for serious and life-threatening infusion reactions. These include limiting the administration of alemtuzumab to certified health care settings that have onsite access to equipment and personnel trained to manage infusion reactions (including anaphylaxis, cerebrovascular, cardiac and respiratory emergencies).
- Contraindications to alemtuzumab amended to include patients with known hypersensitivity or anaphylactic reactions to alemtuzumab or any of the excipients in alemtuzumab (Lemtrada) and patients with active infection.
- Warning added on autoimmunity, stating treatment with alemtuzumab can result in the formation of autoantibodies and increase the risk of serious autoimmune-mediated conditions, which may be life-threatening.
- Warning added on reported cases of pulmonary alveolar hemorrhage, myocardial ischemia, myocardial infarction, stroke (including ischemic and hemorrhagic stroke), and cervicocephalic (e.g., vertebral, carotid) arterial dissection within 1 to 3 days of alemtuzumab infusion.
- Recommendations added on the use of thyroid function tests, prior to initiation of alemtuzumab, during treatment, and for a minimum of 48 months after the last infusion.
- Warning added on the use of alemtuzumab and acquired hemophilia A (anti-Factor VIII antibodies), reported in the clinical trials and in the postmarketing setting.

- Warning added on the association between alemtuzumab and serious, sometimes fatal, infections, including aspergillosis, coccidioidomycosis, histoplasmosis, *Pneumocystis jirovecii* pneumonia, nocardiosis, Epstein-Barr virus, and cytomegalovirus infections.

Cladribine

No new serious harms or warnings were identified since the searches in the most recent systematic review.[1]

Dimethyl Fumarate

No new serious harms or warnings were identified since the searches in the most recent systematic review.[1]

Diroximel Fumarate

In August 2020, the prescribing label for diroximel fumarate was updated to align with the warnings and precautions listed for dimethyl fumarate.[10]

Fingolimod

No new serious harms or warnings were identified since the searches in the most recent systematic review.[1]

Glatiramer Acetate

In July 2020, a warning about hepatic injury, sometimes severe, including liver failure and hepatitis with jaundice, was added to the prescribing label for glatiramer acetate.[11]

Interferon Beta 1a

No new serious harms or warnings were identified since the searches in the most recent systematic review.[1]

Interferon Beta 1b

No new serious harms or warnings were identified since the searches in the most recent systematic review.[1]

Ocrelizumab

In 2020, a series of safety concerns were added to the prescribing label for ocrelizumab[12]:

- In May 2020, warning added on the association of ocrelizumab use and serious infections caused by herpes simplex virus and varicella zoster virus, including central nervous system infections (encephalitis and meningitis), intraocular infections, and disseminated skin and soft tissue infections, as observed in the postmarketing setting.
- In November 2020, warning on the risk of infusion reactions added, based on the clinical trials. The observed infusion reactions were not fatal, but could be serious, resulting in hospitalization.
- In November 2020, warning added on the reactivation of hepatitis B, which may lead to death.
- In November 2020, the link added between ocrelizumab use and decreased immunoglobulin levels, leading to increased rates of infection, based on the pooled results of the clinical trials and extension studies.

- In December 2020, recommendations added on measuring serum immunoglobulins prior to initiation of ocrelizumab.[12]

Ozanimod

Ozanimod was approved for use in MS in March 2020.[3] The prescribing label has no boxed warning, but highlights the following warnings and precautions[3]:

- Risk of infections, including herpes, cryptococcal infection, and progressive multifocal leukoencephalopathy (PML)
- Transient decreases in heart rate and atrioventricular conduction delays
- Liver injury, specifically elevated aminotransferases
- Fetal risk, because of the lack of data
- Increased systolic blood pressure
- Reductions in absolute forced expiratory volume over 1 second (FEV_1)
- Macular edema
- Posterior reversible encephalopathy syndrome
- Unintended additive immunosuppressive effects from prior treatment with immunosuppressive or immune modulating drugs
- Severe exacerbations of MS on stopping ozanimod
- Immune system effects on stopping ozanimod

Peginterferon Beta 1a

In January 2021, the following warnings were added to the prescribing label for peginterferon beta 1a[8]:

- Anaphylaxis, based on reports in the postmarketing setting
- Risk of injection site reactions with intramuscular use compared with subcutaneous use

Siponimod

In January 2021, the prescribing label for siponimod was updated to include a warning on cutaneous malignancies.[13] Long-term use of S1P modulators, including siponimod, is associated with an increased risk of basal cell carcinoma, as observed in 1 clinical trial.[13] Cases of other cutaneous malignancies, including melanoma and squamous cell carcinoma, have also been reported in patients treated with siponimod and in patients treated with another S1P modulator.[13]

Teriflunomide

In November 2020, the prescribing label for teriflunomide was updated with the following warnings[14]:

- Boxed warning on the risk of clinically significant and potentially life-threatening liver injury, including acute liver failure requiring transplant, based on reports in patients treated with teriflunomide in the postmarketing setting.
- Hepatic injury warning, along with recommendations on monitoring liver function before and during teriflunomide treatment, and criteria for stopping treatment.
- Serious skin reaction warning, sometimes fatal, including Stevens-Johnson syndrome, toxic epidermal necrolysis, and drug reaction with eosinophilia and systemic symptoms.

Randomized Controlled Trials

We identified 3 new RCTs published since the searches in the most recent systematic review[1] (Table 3).

- The ASSESS trial compared 2 doses of oral fingolimod with subcutaneous glatiramer acetate over a period of 12 months.[15] The trial was stopped prematurely because of slow recruitment.[15] Based on the final sample size of 1,064, the authors estimated the statistical power to be reduced to 71% for the comparison between fingolimod 0.5 mg and glatiramer acetate, and to 44% for the comparison between fingolimod 0.25 mg and glatiramer acetate.[15]
- The RELIEF trial compared the use of subcutaneous interferon beta-1a administered in the morning with subcutaneous interferon beta-1a administered in the evening over a period of 12 weeks.[16]
- The MOVING trial compared the use of oral fingolimod and subcutaneous interferon beta-1b for the treatment of acute optic neuritis over a period of 6 months.[17] The trial was stopped prematurely because of slow recruitment, and only preliminary results for 13 patients were reported.[17]

Table 3. Newly Published RCTs of Disease-modifying Drugs in Multiple Sclerosis

Citation Trial Registry Number Study Name	Population Sample Size	Intervention	Comparator	Outcomes
Relapsing Multiple Sclerosis				
Cree et al., 2020[15] NCT01633112 ASSESS	Adults, aged 18 to 65, with RRMS N = 1,064	• Oral fingolimod 0.5 mg, once daily • Oral fingolimod 0.25 mg, once daily	• Subcutaneous glatiramer acetate 20 mg, once daily	• Annualized relapse rate • Function • Withdrawal rates • AEs
Patti et al, 2020[16] NCT02064816 RELIEF	Adults, aged 18 and older, with relapsing MS N = 200	• Subcutaneous interferon beta-1a 44 µg, administered in the morning	• Subcutaneous interferon beta-1a 44 µg, administered in the evening	• Flu-like symptoms • Injection site reactions • Anxiety • Fatigue • Sleep • QoL • AEs
Acute Optic Neuritis				
Albert et al., 2020[17] NCT01647880 MOVING	Adults, aged 18 to 55, with an acute first manifestation of unilateral optic neuritis, and a diagnosis of RRMS or CIS N = 13	• Oral fingolimod 0.5 mg, once daily	• Subcutaneous interferon beta-1b 250 µg, every other day	• Relapse • Disability • Visual QoL • Optical function • AEs

Abbreviations. AE: adverse event; CIS: clinically isolated syndrome; MS: multiple sclerosis; RCT: randomized controlled trial; RRMS: relapsing-remitting multiple sclerosis; NCT: US National Clinical Trial; QoL: quality of life.

Cohort Studies

No new cohort studies were identified since the searches in the most recent systematic review.[1]

Ongoing Studies

We identified 6 ongoing studies (2 RCTs and 4 cohort studies) that have been completed in the last 3 years (Table 4). The 2 RCTs compared the use of peginterferon beta-1a with interferon beta-1a and interferon beta-1b.[18,19] The 4 cohort studies focused on the safety of disease-modifying therapies for MS, specifically adverse events with fingolimod,[20] pregnancy outcomes,[21] cancer,[23] and mortality.[22] Sample sizes ranged from 2,089 to 200,000.[20-23]

Table 4. Ongoing Studies of Disease-modifying Drugs in Multiple Sclerosis

Trial Registry Number Study Name	Population Sample Size	Intervention	Comparator	Outcomes	Primary Completion Date
Randomized Controlled Trials					
NCT02744222[18] NR	Adults with RRMS N = 399 (actual)	• Peginterferon beta-1a 180 µg IM every 2 weeks • Peginterferon beta-1a 240 µg IM every 2 weeks • Placebo injections every other week in both groups	• Interferon beta-1a 30 µg IM once a week • Placebo IM once a week	• Time to relapse • Annual relapse rate • Disability • Function • AEs • Withdrawal rates • Neutralizing antibodies	January 2020 (estimated)
NCT03177083[19] PLENO	Adults with RRMS N = 80 (actual)	• Peginterferon beta-1a SC every 2 weeks	• Interferon beta-1a • Interferon beta-1b	• AEs • Quality of life • Work productivity and activity impairment • Disability • Fatigue • Relapses	October 2020 (actual)
Cohort Studies					
NCT01442194[20] PASSAGE	Adults and children with relapsing MS N = 3,076 (actual)	• Fingolimod	• Other disease-modifying therapies	• AEs	July 2020 (actual)
NCT02749396[21] EPID MS Pregnancy Study	Pregnant women with MS N = 2,089 (actual)	• Interferon beta-1a • Interferon beta-1b • Peginterferon beta-1a	• Other disease-modifying drugs • No disease-modifying drugs	• Pregnancy outcomes • Live births	August 2018 (actual)

Trial Registry Number Study Name	Population Sample Size	Intervention	Comparator	Outcomes	Primary Completion Date
NCT04237337[23] PVSEPK	Adults and children with MS N = 200,000 (estimated)	• MS drugs (not specified)	• Other MS drugs (not specified)	• Cancer	February 2020 (estimated)
NCT04472975[22] DRUMS	Adults with MS N = 35,000 (actual)	• MS drugs (interferon beta, glatiramer acetate, natalizumab, fingolimod, dimethyl fumarate, teriflunomide, alemtuzumab, daclizumab, ocrelizumab)	• Other MS drugs (interferon beta, glatiramer acetate, natalizumab, fingolimod, dimethyl fumarate, teriflunomide, alemtuzumab, daclizumab, ocrelizumab)	• Hospitalization • Mortality • AEs	March 2018 (actual)

Abbreviations. AE: adverse event; IM: intramuscular delivery; MS: multiple sclerosis; NCT: US National Clinical Trial; NR: not reported; RRMS: relapsing-remitting MS; SC: subcutaneous delivery.

Summary

Since the completion of the most recent DERP systematic review, we identified:

- 3 new RCTs (in this surveillance document)
  - 1 RCT comparing fingolimod and glatiramer acetate in adults with RRMS
  - 1 RCT comparing morning and evening administration of interferon beta-1a in adults with relapsing MS
  - 1 RCT comparing fingolimod and interferon beta-1b in adults with acute optic neuritis
- 6 ongoing studies
  - 2 head-to-head RCTs comparing peginterferon beta-1a with interferon beta-1a and interferon beta-1b
  - 4 cohort studies comparing the harms of different disease-modifying therapies for MS
- 1 new indication (in this surveillance document)
  - The use of alemtuzumab was restricted because of safety concerns
- New warnings and serious harms (in this surveillance document)
  - A series of warnings for alemtuzumab, including HLH and serious and life-threatening infusion reactions
  - Alignment of warnings for dimethyl fumarate and diroximel fumarate
  - Hepatic injury for glatiramer acetate
  - A series of warnings for ocrelizumab, including serious infections and the reactivation of hepatitis B
  - A series of warnings for the newly-approved ozanimod, including the risk of infection and liver injury
  - Anaphylaxis and injection site reactions for peginterferon beta-1a

- Cutaneous malignancies for siponimod
- A series of warnings for teriflunomide, including a boxed warning on hepatic injury

- 3 new drugs and 1 new formulation (in this surveillance document)
  - Ozanimod was FDA-approved in March 2020
  - Ofatumumab was FDA-approved in August 2020
  - Ponesimod was FDA-approved in March 2021
  - Intramuscular use of peginterferon beta-1a

Using the *Is There a There There Scale* (ITS; Table 5), we rated this topic as *Maybe* (see Appendix B for ratings and definitions).

Table 5. Summary and ITS Rating

Clinical Evidence	Yes How many?	No
New Comparative Trial	☑ 3 RCTs	
New Placebo-Controlled Trial		☒
New Cohort Study of Harms		☒
New Meaningful[a] Study	☑ 1 comparing fingolimod and glatiramer acetate for RRMS	
Ongoing Study Likely to be Published in the Next Year	☑ 2 RCTs and 4 cohort studies	
FDA Actions	Yes Description	No
New Drug or Formulation	☑ New approvals for ozanimod, ofatumumab, and ponesimod	
New Indication	☑ Limited indications for alemtuzumab	
New Serious Harm or Warning	☑ Updated warnings for alemtuzumab, dimethyl fumarate, glatiramer acetate, ocrelizumab, ozanimod, peginterferon beta-1a, siponimod, and teriflunomide	
ITS Rating: *Maybe*		

Note. [a] Large studies (≥ 250 participants), studies that have long-term follow-up (≥ 12 months), studies that compare one drug with another that is considered the standard of care or has not been reported and is clinically important, and studies that include an intervention or outcome that is not previously reported in the literature or is clinically important (e.g., mortality) and adds to the body of literature.
Abbreviations. FDA: US Food and Drug Administration; ITS: Is There a There There Scale; MS: multiple sclerosis; RRMS: relapsing-remitting multiple sclerosis.

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Appendix A. Abstracts of New Eligible Studies

Albert C, Mikolajczak J, Liekfeld A, et al. Fingolimod after a first unilateral episode of acute optic neuritis (MOVING) - preliminary results from a randomized, rater-blind, active-controlled, phase 2 trial. *BMC Neurol.* 2020;20(1):75.

BACKGROUND: Neuroprotection and promotion of remyelination represent important therapeutic gaps in multiple sclerosis (MS). Acute optic neuritis (ON) is a frequent MS manifestation. Based on the presence and properties of sphingosine-1-phosphate receptors (S1PR) on astrocytes and oligodendrocytes, we hypothesized that remyelination can be enhanced by treatment with fingolimod, a S1PR modulator currently licensed for relapsing-remitting MS. METHODS: MOVING was an investigator-driven, rater-blind, randomized clinical trial. Patients with acute unilateral ON, occurring as a clinically isolated syndrome or MS relapse, were randomized to 6 months of treatment with 0.5 mg oral fingolimod or subcutaneous IFN-beta 1b 250 mug every other day. The change in multifocal visual evoked potential (mfVEP) latency of the qualifying eye was examined as the primary (month 6 vs. baseline) and secondary (months 3, 6 and 12 vs. baseline) outcome. In addition, full field visual evoked potentials, visual acuity, optical coherence tomography as well as clinical relapses and measures of disability, cerebral MRI, and self-reported visual quality of life were obtained for follow-up. The study was halted due to insufficient recruitment (n = 15), and available results are reported. RESULTS: Per protocol analysis of the primary endpoint revealed a significantly larger reduction of mfVEP latency at 6 months compared to baseline with fingolimod treatment (n = 5; median decrease, 15.7 ms) than with IFN-beta 1b treatment (n = 4; median increase, 8.15 ms) ($p < 0.001$ for interaction). Statistical significance was maintained in the secondary endpoint analysis. Descriptive results are reported for other endpoints. CONCLUSION: Preliminary results of the MOVING trial argue in support of a beneficial effect of fingolimod on optic nerve remyelination when compared to IFN-beta treatment. Interpretation is limited by the small number of complete observations, an unexpected deterioration of the control group and a difference in baseline mfVEP latencies. The findings need to be confirmed in larger studies. TRIAL REGISTRATION: The trial was registered as EUDRA-CT 2011-004787-30 on October 26, 2012 and as NCT01647880 on July 24, 2012.

Cree BAC, Goldman MD, Corboy JR, et al. Efficacy and safety of 2 fingolimod doses vs glatiramer acetate for the treatment of patients with relapsing-remitting multiple sclerosis: a randomized clinical trial. *JAMA Neurol.* 2020;24:24.

Importance: Doses of fingolimod lower than 0.5 mg per day were not investigated during the fingolimod clinical development program. Whether lower doses of fingolimod might retain efficacy with fewer safety risks remains unknown. Objective: To evaluate the efficacy and safety of fingolimod, 0.5 mg, and fingolimod, 0.25 mg, compared with glatiramer acetate and to assess whether these doses of fingolimod show superior efficacy to glatiramer acetate in adult patients with relapsing-remitting multiple sclerosis. Interventions: Fingolimod, 0.5 mg, or fingolimod, 0.25 mg, orally once per day or glatiramer acetate, 20 mg, subcutaneously once per day. Design, Setting, and Participants: The Multiple Sclerosis Study Evaluating Safety and Efficacy of Two Doses of Fingolimod Versus Copaxone (ASSESS) was a phase 3b multicenter randomized rater-blinded and dose-blinded 12-month clinical trial conducted between August 9, 2012, and April 30, 2018 (including the time required to recruit participants). A total of 1461 patients aged 18 to 65 years with relapsing-remitting multiple sclerosis were screened, and 1064 participants were randomized. These participants had at least 1 documented

relapse during the previous year or 2 documented relapses during the previous 2 years and an Expanded Disability Status Scale score of 0 to 6 at screening. Data were analyzed between September and November 2018. Main Outcomes and Measures: The superiority of the fingolimod doses was tested hierarchically, with fingolimod, 0.5 mg, vs glatiramer acetate, 20 mg, tested first, followed by fingolimod, 0.25 mg, vs glatiramer acetate, 20 mg. The primary end point was the reduction in annualized relapse rate (ARR). Magnetic resonance imaging parameters, safety, and tolerability were also assessed. Results: Of 1461 adult patients screened, 1064 participants (72.8%) were randomized (mean [SD] age, 39.6 [11.0] years; 792 women [74.4%]) to 3 treatment groups: 352 participants received fingolimod, 0.5 mg, 370 participants received fingolimod, 0.25 mg, and 342 participants received glatiramer acetate, 20 mg. In total, 859 participants (80.7%) completed the study. Treatment with fingolimod, 0.5 mg, was superior to treatment with glatiramer acetate, 20 mg, in reducing ARR (40.7% relative reduction); the relative reduction with fingolimod, 0.25 mg, was 14.6%, which was not statistically significant (for fingolimod, 0.5 mg, ARR, 0.15; 95% CI, 0.11-0.21; for fingolimod, 0.25 mg, ARR, 0.22; 95% CI, 0.17-0.29; for glatiramer acetate, 20 mg, ARR, 0.26; 95% CI, 0.20-0.34). Treatment with both fingolimod doses (0.5 mg and 0.25 mg) significantly reduced new or newly enlarging T2 and gadolinium-enhancing T1 lesions compared with treatment with glatiramer acetate. Adverse events were reported in similar proportions across treatment groups (312 participants [90.4%] in the fingolimod, 0.5 mg, group, 323 participants [88.3%] in the fingolimod, 0.25 mg, group, and 283 participants [87.3%] in the glatiramer acetate group). Conclusions and Relevance: Fingolimod, 0.5 mg, demonstrated superior clinical efficacy compared with glatiramer acetate, 20 mg, and had a superior benefit-risk profile compared with fingolimod, 0.25 mg, in adult participants with relapsing-remitting multiple sclerosis. Trial Registration: ClinicalTrials.gov Identifier: NCT01633112.

Patti F, Zimatore GB, Brescia Morra V, et al. Administration of subcutaneous interferon beta 1a in the evening: data from RELIEF study. *J Neurol.* 2020;267(6):1812-1823.

BACKGROUND: Subcutaneous recombinant interferon-beta 1a (IFN-beta1a SC) is indicated for treatment of relapsing multiple sclerosis (RMS); however, it is associated with development of flu-like syndrome (FLS) in 75% of patients. No recommendations are available on whether evening or morning administration could induce better or worse FLS. OBJECTIVE: Primary objective was to investigate whether morning administration of IFN-beta1a 44 microg (Rebif) would affect the severity of FLS versus evening administration, in patients with RMS. Secondary objectives were to investigate whether timing of administration could lead to a better quality of life. METHODS: Multicenter, open-label, 12-week, randomized, controlled, parallel-group, phase 4 study. RESULTS: Of 217 patients screened at 29 Italian sites, 200 were included in the study. Among these, 104 patients were randomized to IFN-beta1a SC administration in the morning and 96 in the evening. Morning administration resulted in higher FLS scores, as measured by the Multiple Sclerosis Treatment Concern Questionnaire, at week 4 ($p = 0.0083$) and week 8 ($p = 0.0079$); however, the difference was no longer significant at the end of 12 weeks. CONCLUSION: IFN-beta1a evening injections in the first 8 weeks of treatment led to an improvement in FLS; when continuing therapy, time of administration could be decided according to patient's lifestyle and preference.

Appendix B. ITS Ratings and Definitions

The *Is There a There There Scale* (ITS) consists of 3 ratings: *no*, *maybe,* and *yes*. The definitions of these ratings and methods for selection are described below. Center for Evidence-based Policy (Center) researchers will use these definitions to rate each surveillance topic. The assigned rating is offered as guidance and does not require DERP participants to follow this recommendation. Each rating is strictly based on the identified new research and clinical information and is not comprehensive to all aspects of policy decision making, such as competing priorities, budget, contracting, or internal and external state agency needs.

No

- We did not find clinical evidence or information that would indicate a need to update the report or develop a derivative research product.
- A rating of No is typically given when there are few new studies and/or no new meaningful studies, and no new serious harms.

Maybe

- We found some clinical evidence or information that might suggest a need to update the report or develop a derivative research product.
- A rating of Maybe is typically given when there are multiple new comparative trials or at least 1 new meaningful study or serious harm.

Yes

- We found clinical evidence or information that suggests a need to update the report or develop a derivative research product.
- A rating of Yes is typically given when there are multiple new comparative trials and meaningful studies and/or new serious harms, drugs, formulations, or indications.