Drug Class Review Disease-modifying Drugs for Multiple Sclerosis

Preliminary Scan Report #1

June 2017

The purpose of Drug Effectiveness Review Project reports is to make available information regarding the comparative clinical effectiveness and harms of different drugs. Reports are not usage guidelines, nor should they be read as an endorsement of or recommendation for any particular drug, use, or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

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OBJECTIVE

The purpose of this preliminary updated literature scan process is to provide the Participating Organizations with a preview of the volume and nature of new research that has emerged subsequent to the previous full review process. Provision of the new research presented in this report is meant to assist with Participating Organizations' consideration of allocating resources toward a full report update, a single drug addendum, or a summary review. Comprehensive review, quality assessment, and synthesis of evidence from the full publications of the new research presented in this report would follow only under the condition that the Participating Organizations ruled in favor of a full update. The literature search for this report focuses on new randomized controlled trials and comparative effectiveness reviews as well as actions taken by the U.S. Food and Drug Administration (FDA) since the last report. Other important studies could exist.

Date of Last Update Report

Update #3: May 2016 (searches through January 2016)

Date of Last Preliminary Update Scan Report

None since most recent update report.

Scope and Key Questions

The scope of the review and key questions were originally developed and refined by the Pacific Northwest Evidence-based Practice Center with input from a statewide panel of experts (pharmacists, primary care clinicians, and representatives of the public). Subsequently, the key questions were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project (DERP). The Participating Organizations of DERP are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients. The Participating Organizations approved the following key questions to guide this review:

- 1. What is the comparative effectiveness of disease-modifying treatments for multiple sclerosis?
- 2. Does the relationship between neutralizing antibodies and outcomes differ by treatment?
- 3. What is the effectiveness of disease-modifying treatments for patients with a clinically isolated syndrome?
- 4. Do disease-modifying treatments for multiple sclerosis or a clinically isolated syndrome differ in harms?
- 5. Are there subgroups of patients based on demographics (age, racial or ethnic groups, and gender), socioeconomic status, other medications, severity of disease, or co-morbidities for which one disease-modifying treatment is more effective or associated with fewer adverse events?

Inclusion Criteria

Populations

- Adult outpatients (age ≥ 18 years) with multiple sclerosis
 - Relapsing-remitting multiple sclerosis
 - Secondary progressive multiple sclerosis
 - Primary progressive multiple sclerosis
 - Progressive relapsing multiple sclerosis
- Adult outpatients with a clinically isolated syndrome (also known as "first demyelinating event", first clinical attack suggestive of multiple sclerosis, or monosymptomatic presentation).

Interventions

Agent	FDA approval date	Dosage, route and frequency	Indication
Ocrelizumab Ocrevus™	3/28/17	300 mg/10 mL (30 mg/mL) in a single dose vial via intravenous infusion	Treatment of relapsing or primary progressive forms of MS.
Daclizumab Zinbryta™	5/27/16	150 mg once monthly via subcutaneous injection	Treatment of adult patients with relapsing forms of MS. Because of its safety profile, use should generally be reserved for patients who have had inadequate response to two of more drugs indicated for the treatment of MS.
Peginterferon beta- 1a Plegridy™	8/15/14	125 µ Subcutaneously every 14 days	Treatment of relapsing forms of multiple sclerosis
Dimethyl fumarate Tecfidera®	3/27/13	Maintenance dose: 240 mg Orally twice daily	Treatment of relapsing forms of multiple sclerosis
Teriflunomide Aubagio [®]	9/12/12	7 mg or 14 mg Orally once daily	Treatment of relapsing forms of multiple sclerosis
Fingolimod Gilenya™	9/21/10	0.5 mg Orally once daily	Patients with relapsing forms of multiple sclerosis to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability
Interferon beta-1a Rebif [®]	3/7/02	22 or 44 μ Subcutaneously three times weekly	Treatment of relapsing forms of MS to decrease the frequency of clinical exacerbations and delay the accumulation of physical disability
Alemtuzumab Lemtrada™	5/7/01	Intravenous infusion for 2 treatment courses. First course: 12 mg/day for 5 days. Second course: 12 mg/day for 3 days 12 months after first treatment course	Treatment of relapsing forms of MS. Because of its safety profile, use should be reserved for patients who have had an inadequate response to two or more drugs indicated for the treatment of MS.
Glatiramer Acetate Copaxone [®] , Glatopa ^{™a}	10/20/96	20 mg in 1 mL Subcutaneously once daily, 40mg in 1 mL subcutaneously three times weekly at least 48	Treatment of relapsing forms of multiple sclerosis

Table 1. Included interventions

Agent	FDA approval date	Dosage, route and frequency	Indication
	••	hours apart	
Interferon beta-1a Avonex [®]	5/17/96	30 µg Intramuscularly once weekly	Treatment of patients with relapsing forms of MS to slow accumulation of physical disability and decrease frequency of clinical exacerbations. Effective in patients who experienced first clinical episode and have MRI features consistent with MS
Interferon beta-1b Betaseron [®] , Extavia [®]	7/23/93	0.25 mg in 1 mL Subcutaneously every other day	Treatment of relapsing forms of MS to reduce the frequency of clinical exacerbations. Effective in patients who experienced first clinical episode and have MRI features consistent with MS

Abbreviations: MRI, magnetic resonance imaging; MS, multiple sclerosis; NA, not applicable; PPMS, primary-progressive multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis. ^aAdministered 20 mg in 1 ml once daily

Effectiveness Outcomes

Multiple Sclerosis

- Disability
- Clinical exacerbation/relapse
- Quality of life
- Functional outcomes (e.g., wheel chair use, time lost from work)
- Persistence (discontinuation rates).

Clinically Isolated Syndrome

- Disability
- Clinical exacerbation/relapse of symptoms
- Quality of life
- Functional outcomes (e.g., wheel chair use, time lost from work)
- Persistence (discontinuation rates)
- Progression to multiple sclerosis diagnosis.

Note: Magnetic resonance imaging findings are not included, as they are intermediate or surrogate outcomes.

Harms Outcomes

- Overall rate of adverse effects
- Withdrawals due to adverse effects or drug discontinuations due to adverse events
- Serious adverse events
- Specific adverse events (cardiovascular, hepatotoxicity, progressive multifocal leukoencephalopathy, secondary cancers, etc.).

Study Designs

- For effectiveness and harms, head-to-head controlled clinical trials and good-quality comparative systematic reviews were included. Comparative observational studies with 2 concurrent arms of at least 100 patients each and duration ≥1 year are also included for evaluation of harms.
- 2. Placebo-controlled trials (PCT) were included for network meta-analysis, and for new drugs or formulations with no head-to-head evidence in a given population.

METHODS FOR SCAN

Literature Search

To identify relevant citations, we searched Ovid MEDLINE[®] and Ovid MEDLINE[®] In-Process & Other Non-Indexed Citations from November 2015 through May 2017 using terms for specific included drugs and limits for English language and humans. Literature searches included any new drugs identified in the present scan in addition to those included in Table 1. We also searched the FDA website (http://www.fda.gov/medwatch/safety.htm) for identification of new drugs, new populations, and new serious harms (e.g., boxed warnings). To identify new drugs, we also searched CenterWatch (http://www.centerwatch.com), a privately-owned database of clinical trials information, and conducted a limited internet search. To identify comparative effectiveness reviews, we searched the websites of the Agency for Healthcare Research and Quality (http://www.ahrq.gov/) (http://www.effectivehealthcare.ahrq.gov/), the Canadian Agency for Drugs and Technology in Health (http://www.cadth.ca/), the VA Evidence-based Synthesis Program (http://www.hsrd.research.va.gov/publications/esp/reports.cfm), and University of York Centre for Reviews and Dissemination (http://www.york.ac.uk/inst/crd/crdreports.htm - "Our Publications" and "Our Databases"). All citations were imported into an electronic database (EndNote X7) and duplicate citations were removed.

Study Selection

We included only potentially relevant randomized controlled trials and comparative effectiveness reviews. One reviewer assessed abstracts of citations identified from literature searches for inclusion, using the criteria described above.

RESULTS

New Drugs

Identified in this Preliminary Update Scan

Daclizumab (ZinbrytaTM)*: an injectable interleukin-2 receptor blocking antibody approved on 5/27/2016 and indicated for the treatment of adult patients with relapsing forms of MS (should be reserved for patients with inadequate response to 2 or more drugs indicated to treat MS).

Ocrelizumab (OcrevusTM)*: an injectable CD20-directed cytologic antibody approved on 3/28/2017 and indicated for the treatment of patients with relapsing or primary progressive forms of MS.

*Both drugs were under FDA review at the time of the 2016 report and were included in that report.

Identified in previous Preliminary Update Scan

No scan since most recent update report

New Serious Harms (e.g., Boxed Warnings)

Identified in this Preliminary Update Scan

Teriflunomide (Aubagio[®]): the boxed warning on the risk of teratogenicity was edited in November 2016; however, this risk was known at the time of approval in 2012. Please refer to Appendix A for more details.

Identified in previous Preliminary Update Scan

No scan since most recent update report

Comparative Effectiveness Reviews

Identified in this Preliminary Update Scan

We did not identify potentially relevant comparative effectiveness reviews that cover the entire scope of this scan nor did we identify potentially relevant comparative effectiveness reviews that could be used to answer specific pieces of an update report.

Identified in previous Preliminary Update Scan

No other scans since most recent update report

Randomized Controlled Trials

Trials identified since the most recent Full Report

Medline searches yielded 126 new citations. Of these, 7 trials (5 head-to-head and 2 placebocontrolled trials) and 5 secondary analyses (in 6 publications) were considered to be potentially relevant and included in this scan. The OPERA I and II trials (Table 2) compared the new drug ocrelizumab to interferon in patients with relapsing-remitting multiple sclerosis. The 2016 update report included unpublished results from the OPERA trials, and also one smaller head-to-head trial of ocrelizumab. Two placebo-controlled trials identified in this scan assessed patients with primary progressive MS, one treating PPMS patients with ocrelizumab and the other with fingolimod (Table 3). We found no new trials of the new drub daclizumab, but did identify two secondary analyses of earlier trials (Table 4). Please see Appendix B for abstracts.

	Ν			
Study	Duration	Population	Comparison	Outcomes
Hauser, 2017	821 (trial 1),	RRMS	Ocrelizumab vs. subcutaneous	Relapse, disability,
(2 trials)	835 (trial 2)		interferon beta-1a	function, adverse
OPERA I	96 weeks			events
NCT01247324				
OPERA II				
NCT01412333				
Mokhber, 2015	90	Newly diagnosed,	Interferon beta-1a (Rebif) vs.	Quality of life
	12 months	definite MS patients	Interferon beta-1a (Avonex) vs.	
			Interferon beta-1b	
			(Betaferon)	
Fox, 2016	334	Treatment-naïve	Subcutaneous Interferon beta-1a	Function, disability
CAMMS223	36 months	RRMS	vs. Alemtuzumab	
NCT00050778				
Wolinsky, 2015	209	RRMS	Glatiramer acetate 40 mg 3-times	Injection-related
GLACIER	4 months		weekly vs. 20 mg daily	adverse events
NCT01874145				

Table 2. New head-to-head trials (N=5 in 4 publications)

Abbreviations: MS, multiple sclerosis; RRMS, relapsing remitting multiple sclerosis

			A /	
	Ν			
Study	Duration	Population	Comparison	Outcomes
Montalban, 2017	732	PPMS	Ocrelizumab vs. placebo	Disability progression, function
NCT01194570	120 weeks (at least)			
Lublin, 2016	970	PPMS	Fingolimod vs. placebo	Disability, adverse events
INFORMS	36 months - 5 years			
NCT00731692				

Table 3. New placebo-controlled trials (N=2)

Abbreviations: PPMS, primary progressive multiple sclerosis

Table 4. Secondary analyses of included primary trial publications (N=5 in 6 publications)

Study	Ν				
Primary Trial	Duration	Population	Comparison	Outcomes	
Head-to-head trials					
Liu, 2017	1,841	RRMS	Daclizumab vs. intramuscular	Quality of life	
DECIDE	96 weeks		interferon beta-1a		
NCT01064401					
Calkwood,	1,053	RRMS	Fingolimod (switch) vs.	Satisfaction (global,	
2014	6 months		subcutaneous Interferon beta-1a	treatment), adverse events,	
EPOC			or Glatiramer acetate or	depression, fatigue, SF-36,	
			Interferon beta-1b (stay)	improvement	
Schippling,	2,244	RRMS	Glatiramer acetate 20 mg once	Depression	
2016	2-3.5 years		daily vs. subcutaneous Interferon		
BEYOND			beta-1b		
Placebo-controlled trials					
Phillips, 2016	621	RRMS	Daclizumab HYP vs. placebo	Quality of life	
SELÉCT	52 weeks			-	
Arnold, 2014	1,512	RRMS	Peginterferon beta-1a vs. placebo	Quality of life, relapse,	
Newsome,	1 year			disability progression	
2015	(placebo-				
ADVANCE	controlled)				
NCT00906399	-				

Abbreviations: HYP, high-yield process; RRMS, relapsing remitting multiple sclerosis

SUMMARY

Since the 2016 update report, 2 drugs have been approved to treat multiple sclerosis, ocrelizumab and daclizumab; however, both drugs were included before approval in the 2016 report. No new harms or comparative effectiveness reviews were identified for this update scan. Head-to-head evidence comparing ocrelizumab to interferon was published in 2017, from the 2 OPERA trials in a total of 1,656 patients with relapsing-remitting MS. Unpublished evidence from these trials was included in the prior report. We also identified 2 placebo-controlled studies; 1 of ocrelizumab and the other of fingolimod, in patients with primary progressive MS. Unpublished evidence on fingolimod in PPMS is new. Several secondary analyses of previously included trials have been published as well, including 2 studies of daclizumab.

APPENDIX A. NEW SERIOUS HARMS (BOXED WARNINGS)

Teriflunomide (Aubagio) – November 2016

Boxed Warning

(additions and/or revisions are underlined)

• Risk of Teratogenicity

AUBAGIO is contraindicated <u>for use</u> in pregnant women <u>and in women</u> of <u>reproductive</u> potential who are not using <u>effective</u> contraception <u>because of the</u> potential for fetal harm. Teratogenicity and embryolethality occurred in animals at plasma teriflunomide exposures lower than that in humans. Exclude pregnancy before the start of treatment with AUBAGIO in females of reproductive potential. Advise females of reproductive potential to use effective contraception during AUBAGIO treatment and during an accelerated <u>drug</u> elimination procedure after AUBAGIO treatment. Stop AUBAGIO and use an accelerated drug elimination procedure if the patient becomes pregnant.

https://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/index.cfm?event=searchdetail .page&DrugNameID=103

APPENDIX B. POTENTIALLY RELEVANT NEW TRIALS

Head-to-head trials

Fox, E. J., et al. (2016). Alemtuzumab improves neurological functional systems in treatmentnaive relapsing-remitting multiple sclerosis patients. Journal of the Neurological Sciences. **363**: 188-194.

BACKGROUND: Individual functional system scores (FSS) of the Expanded Disability Status Scale (EDSS) play a central role in determining the overall EDSS score in patients with early-stage multiple sclerosis (MS). Alemtuzumab treatment improves preexisting disability for many patients; however, it is unknown whether improvement is specific to certain functional systems.

- OBJECTIVE: We assessed the effect of alemtuzumab on individual FSS of the EDSS.
- METHODS: CAMMS223 was a 36-month, rater-blinded, phase 2 trial; treatment-naive patients with active relapsing-remitting MS, EDSS <3, and symptom onset within 3 years were randomized to annual courses of alemtuzumab or subcutaneous interferon beta-1a (SC IFNB-1a) 44 mug three times weekly.
- RESULTS: Alemtuzumab-treated patients had improved outcomes versus SC IFNB-1a patients on most FSS at Month 36; the greatest effect occurred for sensory, pyramidal, and cerebellar FSS. Among patients who experienced 6-month sustained accumulation of disability, clinical worsening occurred most frequently in the brainstem and sensory systems. For patients with 6-month sustained reduction in preexisting disability, pyramidal and sensory systems contributed most frequently to clinical improvement.
- CONCLUSIONS: Alemtuzumab demonstrated a broad treatment effect in improving preexisting disability. These findings may influence treatment decisions in patients with early, active relapsing-remitting MS displaying neurological deficits. ClinicalTrials.gov Identifier NCT00050778.

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Hauser, S. L., et al. (2017). Ocrelizumab versus Interferon Beta-1a in Relapsing Multiple Sclerosis. <u>New England Journal of Medicine</u>. **376:** 221-234.

Background B cells influence the pathogenesis of multiple sclerosis. Ocrelizumab is a humanized monoclonal antibody that selectively depletes CD20+ B cells. Methods In two identical phase 3 trials, we randomly assigned 821 and 835 patients with relapsing multiple sclerosis to receive intravenous ocrelizumab at a dose of 600 mg every 24 weeks or subcutaneous interferon beta-1a at a dose of 44 mug three times weekly for 96 weeks. The primary end point was the annualized relapse rate. Results The annualized relapse rate was lower with ocrelizumab than with interferon beta-1a in trial 1 (0.16 vs. 0.29; 46% lower rate with ocrelizumab; P<0.001) and in trial 2 (0.16 vs. 0.29; 47% lower rate; P<0.001). In prespecified pooled analyses, the percentage of patients with disability progression confirmed at 12 weeks was significantly lower with ocrelizumab than with interferon beta-1a (9.1% vs. 13.6%; hazard ratio, 0.60; 95% confidence interval [CI], 0.45 to 0.81; P<0.001), as was the percentage of patients with disability progression confirmed at 24 weeks (6.9% vs. 10.5%; hazard ratio, 0.60; 95% CI, 0.43 to 0.84; P=0.003). The mean number of gadolinium-enhancing lesions per T₁-weighted magnetic resonance scan was 0.02 with ocrelizumab versus 0.29 with interferon

beta-1a in trial 1 (94% lower number of lesions with ocrelizumab, P<0.001) and 0.02 versus 0.42 in trial 2 (95% lower number of lesions, P<0.001). The change in the Multiple Sclerosis Functional Composite score (a composite measure of walking speed, upper-limb movements, and cognition; for this z score, negative values indicate worsening and positive values indicate improvement) significantly favored ocrelizumab over interferon beta-1a in trial 2 (0.28 vs. 0.17, P=0.004) but not in trial 1 (0.21 vs. 0.17, P=0.33). Infusion-related reactions occurred in 34.3% of the patients treated with ocrelizumab and in 2.9% of those treated with interferon beta-1a. Neoplasms occurred in 0.5% of the patients treated with ocrelizumab and in 0.2% of those treated with interferon beta-1a. Conclusions Among patients with relapsing multiple sclerosis, ocrelizumab was associated with lower rates of disease activity and progression than interferon beta-1a over a period of 96 weeks. Larger and longer studies of the safety of ocrelizumab are required. (Funded by F. Hoffmann-La Roche; OPERA I and II ClinicalTrials.gov numbers, NCT01247324 and NCT01412333, respectively.).

Mokhber, N., et al. (2015). Therapeutic effect of Avonex, Rebif and Betaferon on quality of life in multiple sclerosis. <u>Psychiatry and Clinical Neurosciences</u>. **69**: 649-657.

- AIMS: The aim of this study was to evaluate the effect of various disease-modifying therapies (DMT) on quality of life in multiple sclerosis (MS).
- METHODS: This was a three-arm parallel study with balanced randomization in which 90 newly diagnosed, definite MS subjects referred to Ghaem Medical Center, Mashhad, Iran were enrolled between 2006 and 2009. Patients were randomly allocated into three DMT groups: Avonex, Rebif and Betaferon. Health-related quality of life was assessed in MS patients at baseline and 12 months after treatment with DMT using the MS Quality of Life-54 questionnaire.
- RESULTS: Both mental and physical health scores improved within all three treatment groups after 12 months of treatment; however, this increase was only significant in the mental health composite in the Betaferon group (P=0.024). Betaferon had the highest mental health score change (14.04) while this change was 7.26 for Avonex (P=0.031) and 5.08 for Rebif (P=0.017). A physical health composite score comparison among the three treatment groups revealed no significant results.
- CONCLUSIONS: With a positive impact of DMT on mental and physical dimensions of QOL in MS patients, initiation of treatment soon after diagnosis is recommended. In MS patients with more mental issues and fewer physical disabilities, Betaferon might be considered as a better choice of treatment.
- Copyright © 2015 The Authors. Psychiatry and Clinical Neurosciences © 2015 Japanese Society of Psychiatry and Neurology.

Wolinsky, J. S., et al. (2015). GLACIER: An open-label, randomized, multicenter study to assess the safety and tolerability of glatiramer acetate 40 mg three-times weekly versus 20 mg daily in patients with relapsing-remitting multiple sclerosis. <u>Multiple Sclerosis and Related Disorders</u>. **4:** 370-376.

BACKGROUND: The efficacy and safety of glatiramer acetate (GA) 20 mg/mL oncedaily subcutaneous injections (GA20) in relapsing-remitting multiple sclerosis (RRMS) is well-established. However, injection-related adverse events (IRAEs) may impede treatment adherence and tolerability. GA 40 mg/mL three-times weekly (GA40) also has a favorable efficacy and safety profile.

- OBJECTIVE: To evaluate the safety, tolerability, and patient experience when converting from GA20 to GA40.
- METHODS/TRIAL DESIGN: GLACIER was an open-label, randomized, parallel-group trial conducted at 31 sites in the US between June 2013 and December 2013. Stable RRMS patients on GA20 were randomized in a 1:1 ratio to continue with GA20 or convert to GA40. The adjusted mean annualized rate of IRAEs was the primary endpoint for this study. Additionally, the severity of IRAEs, rate of injection-site reactions (ISRs), and patient-reported MS impact and treatment satisfaction were compared for the two treatment groups over the 4-month core study.
- RESULTS: A total of 209 patients were randomized to convert to GA40 (n=108) or continue with GA20 (n=101). The adjusted mean annualized rate of IRAEs was reduced by 50% with GA40 (35.3 events per year; n=108) versus GA20 (70.4 events per year; n=101) (risk ratio (RR)=0.50; 95% confidence interval [CI]=0.34-0.74; p=0.0006). There was a 60% reduction in the rate of moderate/severe events (GA40 (n=108): 0.9 events per year versus GA20 (n=101): 2.2 events per year; RR=0.40; p=0.0021). Perception of treatment convenience improved for GA40-treated patients soon after converting and was sustained.
- CONCLUSIONS: The GLACIER study demonstrates a favorable IRAE and convenience profile of GA40 for RRMS patients.

TRIAL REGISTRATION: NCT01874145 available at clinicaltrial.gov.

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Placebo-controlled trials

Lublin, F., et al. (2016). Oral fingolimod in primary progressive multiple sclerosis (INFORMS): a phase 3, randomised, double-blind, placebo-controlled trial. <u>Lancet</u>. **387**: 1075-1084.

- BACKGROUND: No treatments have been approved for primary progressive multiple sclerosis. Fingolimod, an oral sphingosine 1-phosphate receptor modulator, is effective in relapse-onset multiple sclerosis, but has not been assessed in primary progressive multiple sclerosis. We assessed the safety and efficacy of fingolimod in patients with primary progressive multiple sclerosis.
- METHODS: In INFORMS, a multicentre, double-blind, placebo-controlled parallel-group study, patients with primary progressive multiple sclerosis recruited across 148 centres in 18 countries were randomly allocated (1:1) with computer-generated blocks to receive oral fingolimod or placebo for at least 36 months and a maximum of 5 years. Patients were initially assigned to fingolimod 1.25 mg per day or placebo (cohort 1); however, after a protocol amendment on Nov 19, 2009, patients were switched in a masked manner to fingolimod 0.5 mg, whereas those on placebo continued on matching placebo. From then onwards, patients were assigned to receive fingolimod 0.5 mg/day or placebo (cohort 2). Key inclusion criteria were age 25-65 years, clinical diagnosis of primary progressive multiple sclerosis, 1 year or more of disease progression, and two of the following criteria: positive brain MRI; positive spinal cord MRI; or positive cerebrospinal fluid. Additional eligibility criteria included disease duration of 2-10 years and objective evidence of disability progression in the previous 2 years. Patients and study investigators

were masked to group assignment. We used a novel primary composite endpoint based on change from baseline in Expanded Disability Status Scale (EDSS), 25' Timed-Walk Test, or Nine-Hole Peg Test to assess time to 3-month confirmed disability progression in study participants treated for at least 3 years. All randomised patients took at least one dose of study drug. The primary efficacy analysis included all patients in cohort 2 and those assigned to placebo in cohort 1. The safety analysis included all patients in cohorts 1 and 2. This study is registered with ClinicalTrials.gov, number NCT00731692. The study is now closed.

- FINDINGS: 970 patients were randomly assigned between Sept 3, 2008, and Aug 30, 2011 (147 to fingolimod 1.25 mg and 133 to placebo in cohort 1; 336 to fingolimod 0.5 mg and 354 to placebo in cohort 2). The efficacy analysis set (n=823) consisted of 336 patients randomly allocated to fingolimod 0.5 mg and 487 to placebo. Baseline characteristics were similar across groups and representative of a primary progressive multiple sclerosis population (48% women, mean age 48.5 years [SD 8.4], mean EDSS 4.67 [SD 1.03], 87% free of gadolinium-enhancing lesions). By end of study, 3-month confirmed disability progression had occurred in 232 and 338 patients in the fingolimod and placebo groups, respectively, resulting in Kaplan-Meier estimates of 77.2% (95% CI 71.87-82.51) of patients in the fingolimod group versus 80.3% (73.31-87.25) of patients in the placebo group (risk reduction 5.05%; hazard ratio 0.95, 95% CI 0.80-1.12; p=0.544). Safety results were generally consistent with those of studies of fingolimod in patients with relapse-onset multiple sclerosis. Lymphopenia occurred in 19 (6%) patients in the fingolimod group versus none in the placebo group, bradycardia in five (1%) versus one (<1%), and first-degree atrioventricular block in three (1%) versus six (1%). Serious adverse events occurred in 84 (25%) patients in the fingolimod group and 117 (24%) in the placebo group, including macular oedema in six (2%) versus six (1%), and basal-cell carcinoma in 14 (4%) versus nine (2%).
- INTERPRETATION: The anti-inflammatory effects of fingolimod did not slow disease progression in primary progressive multiple sclerosis. Therapeutic strategies for primary progressive multiple sclerosis might need different approaches to those used for relapseonset multiple sclerosis.

FUNDING: Novartis Pharma AG.

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Montalban, X., et al. (2017). Ocrelizumab versus Placebo in Primary Progressive Multiple Sclerosis. <u>New England Journal of Medicine</u>. **376:** 209-220.

Background An evolving understanding of the immunopathogenesis of multiple sclerosis suggests that depleting B cells could be useful for treatment. We studied ocrelizumab, a humanized monoclonal antibody that selectively depletes CD20-expressing B cells, in the primary progressive form of the disease. Methods In this phase 3 trial, we randomly assigned 732 patients with primary progressive multiple sclerosis in a 2:1 ratio to receive intravenous ocrelizumab (600 mg) or placebo every 24 weeks for at least 120 weeks and until a prespecified number of confirmed disability progression events had occurred. The primary end point was the percentage of patients with disability progression confirmed at 12 weeks in a time-to-event analysis. Results The percentage of patients with 12-week confirmed disability progression was 32.9% with ocrelizumab versus 39.3% with placebo (hazard ratio, 0.76; 95% confidence interval [CI], 0.59 to 0.98; P=0.03). The percentage

of patients with 24-week confirmed disability progression was 29.6% with ocrelizumab versus 35.7% with placebo (hazard ratio, 0.75; 95% CI, 0.58 to 0.98; P=0.04). By week 120, performance on the timed 25-foot walk worsened by 38.9% with ocrelizumab versus 55.1% with placebo (P=0.04); the total volume of brain lesions on T₂weighted magnetic resonance imaging (MRI) decreased by 3.4% with ocrelizumab and increased by 7.4% with placebo (P<0.001); and the percentage of brain-volume loss was 0.90% with ocrelizumab versus 1.09% with placebo (P=0.02). There was no significant difference in the change in the Physical Component Summary score of the 36-Item Short-Form Health Survey. Infusion-related reactions, upper respiratory tract infections, and oral herpes infections were more frequent with ocrelizumab than with placebo. Neoplasms occurred in 2.3% of patients who received ocrelizumab and in 0.8% of patients who received placebo; there was no clinically significant difference between groups in the rates of serious adverse events and serious infections. Conclusions Among patients with primary progressive multiple sclerosis, ocrelizumab was associated with lower rates of clinical and MRI progression than placebo. Extended observation is required to determine the long-term safety and efficacy of ocrelizumab. (Funded by F. Hoffmann-La Roche; ORATORIO ClinicalTrials.gov number, NCT01194570.).

Secondary analyses of included primary trial publications

Arnold, D. L., et al. (2014). Effect of peginterferon beta-1a on MRI measures and achieving no evidence of disease activity: results from a randomized controlled trial in relapsing-remitting multiple sclerosis. <u>BMC Neurology</u>. **14**: 240.

BACKGROUND: Subcutaneous peginterferon beta-1a provided clinical benefits at Year 1 (placebo-controlled period) of the 2-Year Phase 3 ADVANCE study in relapsingremitting multiple sclerosis (RRMS). Here we report the effect of peginterferon beta-1a on brain magnetic resonance imaging (MRI) lesions, and no evidence of disease activity (NEDA; absence of clinical [relapses and 12-week confirmed disability progression] and MRI [gadolinium-enhancing, and new or newly-enlarging T2 hyperintense lesions] disease activity) during Year 1.

- METHODS: RRMS patients (18-65 years; Expanded Disability Status Scale score <5) were randomized to double-blind placebo or peginterferon beta-1a 125 mug every 2 or 4 weeks. Sensitivity analyses of last observation carried forward and composite disease activity (using minimal MRI allowance definitions) were conducted.
- RESULTS: 1512 patients were randomized and dosed (placebo n=500; peginterferon beta-1a every 2 [n=512] or 4 [n=500] weeks). Every 2 week dosing significantly reduced, versus placebo and every 4 week dosing, the number of new or newly-enlarging T2 hyperintense lesions at Weeks 24 (by 61% and 51%, respectively) and 48 (secondary endpoint; by 67% and 54%, respectively); all p<0.0001. Every 2 week dosing also provided significant reductions versus placebo and every 4 week dosing in the number of new T1 hypointense, gadolinium-enhancing, and new active (gadolinium-enhancing plus non-enhancing new T2) lesions (all p<0.0001), as well as the volume of T2 and T1 lesions (p<0.05) at Weeks 24 and 48. Significantly more patients dosed every 2 weeks had NEDA versus placebo and every 4 weeks (all p<0.01) from baseline to Week 48 (33.9% versus 15.1% and 21.5%, respectively [odds ratios, ORs: 2.89 and 1.87]), from baseline to Week 24 (41.0% versus 21.9% and 30.7%, [ORs: 2.47 and 1.57]) and from Week 24 to

Week 48 (60.2% versus 28.9% and 36.6%, [ORs: 3.71 and 2.62]). Consistent results were seen when allowing for minimal MRI activity.

- CONCLUSION: During Year 1 of ADVANCE, significantly more RRMS patients receiving peginterferon beta-1a every 2 weeks had NEDA, and early and sustained improvements in all MRI endpoints, versus placebo and every 4 week dosing. NEDA sensitivity analyses align with switch strategies in clinical practice settings and provide insight into future responders/non-responders.
- TRIAL REGISTRATION: ClinicalTrials.gov: NCT00906399.

Calkwood, J., et al. (2014). Impact of a switch to fingolimod versus staying on glatiramer acetate or beta interferons on patient- and physician-reported outcomes in relapsing multiple sclerosis: post hoc analyses of the EPOC trial. <u>BMC Neurology</u>. **14:** 220.

BACKGROUND: The Evaluate Patient OutComes (EPOC) study assessed physicianand patient-reported outcomes in individuals with relapsing multiple sclerosis who switched directly from injectable disease-modifying therapy (iDMT; glatiramer acetate, intramuscular or subcutaneous interferon beta-1a, or interferon beta-1b) to once-daily, oral fingolimod. Post hoc analyses evaluated the impact of a switch to fingolimod versus staying on each of the four individual iDMTs.

- METHODS: Overall, 1053 patients were randomized 3:1 to switch to fingolimod or remain on iDMT. The primary endpoint was the change in Treatment Satisfaction Questionnaire for Medication (TSQM) Global Satisfaction score. Secondary endpoints included changes in scores for TSQM Effectiveness, Side Effects and Convenience subscales, Beck Depression Inventory-II (BDI-II), Fatigue Severity Scale (FSS), Patient-Reported Outcome Indices for Multiple Sclerosis (PRIMUS) Activities, 36-item Short-Form Health Survey (SF-36) Mental Component Summary (MCS) and Physical Component Summary (PCS) and mean investigator-reported Clinical Global Impressions of Improvement (CGI-I). All outcomes were evaluated after 6 months of treatment.
- RESULTS: Changes in TSQM Global Satisfaction scores were superior after a switch to fingolimod when compared with scores in patients remaining on any of the iDMTs (all p <0.001). Likewise, all TSQM subscale scores improved following a switch to fingolimod (all p <0.001), except when compared with glatiramer acetate for the TSQM Side Effects subscale (p=0.111). FSS scores were found to be superior for fingolimod versus remaining on subcutaneous interferon beta-1a and interferon beta-1b, BDI-II scores were significantly improved for fingolimod except for the comparison with intramuscular interferon beta-1a, and SF-36 scores were superior with fingolimod compared with remaining on interferon beta-1b (MCS and PCS; p=0.030 and p=0.022, respectively) and subcutaneous interferon beta-1a (PCS only; p=0.024). Mean CGI-I scores were superior with fingolimod when compared with continuing treatment with any of the iDMTs (all p <0.001).
- CONCLUSIONS: After 6 months, a switch to fingolimod showed superiority compared with remaining on each iDMT for a range of patient- and physician-reported outcomes, including global satisfaction with treatment.
- TRIAL REGISTRATION: ClinicalTrials.gov NCT01216072.

Liu, Y., et al. (2017). Impact of daclizumab versus interferon beta-1a on patient-reported outcomes in relapsing-remitting multiple sclerosis. <u>Multiple Sclerosis and Related Disorders</u>. **11:** 18-24.

BACKGROUND: Patient-reported outcomes (PROs) provide information on treatment effects from the patient's perspective that complement outcomes on clinical measures. In DECIDE, daclizumab demonstrated superior efficacy in reducing relapses, 24-week confirmed disability progression, and brain lesions (assessed by magnetic resonance imaging [MRI]) versus intramuscular interferon beta-1a in relapsing-remitting multiple sclerosis.

OBJECTIVE: To examine the impact of daclizumab versus interferon beta-1a on PROs in DECIDE.

- METHODS: DECIDE was a randomized, double-blind, active-controlled, phase 3 study comparing daclizumab 150mg subcutaneous every 4 weeks with interferon beta-1a 30mcg intramuscular once weekly. The 29-item Multiple Sclerosis Impact Scale (MSIS-29) and EuroQoL 5-Dimensions (EQ-5D) were assessed at baseline and every 24 weeks. Mean changes from baseline were analyzed using analysis of covariance models. Individual items for the MSIS-29 physical (PHYS) and psychological (PSYCH) subscales were analyzed post hoc.
- RESULTS: Daclizumab treatment resulted in greater mean improvements relative to baseline in MSIS-29 PHYS and PSYCH scores starting at week 24 that persisted over 96 weeks. Mean improvements from baseline in MSIS-29 PHYS and PSYCH scores were significantly greater for daclizumab versus intramuscular interferon beta-1a at week 96. Daclizumab-treated patients showed steady improvements in EQ-5D health utility index and EQ-5D visual analog scale scores over the study period, with significantly greater improvements versus intramuscular interferon beta-1a at week 96 (p=0.0048 and p=0.0006, respectively).
- CONCLUSIONS: Improvements in patient-reported physical and psychological functioning and general health status with daclizumab compared with intramuscular interferon beta-1a are consistent with outcomes on clinical and brain MRI lesion measures in DECIDE (NCT01064401).

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Newsome, S. D., et al. (2015). Impact of peginterferon beta-1a and disease factors on quality of life in multiple sclerosis. <u>Multiple Sclerosis and Related Disorders</u>. **4:** 350-357.

BACKGROUND: The Phase III ADVANCE study has shown clinical benefits for peginterferon beta-1a 125 micro g dosed every 2 weeks versus placebo at 1 year in patients with relapsing-remitting multiple sclerosis (MS). This study assessed the impact of peginterferon beta-1a and disease factors on health-related quality of life (HRQoL) using data from ADVANCE.

METHODS: HRQoL was assessed at baseline and 12, 24, and 48 weeks using the 29-item Multiple Sclerosis Impact Scale (MSIS-29) and other generic HRQoL measures. Changes in scores from baseline within each group and differences in mean change from baseline between groups were evaluated. Post-hoc mixed-effects repeated measures analyses were performed to assess the impact of confirmed disability progression and relapses, and the interactions of treatment and these MS events on HRQoL. Predictors with p>0.1 were excluded from the final models, unless they were clinically meaningful.

- RESULTS: Relapses and confirmed disability progression were major drivers of HRQoL. When comparing week 48 to baseline, in placebo-treated patients (n=500), confirmed disability progression was associated with a 6.0-point worsening (p<0.0001) of MSIS-29 physical scores, relative to a 1.9-point worsening (p=0.044) with peginterferon beta-1a every 2 weeks (n=512). Such findings were observed consistently with other generic HRQoL measures. Additionally, having a recent relapse (<29 days before the HRQoL assessment) was associated with a 10.0-point worsening (p<0.0001) of MSIS-29 psychological scores in placebo-treated patients, compared with a 3.5-point (p=0.031) worsening with peginterferon beta-1a every 2 weeks.
- CONCLUSION: Treatment with peginterferon beta-1a could help to improve or maintain HRQoL in addition to clinical outcomes.

TRIAL REGISTRATION: ClinicalTrials.gov: NCT00906399.

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Phillips, G., et al. (2016). Assessing the impact of multiple sclerosis disease activity and daclizumab HYP treatment on patient-reported outcomes: Results from the SELECT trial. <u>Multiple Sclerosis and Related Disorders</u>. **6:** 66-72.

BACKGROUND: The SELECT study demonstrated superior effects of daclizumab highyield process (DAC HYP) to placebo in key endpoints in patients with relapsing and remitting multiple sclerosis (RRMS).

- OBJECTIVE: To assess the impact of DAC HYP and disease activity on health-related quality of life (HRQoL) using data from this study.
- METHODS: HRQoL was assessed at baseline, 12, 24, and 52 weeks using the Multiple Sclerosis Impact Scale (MSIS-29), the 12-items Short Form Health Survey, and the EuroQoL-5 Dimensions. An analysis of covariance model was used to compare treatment difference in change from baseline. Mixed-effects models were used to assess the impact of disability progression, relapse, treatment, and interaction between treatment and these events on HRQoL outcome.
- RESULTS: DAC HYP 150mg resulted in significant positive impacts on HRQoL compared to placebo. It was also found to significantly reduce the adverse impact of relapse on the MSIS-29 physical scale (-12.45; p=0.0006). Relapse and disability progression were significantly associated with impaired HRQoL.
- CONCLUSION: DAC HYP 150mg improved HRQoL in patients with RRMS compared to placebo. The treatment benefit can be partially attributed to reduction in disease activity and attenuation of the adverse impact of relapse on HRQoL.
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Schippling, S., et al. (2016). Incidence and course of depression in multiple sclerosis in the multinational BEYOND trial. Journal of Neurology. **263:** 1418-1426.

Early experience in MS generated concerns that interferon beta treatment might provoke onset or worsening of depression. The objective of the study was to compare depression incidence in relapsing-remitting MS patients receiving interferon beta-1b (IFNB-1b) or glatiramer acetate (GA) in the BEYOND trial. 891/897 (99 %) of English, French, Spanish and Italian speakers among 2244 patients randomized (2:2:1) to receive either IFNB-1b 500 micro g, 250 micro g, or GA 20 mg QD for 2-3.5 years submitted Beck Depression Inventory Second Edition (BDI-II) scores at screening and serially thereafter, in which scores >14 indicated depression. Baseline BDI-II scores >14 were reported in 232/891 patients (26.3 %), with no meaningful difference among the three treatment arms noted at this or at any other time during the study including trial end. Percentages of patients depressed by BDI-II scores deviated little in any arm at any time (IFNB-1b 500 micro g: 24.7 %, IFNB-1b 250 micro g: 24.4 %, GA: 32.4 %). Antidepressant usage was likewise similar among the three treatment arms (IFNB-1b 500 micro g: 33.7 %, IFNB-1b 250 micro g: 31.8 %, GA: 28.8 %) as was depression severity and the frequency with which non-blinded treating physicians recorded depression as an adverse event (IFNB-1b 500 micro g: 17.2 %, IFNB-1b 250 micro g: 17.0 %, GA: 14.4 %). Treating physicians attributed depression to IFNB-1b 250 micro g therapy in 53.6 % and to GA in 21.9 % of instances. This large, prospective, randomized-controlled MS dataset showed no increased risk of depression above baseline values with standard or double-dose IFNB-1b or GA QD treatment.