Rationale ranking “Prevention of relapses”

The better a disease-modulating therapy (DMT) is at preventing flare-ups, the higher the score on a scale from 0.1 to 1.0. The DMT estimated to be the lowest receives a score of 0.1, and the one estimated to be the highest receives a score of 1.0. All other DMTs receive a score between 0.1 and 1 based on their characteristics compared to the DMT with the highest and lowest scores. This score is determined based on research data and the clinical experience of the researchers.

In the DMT tool, you indicate the importance of preventing flare-ups based on a questionnaire with five response options. The score in the DMT tool is then multiplied by the degree to which you consider the prevention of flare-ups important. This result is added for eight queried factors to rank the treatments in order of suitability based on all your personal preferences.

ZMT	Score ZMT tool	Effect size based on network meta-analysis[1]	Effect size based on network meta-analysis[2]
Interferon-beta	0.1	0.79	0.72
Glatirameer acetaat	0.2	0.62	0.66
Teriflunomide	0.2	0.66	0.68
Dimethyl Fumaraat	0.4	0.50	0.55
Fingolimod	0.5	0.46	0.45
Ozanimod	0.5	0.45	0.53
Ponesimod	0.5	NA	0.48
Siponimod	0.5	NA	NA
Cladribine	0.6	0.42	0.44
Natalizumab	0.8	0.31	0.32
Ocrelizumab	0.8	0.33	0.40
Ofatumumab	0.9	0.30	0.30
Alemtuzumab	1	0.28	0.32

The references for the above table can be found in Table 1 and 2 at the end of this document. Additional references used to establish this ranking are:

1. Samjoo et al. 2021 Efficacy classification of modern therapies in multiple sclerosis doi: 10.2217/cer-2020-0267

2. Corsten et al. 2023 Benefits of sphingosine-1-phosphate receptor modulators in relapsing MS estimated with a treatment sequence model doi: 10.1101/2022.12.23.22283885

Rationale ranking “Long-term disability”

The better a disease-modulating therapy (DMT) is at preventing long-term disability, the higher the score on a scale from 0.1 to 1.0. The DMT estimated to be the lowest receives a score of 0.1, and the one estimated to be the highest receives a score of 1.0. All other DMTs receive a score between 0.1 and 1 based on their characteristics compared to the DMT with the highest and lowest scores. This score is determined based on research data and the clinical experience of the researchers.

In the DMT tool, you indicate the importance of preventing long-term disability based on a questionnaire with five response options. The score in the DMT tool is then multiplied by the degree to which you consider the prevention of long-term disability important. This result is added for eight queried factors to rank the treatments in order of suitability based on all your personal preferences.

ZMT	Score ZMT tool	Effect size based on network meta-analysis[1]
Glatiramer acetate	0.1	0.76
Interferon-beta	0.1	0.71
Teriflunomide	0.4	0.78
Dimethyl fumarate	0.4	0.68
Ozanimod	0.4	1.02
Ponesimod	0.4	0.64
Fingolimod	0.5	0.71
Siponimod	0.6	NA
Natalizumab	0.8	0.48
Ocrelizumab	0.8	0.45
Ofatumumab	0.8	0.55
Cladribine	0.8	0.58
Alemtuzumab	1	0.43

The references for the above table can be found in Table 1 and 2 at the end of this document. Additional references used to establish this ranking are:

1. Corsten et al. 2023 Benefits of sphingosine-1-phosphate receptor modulators in relapsing MS estimated with a treatment sequence model doi: 10.1101/2022.12.23.22283885

Rationale ranking “Known long-term side effects”

The better a disease-modulating therapy (DMT) is at preventing long-term side effects, the higher the score on a scale from 0.1 to 1.0. The DMT estimated to be the lowest receives a score of 0.1, and the one estimated to be the highest receives a score of 1.0. All other DMTs receive a score between 0.1 and 1 based on their characteristics compared to the DMT with the highest and lowest scores. This score is determined based on research data and the clinical experience of the researchers.

In the DMT tool, you indicate the importance of preventing long-term side effects based on a questionnaire with five response options. The score in the DMT tool is then multiplied by the degree to which you consider the prevention of long-term side effects important. This result is added for eight queried factors to rank the treatments in order of suitability based on all your personal preferences.

ZMT	Score ZMT tool
Alemtuzumab	0.1
Ocrelizumab	0.3
Ofatumumab	0.3
Ozanimod	0.5
Ponesimod	0.5
Fingolimod	0.5
Siponimod	0.5
Natalizumab	0.5
Dimethyl fumarate	0.7
Cladribine	0.8
Teriflunomide	0.9
Glatiramer acetate	1
Interferon-beta	1

The references for the above table can be found in Table 1 and 2 at the end of this document. Additional references used to establish this ranking are:

1. Luna et al. 2020 Infection Risks Among Patients With Multiple Sclerosis Treated With Fingolimod, Natalizumab, Rituximab, and Injectable Therapies doi:10.1001/jamaneurol.2019.3365
2. Smets & Giovannoni 2022 Derisking CD20-therapies for long-term use doi: 10.1016/j.msard.2021.103418
3. Oksbjerg et al. 2021 Anti-CD20 antibody therapy and risk of infection in patients with demyelinating diseases doi: 10.1016/j.msard.2021.102988
4. Foley et al. 2022 Comparison of switching to 6-week dosing of natalizumab versus continuing with 4-week dosing in patients with relapsing-remitting multiple sclerosis (NOVA): a randomised, controlled, open-label, phase 3b trial doi: 10.1016/S1474-4422(22)00143-0

Rationale ranking “Regular side effects”

The better a disease-modulating therapy (DMT) is at preventing regular side effects, the higher the score on a scale from 0.1 to 1.0. The DMT estimated to be the lowest receives a score of 0.1, and the one estimated to be the highest receives a score of 1.0. All other DMTs receive a score between 0.1 and 1 based on their characteristics compared to the DMT with the highest and lowest scores. This score is determined based on research data and the clinical experience of the researchers.

In the DMT tool, you indicate the importance of preventing regular side effects based on a questionnaire with five response options. The score in the DMT tool is then multiplied by the degree to which you consider the prevention of regular side effects important. This result is added for eight queried factors to rank the treatments in order of suitability based on all your personal preferences.

ZMT	Score ZMT tool
Glatiramer acetate	0.1
Interferon-beta	0.3
Teriflunomide	0.4
Dimethyl fumarate	0.5
Alemtuzumab	0.6
Ozanimod	0.6
Ponesimod	0.6
Fingolimod	0.7
Siponimod	0.7
Natalizumab	0.7
Ocrelizumab	0.8
Ofatumumab	0.8
Cladribine	1

The references for the above table can be found in Table 1 and 2 at the end of this document.
Additional references used to establish this ranking are:

None

Rationale ranking “Regular external visits”

The better a disease-modulating therapy (DMT) is at preventing regular external visits, the higher the score on a scale from 0.1 to 1.0. The DMT estimated to be the lowest receives a score of 0.1, and the one estimated to be the highest receives a score of 1.0. All other DMTs receive a score between 0.1 and 1 based on their characteristics compared to the DMT with the highest and lowest scores. This score is determined based on research data and the clinical experience of the researchers.

In the DMT tool, you indicate the importance of preventing regular external visits based on a questionnaire with five response options. The score in the DMT tool is then multiplied by the degree to which you consider the prevention of regular external visits important. This result is added for eight queried factors to rank the treatments in order of suitability based on all your personal preferences.

ZMT	Score ZMT tool
Teriflunomide	0.1
Interferon-beta	0.2
Glatiramer acetate	0.3
Dimethyl fumarate	0.4
Ozanimod	0.5
Ponesimod	0.5
Fingolimod	0.5
Siponimod	0.5
Alemtuzumab	0.6
Natalizumab	0.7
Ocrelizumab	0.8
Ofatumumab	0.8
Cladribine	1

The references for the above table can be found in Table 1 and 2 at the end of this document.
Additional references used to establish this ranking are:

None

Rationale ranking “Family planning”

The better a disease-modulating therapy (DMT) allows family planning, the higher the score on a scale from 0.1 to 1.0. The DMT estimated to be the lowest receives a score of 0.1, and the one estimated to be the highest receives a score of 1.0. All other DMTs receive a score between 0.1 and 1 based on their characteristics compared to the DMT with the highest and lowest scores. This score is determined based on research data and the clinical experience of the researchers.

In the DMT tool, you indicate the importance of family planning based on a questionnaire with five response options. The score in the DMT tool is then multiplied by the degree to which you consider family planning mportant. This result is added for eight queried factors to rank the treatments in order of suitability based on all your personal preferences.

ZMT	Score ZMT tool
Teriflunomide	0.1
Ozanimod	0.2
Ponesimod	0.2
Fingolimod	0.2
Siponimod	0.2
Natalizumab	0.5
Ocrelizumab	0.6
Ofatumumab	0.6
Alemtuzumab	0.7
Cladribine	0.7
Dimethyl fumarate	0.8
Interferon-beta	1
Glatiramer acetate	1

The references for the above table can be found in Table 1 and 2 at the end of this document.
Additional references used to establish this ranking are:

1. Krysko et al. 2023 Family planning considerations in people with multiple sclerosis doi: 10.1016/S1474-4422(22)00426-4
2. Dobson et al. 2023 Anti-CD20 therapies in pregnancy and breast feeding: a review and ABN guidelines doi: 10.1136/pn-2022-003426
3. Dobson et al. 2019 UK consensus on pregnancy in multiple sclerosis: 'Association of British Neurologists' guidelines doi: 10.1136/practneurol-2018-002060

Rationale ranking “Vaccination”

The better a disease-modulating therapy (DMT) allows vaccinations, the higher the score on a scale from 0.1 to 1.0. The DMT estimated to be the lowest receives a score of 0.1, and the one estimated to be the highest receives a score of 1.0. All other DMTs receive a score between 0.1 and 1 based on their characteristics compared to the DMT with the highest and lowest scores. This score is determined based on research data and the clinical experience of the researchers.

In the DMT tool, you indicate the importance of vaccination based on a questionnaire with five response options. The score in the DMT tool is then multiplied by the degree to which you consider vaccination important. This result is added for eight queried factors to rank the treatments in order of suitability based on all your personal preferences.

ZMT	Score ZMT tool
Fingolimod	0.1
Ocrelizumab	0.3
Ofatumumab	0.3
Siponimod	0.4
Ozanimod	0.5
Ponesimod	0.5
Natalizumab	0.7
Teriflunomide	0.8
Dimethyl fumarate	0.8
Alemtuzumab	0.8
Cladribine	0.9
Interferon-beta	1
Glatirameer acetate	1

The references for the above table can be found in Table 1 and 2 at the end of this document. Additional references used to establish this ranking are:

1. Reyes et al. 2020 Protecting people with multiple sclerosis through vaccination doi: 10.1136/practneurol-2020-002527
2. Tallantyre et al. 2022 COVID-19 Vaccine Response in People with Multiple Sclerosis doi: 10.1002/ana.26251
3. Baker et al. 2023 The impact of sphingosine-1-phosphate receptor modulators on COVID-19 and SARS-CoV-2 vaccination doi: 10.1016/j.msard.2022.104425
4. Bar or et al. 2020 Effect of ocrelizumab on vaccine responses in patients with multiple sclerosis The VELOCE study doi: 10.1212/WNL.0000000000010380

Table 1. References phase 3 trials ZMT in MS

Cadavid D, Wolansky LJ, Skurnick J, et al. Efficacy of treatment of MS with IFNbeta-1b or glatiramer acetate by monthly brain MRI in the BECOME study. *Neurology.* 2009;72(23):1976-1983.
Calabresi PA, Kieseier BC, Arnold DL, et al. Pegylated interferon beta-1a for relapsing-remitting multiple sclerosis (ADVANCE): a randomised, phase 3, double-blind study. *The Lancet Neurology.* 2014;13(7):657-665.
Calabresi PA, Radue EW, Goodin D, et al. Safety and efficacy of fingolimod in patients with relapsing-remitting multiple sclerosis (FREEDOMS II): a double-blind, randomised, placebo-controlled, phase 3 trial. *The Lancet Neurology.* 2014;13(6):545-556.
Cohen JA, Barkhof F, Comi G, et al. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. *The New England journal of medicine.* 2010;362(5):402-415.
Cohen JA, Coles AJ, Arnold DL, et al. Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomised controlled phase 3 trial. *Lancet (London, England).* 2012;380(9856):1819-1828.
Cohen JA, Comi G, Selmaj KW, et al. Safety and efficacy of ozanimod versus interferon beta-1a in relapsing multiple sclerosis (RADIANCE): a multicentre, randomised, 24-month, phase 3 trial. *Lancet Neurol.* 2019;18(11):1021-1033. doi:10.1016/S1474-4422(19)30238-8
Coles AJ, Compston DA, Selmaj KW, et al. Alemtuzumab vs. interferon beta-1a in early multiple sclerosis. *The New England journal of medicine.* 2008;359(17):1786-1801.
Coles AJ, Twyman CL, Arnold DL, et al. Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial. *Lancet (London, England).* 2012;380(9856):1829-1839.
Comi G, Kappos L, Selmaj KW, et al. Safety and efficacy of ozanimod versus interferon beta-1a in relapsing multiple sclerosis (SUNBEAM): a multicentre, randomised, minimum 12-month, phase 3 trial. *The Lancet Neurology*. 2019;18(11):1009-1020. doi:10.1016/S1474-4422(19)30239-X
Confavreux C, O'Connor P, Comi G, et al. Oral teriflunomide for patients with relapsing multiple sclerosis (TOWER): a randomised, double-blind, placebo-controlled, phase 3 trial. *The Lancet Neurology.* 2014;13(3):247-256.
Durelli L, Verdun E, Barbero P, et al. Every-other-day interferon beta-1b versus once-weekly interferon beta-1a for multiple sclerosis: results of a 2-year prospective randomised multicentre study (INCOMIN). *Lancet (London, England).* 2002;359(9316):1453-1460.
Fox RJ, Miller DH, Phillips JT, et al. Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis. *The New England journal of medicine.* 2012;367(12):1087-1097.
Giovannoni G, Comi G, Cook S, et al. A Placebo-Controlled Trial of Oral Cladribine for Relapsing Multiple Sclerosis. New England Journal of Medicine. 2010;362(5):416-426. doi:10.1056/NEJMoa0902533
Giovannoni G, Cook S, Rammohan K, et al. Sustained disease-activity-free status in patients with relapsing-remitting multiple sclerosis treated with cladribine tablets in the CLARITY study: a post-hoc and subgroup analysis. *Lancet Neurol*. 2011;10(4):329-337. doi:10.1016/S1474-4422(11)70023-0
Gold R, Kappos L, Arnold DL, et al. Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis. *The New England journal of medicine.* 2012;367(12):1098-1107.
Hauser SL, Bar-Or A, Comi G, et al. Ocrelizumab versus Interferon Beta-1a in Relapsing Multiple Sclerosis. *New England Journal of Medicine.* 2017;376(3):221-234.
Hauser SL, Bar-Or A, Cohen JA, et al. Ofatumumab versus Teriflunomide in Multiple Sclerosis. *New England Journal of Medicine*. 2020;383(6):546-557. doi:10.1056/NEJMoa1917246
Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. I. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. The IFNB Multiple Sclerosis Study Group. *Neurology.* 1993;43(4):655-661.

Jacobs LD, Cookfair DL, Rudick RA, et al. Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis. The Multiple Sclerosis Collaborative Research Group (MSCRG). *Annals of neurology.* 1996;39(3):285-294.

Johnson KP, Brooks BR, Cohen JA, et al. Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis: results of a phase III multicenter, double-blind placebo-controlled trial. The Copolymer 1 Multiple Sclerosis Study Group. *Neurology.* 1995;45(7):1268-1276.

Kappos L, Radue EW, O'Connor P, et al. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. *The New England journal of medicine.* 2010;362(5):387-401.

Kappos L, Fox RJ, Burcklen M, et al. Ponesimod Compared With Teriflunomide in Patients With Relapsing Multiple Sclerosis in the Active-Comparator Phase 3 OPTIMUM Study: A Randomized Clinical Trial. *JAMA Neurol*. 2021;78(5):558-567. doi:10.1001/jamaneurol.2021.0405

Kappos L., Bar-Or A. Cree B. et al. EXPAND Clinical Investigators Siponimod versus placebo in secondary progressive multiple sclerosis (EXPAND): a double-blind, randomised, phase 3 study Lancet. 2018 Mar 31;391(10127):1263-1273.

Khan O, Rieckmann P, Boyko A, Selmaj K, Zivadinov R. Three times weekly glatiramer acetate in relapsing-remitting multiple sclerosis. Annals of neurology. 2013;73(6):705-713.

Lublin FD, Cofield SS, Cutter GR, et al. Randomized study combining interferon and glatiramer acetate in multiple sclerosis. *Annals of neurology.* 2013;73(3):327-340.

Mikol DD, Barkhof F, Chang P, et al. Comparison of subcutaneous interferon beta-1a with glatiramer acetate in patients with relapsing multiple sclerosis (the REbif vs Glatiramer Acetate in Relapsing MS Disease [REGARD] study): a multicentre, randomised, parallel, open-label trial. *The Lancet Neurology.* 2008;7(10):903-914.

O'Connor P, Filippi M, Arnason B, et al. 250 microg or 500 microg interferon beta-1b versus 20 mg glatiramer acetate in relapsing-remitting multiple sclerosis: a prospective, randomised, multicentre study. *The Lancet Neurology.* 2009;8(10):889-897.

O'Connor P, Wolinsky JS, Confavreux C, et al. Randomized trial of oral teriflunomide for relapsing multiple sclerosis. *The New England journal of medicine.* 2011;365(14):1293-1303.

Panitch H, Goodin DS, Francis G, et al. Randomized, comparative study of interferon beta-1a treatment regimens in MS: The EVIDENCE Trial. *Neurology.* 2002;59(10):1496-1506.

Polman CH, O'Connor PW, Havrdova E, et al. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. *The New England journal of medicine.* 2006;354(9):899-910.

Randomised double-blind placebo-controlled study of interferon beta-1a in relapsing/remitting multiple sclerosis. PRISMS (Prevention of Relapses and Disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis) Study Group. *Lancet (London, England).* 1998;352(9139):1498-1504.

Svenningsson A, Frisell T, Burman J, et al. Safety and efficacy of rituximab versus dimethyl fumarate in patients with relapsing-remitting multiple sclerosis or clinically isolated syndrome in Sweden: a rater-blinded, phase 3, randomised controlled trial. *The Lancet Neurology*. 2022;21(8):693-703. doi:10.1016/S1474-4422(22)00209-5

Vermersch P, Czlonkowska A, Grimaldi LM, et al. Teriflunomide versus subcutaneous interferon beta-1a in patients with relapsing multiple sclerosis: a randomised, controlled phase 3 trial. *Mult Scler.* 2014;20(6):705-716.

Table 2. References summary of product characteristics ZMT in MS

Biogen, Summary of Product Characteristics, Avonex, 2007
Biogen, Summary of Product Characteristics Tysabri, 2009
Biogen, Summary of Product Characteristics Tecfidera, 2013
Biogen, Summary of Product Characteristics Plegridy, 2014
Bristol-Myers Squibb, Summary of Product Characteristics, Zeposia, 2020
Genzyme, Summary of Product Characteristics, Lemtrada, 2018
Janssen-Cilag, Summary of Product Characteristics, Ponvory, 2021
Merck, Summary of Product Characteristics, Mavenclad, 2017
Novartis, Summary of Product Characteristics, Kesimpta, 2021
Novartis, Summary of Product Characteristics, Mayzent, 2020
Novartis, Summary of Product Characteristics, Gilenya, 2020
Roche, Summary of Product Characteristics, Ocrevus, 2022
Sanofi, Summary of Product Characteristics, Aubagio, 2018
Teva, Summary of Product Characteristics, Copaxone, 2022