

Supplementary Materials

Title:

Comparative efficacy of therapies for relapsing multiple sclerosis: a systematic review and network meta-analysis

Appendix A Literature Review Methods and Results

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Appendix A Literature Review Methods and Results

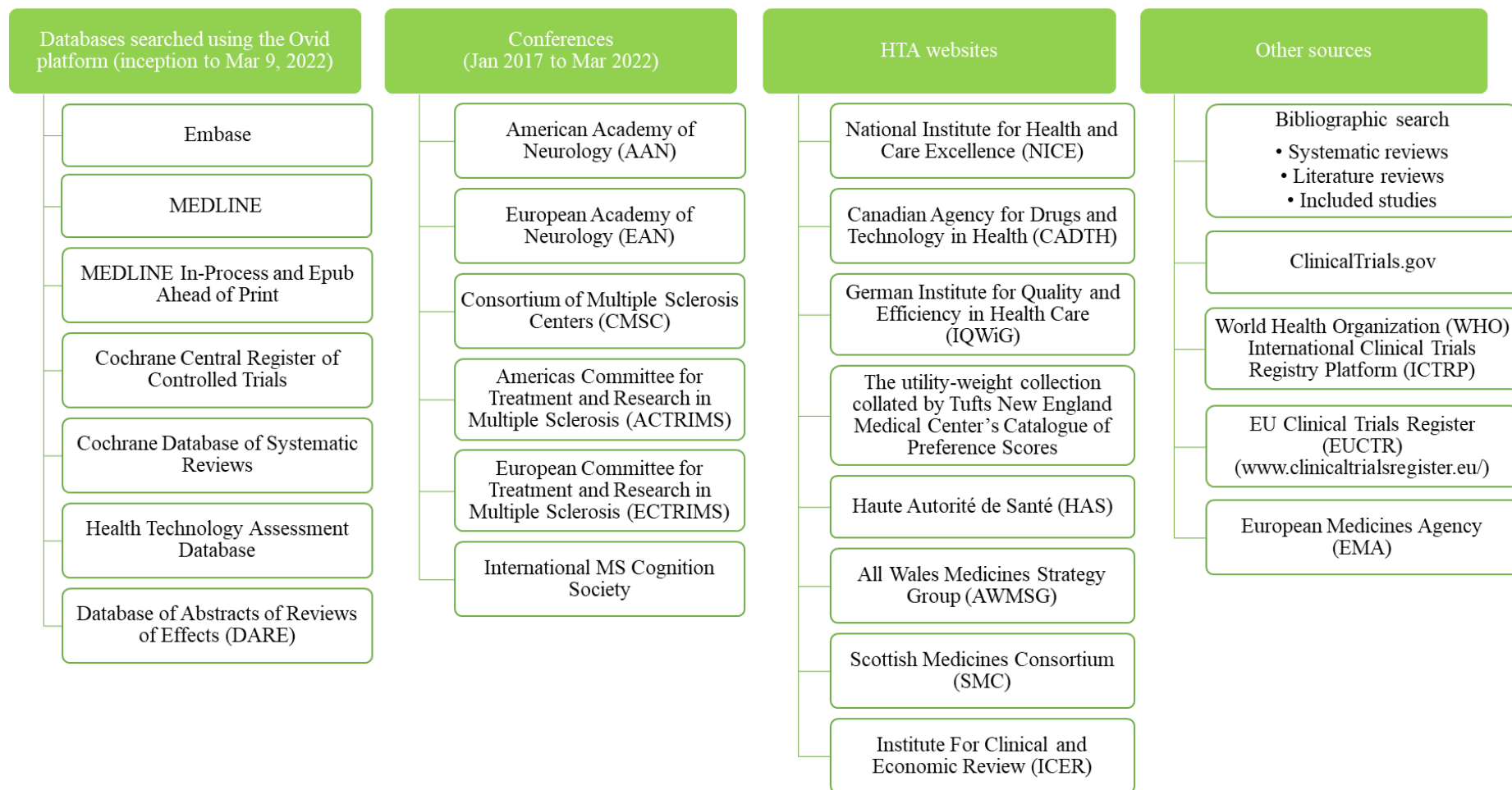


Figure A.1. Data sources used for the systematic review.

Embase Excerpta Medica Database, *HTA* health technology assessment, *MEDLINE* Medical Literature Analysis and Retrieval System Online.

Table A.1. Main search strategy on the Ovid platform (searched March 9, 2022).

Facet	Search Number	Search String	Number of Hits
Disease terms	1	exp multiple sclerosis/	414,951
	2	exp myelitis, transverse/	71,347
	3	exp neuromyelitis optica/	27,576
	4	exp demyelinating diseases/	595,877
	5	1 or 2 or 3 or 4	647,283
	6	(multiple sclerosis or encephalomyelitis or demyelinating disease or neuromyelitis optica or devic or transverse myelitis or optic neuritis).mp.	644,477
	7	(relapsing or relaps* or remit* or relapsing remitting*).mp.	1,342,043
	8	(RRMS or RMS).mp.	103,510
	9	5 or 6	795,287
	10	7 and 9	131,115
	11	8 or 10	203,683
Study design terms	12	exp clinical trial/	5,110,576
	13	exp control groups/ or exp cross-over studies/ or exp double-blind method/ or exp random allocation/ or exp single-blind method/	1,980,422
	14	exp randomization/ or exp randomized controlled trial/ or exp "randomized controlled trial (topic)"/	3,231,181
	15	exp controlled clinical trial/ or exp "controlled clinical trial (topic)"/	3,448,859
	16	exp clinical trials as topic/	1,554,476
	17	exp single blind procedure/	88,296
	18	exp double blind procedure/	379,225
	19	exp placebo/ or exp placebo effect/	768,311
	20	clinical trial*.mp.	6,907,190
	21	control?ed clinical trial.mp.	1,651,384
	22	randomi#ed controlled trial.mp.	4,232,560
	23	randomi#ation.mp.	547,387
	24	rct.mp.	229,564
	25	((random* adj2 allocat*) or (random* adj2 assign*)).tw.	1,153,912
	26	((single or double or triple or treble) adj1 (blind* or mask*)).tw.	1,491,485
	27	placebo*.mp.	2,182,590
	28	exp case mix/ or exp case report/ or exp case study/	9,936,950
	29	exp abstract report/	179,987
	30	exp editorial/ or exp letter/ or exp news/ or exp comment/	8,028,548
	31	28 or 29 or 30	17,244,857
	32	12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27	11,248,621
	33	32 not 31	10,788,880
	34	exp cohort studies/	6,267,922
	35	exp cross-sectional studies/	1,665,271
	36	exp intervention studies/	104,800
	37	exp comparative study/	6,821,188

Facet	Search Number	Search String	Number of Hits
	38	(observational* or real world* or control?ed study).tw.	1,776,453
	39	(compar* or cohort* or group*).tw.	42,186,893
	40	(clinical study or followup or follow up or longitudinal* or prospective*).tw.	10,769,755
	41	33 or 34 or 35 or 36 or 37 or 38 or 39 or 40	54,199,718
Intervention terms	42	(Disease modifying therap* or DMT* or disease modifying drug or DMD* or Immunomodulating drug).mp.	112,707
	43	exp Interferon-beta/	370,919
	44	(interferon adj2 beta).mp.	116,096
	45	(ifn adj2 beta).mp.	52,688
	46	(IFN beta* or IFNbeta*).mp.	50,620
	47	(interferon beta* or interferonbeta*).mp.	62,512
	48	(avonex or rebif).mp.	9,088
	49	((interferon or IFN) adj2 (beta 1a or beta-1a or beta1a)).mp.	25,758
	50	((interferon or IFN) adj2 (beta 1b or beta1b or beta-1b)) or beta interferon 1b).mp.	7,784
	51	(beneseron or betaferon or betaseron or extavia).mp.	6,368
	52	(Glatiramer or cop 1 or copaxone or copolymer 1).mp.	26,583
	53	(glatiramer adj2 (acetate or sodium)).mp.	14,014
	54	(glatopa or Glatiramer acetate).mp.	14,072
	55	(alemtuzumab or campath 1h or anti-CD52 or anti CD52).mp.	44,584
	56	(CD52 adj2 monoclonal antibody).mp.	1,288
	57	(lemtrada or mabcampath).mp.	1,489
	58	(natalizumab or antegren or tysabri or ocrelizumab or ocrevus or humani#se anti CD20 antibody).mp.	35,414
	59	(Fingolimod or FTY720 or FTY 720 or gilenia or gilenya or sphingosine-1-phosphate receptor modulator or sphingosine 1 phosphate receptor modulator or S1P receptor modulator or siponimod or BAF312 or BAF-312 or BAF 312 or mayzent).mp.	33,725
	60	(peginterferon beta-1a or peginterferon beta 1a or peginterferon or beta 1a peginterferon or beta 1a peginterferon or peginterferon beta 1a or peginterferon beta-1a or pegylated human interferon beta 1a or pegylated interferon beta 1a or pegylated interferon beta-1a or pegylated interferon beta 1a or plegridy).mp.	73,268
	61	(Teriflunomide or A 771726 or A77 1726 or A77-1726 or A771726 or aubagio or hmr 1726 or hmr1726).mp.	9,823
	62	(dimethyl fumarate or dimethylfumarate or tecfidera or DMF or BG00012 or "BG 00012" or BG-00012).mp.	70,454
	63	(methyl ester and fumeric acid).mp.	0
	64	(mitoxantrone or novantrone).mp.	66,033
	65	(cladribine or leustatin or mavenclad).mp.	21,186
	66	(Corticosteroid or Methylprednisolone or Medrol or Meprolone or prednisone or dexamethasone or Adrenocorticotropic hormone or ACTH or Acthar or Repository Corticotropin).mp.	2,010,246

Facet	Search Number	Search String	Number of Hits
	67	(Dalfampridine or Ampyra or Fampridine or Amaya or Fampyra or Dalstep).mp.	4,730
	68	(Onabotulinumtoxin A or BOTOX or Incabotulinum toxin A or Botulinum toxin Type A).mp.	37,470
	69	(RPC1063 or Ozanimod).mp.	1,516
	70	(Ublituximab or Anti-CD20 Monoclonal Antibody or TG-1101).mp.	8,762
	71	(Ponesimod or ACT-128800 or ACT128800 or ACT128800).mp.	767
	72	(ATX-MS- 1467 or ATX-MS-1467 or ATXMS1467).mp.	50
	73	(Vumerity or ALKS8700 or ALKS 8700 or BIIB098 or Diroximel fumerate or Laquinimod or Nervenra or ABR-215062 or ABR215062 or ABR 215062).mp.	2,554
	74	(Donepezil or Aricept).mp.	41,592
	75	(GW-1000-02 or Sativex).mp.	2,309
	76	Nomegastrol acetate.mp.	0
	77	(NU 100 or NU100).mp.	48
	78	(ADS-5102 or amantadine).mp.	46,954
	79	(EGb761 or Tanakan).mp.	1,812
	80	(naltrexone or Pravastatin or Apitox).mp.	117,981
	81	(stem cell and (transplantation or therapy or infusion)).mp.	945,437
	82	hsct.mp.	97,223
	83	(rituximab or blitzima or mabThera or ritemvia or rituxan or rituxin or rituzena or rixathon or riximyo or truxima or tuxella).mp.	255,921
	84	brabio.mp.	2
	85	(Monoclonal antibod* or Humani#ed monoclonal antibod* or (R 1594 or R 1594 or R-1594 or RG-1594 or "PR 070769" or PR070769 or PR-070769)).mp.	1,082,861
	86	(Ofatumumab or OMB157 or HYMAX-CD20 2F2 or HUMAXCD20-2F2 or Arzerra or GSK1841157 or GSK-1841157).mp.	8,690
	87	(Opicinumab or BIIB033 or BIIB-033).mp.	407
	88	((Monoclonal antibody and (human endogenous retrovirus or HERV) and envelope protein) or GNbAC1).mp.	294
	89	(Polyethylene glycol-interferon-beta- 1a or PEG IFNbeta-1a or Polyethylene glycol-interferon beta-1a).mp.	46
	90	(Elezanumab or repulsive guidance molecule A or RGMa).mp.	884
	91	(Lanalumab or VAY736).mp.	105
	92	exp Ofatumumab/	6,546
	93	exp Opicinumab/	191
	94	exp Elezanumab/	33
	95	exp fingolimod/	26,925
	96	exp glatiramer/	22,160
	97	exp alemtuzumab/	39,320
	98	exp natalizumab/	26,761

Facet	Search Number	Search String	Number of Hits
	99	exp siponimod/	1,141
	100	exp ocrelizumab/	5,089
	101	exp peginterferon beta1a/	1,151
	102	exp teriflunomide/	7,036
	103	exp fumaric acid dimethyl ester/	5,416
	104	exp mitoxantrone/	58,493
	105	exp cladribine/	18,847
	106	exp Methylprednisolone/	255,137
	107	exp Corticosteroid/	2,806,558
	108	exp Ozanimod/	898
	109	exp Ublituximab/	469
	110	exp Ponesimod/	422
	111	exp Laquinimod/	1,780
	112	exp Donepezil/	33,176
	113	exp Megestrol/	6,850
	114	exp amantadine/	46,256
	115	exp pravastatin/	50,096
	116	exp Tanakan/	15,114
	117	exp Rituximab/	212,994
	118	exp stem cell transplantation/	519,948
	119	Megestrol acetate.mp.	15,405
	120	OR/42-119	6,115,642
Combine (disease, study design, and interventions)	121	11 and 41 and 120	54,390
Limit to English language, humans	122	limit 121 to English language, humans	46,231
Final after removing duplicates	123	remove duplicates from 122	18,803

Table A.2. Additional search strategy on the Ovid platform including additional terms for unlicensed interventions (March 2022 update only, searched March 9, 2022).

Facet	Search Number	Search String	Number of Hits
Disease terms	1	exp multiple sclerosis/	213,048
	2	exp myelitis, transverse/	5,669
	3	exp neuromyelitis optica/	14,572
	4	exp demyelinating diseases/	305,755
	5	1 or 2 or 3 or 4	310,607
	6	(multiple sclerosis or encephalomyelitis or demyelinating disease or neuromyelitis optica or devic or transverse myelitis or optic neuritis).mp.	329,970
	7	(relapsing or relaps* or remit* or relapsing remitting*).mp.	688,881
	8	(RRMS or RMS).mp.	53,254
	9	5 or 6	393,109
	10	7 and 9	67,361
	11	8 or 10	104,531
Study design terms	12	exp clinical trial/	2,608,970
	13	exp control groups/ or exp cross-over studies/ or exp double-blind method/ or exp random allocation/ or exp single-blind method/	1,005,491
	14	exp randomization/ or exp randomized controlled trial/ or exp "randomized controlled trial (topic)"/	1,658,876
	15	exp controlled clinical trial/ or exp "controlled clinical trial (topic)"/	1,767,018
	16	exp clinical trials as topic/	798,106
	17	exp single blind procedure/	45,420
	18	exp double blind procedure/	192,990
	19	exp placebo/ or exp placebo effect/	388,229
	20	clinical trial*.mp.	3,519,787
	21	control?ed clinical trial.mp.	825,683
	22	randomi#ed controlled trial.mp.	2,185,264
	23	randomi#ation.mp.	279,715
	24	rct.mp.	117,963
	25	((random* adj2 allocat*) or (random* adj2 assign*)).tw.	590,471
	26	((single or double or triple or treble) adj1 (blind* or mask*)).tw.	759,122
27	placebo*.mp.	1,107,456	
28	exp case mix/ or exp case report/ or exp case study/	5,050,930	
29	exp abstract report/	89,541	
30	exp editorial/ or exp letter/ or exp news/ or exp comment/	4,069,790	
31	28 or 29 or 30	8,755,417	
32	12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27	5,751,551	
33	32 not 31	5,517,016	
34	exp cohort studies/	3,282,482	
35	exp cross-sectional studies/	886,828	
36	exp intervention studies/	54,288	

Facet	Search Number	Search String	Number of Hits
	37	exp comparative study/	3,450,186
	38	(observational* or real world* or control?ed study).tw.	932,652
	39	(compar* or cohort* or group*).tw.	21,618,233
	40	(clinical study or followup or follow up or longitudinal* or prospective*).tw.	5,534,282
	41	33 or 34 or 35 or 36 or 37 or 38 or 39 or 40	27,757,705
Intervention terms	42	(Disease modifying therap* or DMT* or disease modifying drug or DMD* or Immunomodulating drug).mp.	58,693
	43	exp Interferon-beta/	333,707
	44	(interferon adj2 beta).mp.	58,994
	45	(ifn adj2 beta).mp.	26,756
	46	(IFN beta* or IFNbeta*).mp.	25,786
	47	(interferon beta* or interferonbeta*).mp.	31,601
	48	(avonex or rebif).mp.	4,534
	49	((interferon or IFN) adj2 (beta 1a or beta-1a or beta1a)).mp.	13,044
	50	((interferon or IFN) adj2 (beta 1b or beta1b or beta-1b)) or beta interferon 1b).mp.	4,010
	51	(beneseron or betaferon or betaseron or extavia).mp.	3,170
	52	(Glatiramer or cop 1 or copaxone or copolymer 1).mp.	13,568
	53	(glatiramer adj2 (acetate or sodium)).mp.	7,113
	54	(glatopa or Glatiramer acetate).mp.	7,144
	55	(alemtuzumab or campath 1h or anti-CD52 or anti CD52).mp.	22,842
	56	(CD52 adj2 monoclonal antibody).mp.	662
	57	(lemtrada or mabcampath).mp.	753
	58	(natalizumab or antegren or tysabri or ocrelizumab or ocrevus or humani#se anti CD20 antibody).mp.	18,450
	59	(Fingolimod or FTY720 or FTY 720 or gilenia or gilenya or sphingosine-1-phosphate receptor modulator or sphingosine 1 phosphate receptor modulator or S1P receptor modulator or siponimod or BAF312 or BAF-312 or BAF 312 or mayzent).mp.	17,570
	60	(peginterferon beta-1a or peginterferon beta 1a or peginterferon or beta 1a peginterferon or beta1a peginterferon or peginterferon beta 1a or peginterferon beta-1a or pegylated human interferon beta 1a or pegylated interferon beta 1a or pegylated interferon beta-1a or pegylated interferon beta1a or plegridy).mp.	36,699
	61	(Teriflunomide or A 771726 or A77 1726 or A77-1726 or A771726 or aubagio or hmr 1726 or hmr1726).mp.	5,241
	62	(dimethyl fumarate or dimethylfumarate or tecfidera or DMF or BG00012 or "BG 00012" or BG-00012).mp.	36,254
	63	(methyl ester and fumeric acid).mp.	0
	64	(mitoxantrone or novantrone).mp.	33,269
	65	(cladribine or leustatin or mavenclad).mp.	10,936

Facet	Search Number	Search String	Number of Hits
	66	(Corticosteroid or Methylprednisolone or Medrol or Meprolone or prednisone or dexamethasone or Adrenocorticotrophic hormone or ACTH or Acthar or Repository Corticotropin).mp.	1,025,407
	67	(Dalfampridine or Ampyra or Fampridine or Amaya or Fampyra or Dalstep).mp.	2,446
	68	(Onabotulinumtoxin A or BOTOX or Incabotulinum toxin A or Botulinum toxin Type A).mp.	19,096
	69	(RPC1063 or Ozanimod).mp.	876
	70	(Ublituximab or Anti-CD20 Monoclonal Antibody or TG-1101).mp.	4,572
	71	(Ponesimod or ACT-128800 or ACT128800 or ACT128800).mp.	422
	72	(ATX-MS- 1467 or ATX-MS-1467 or ATXMS1467).mp.	25
	73	(Vumerity or ALKS8700 or ALKS 8700 or BIIB098 or Diroximel fumerate or Laquinimod or Nervertra or ABR-215062 or ABR215062 or ABR 215062).mp.	1,287
	74	(Donepezil or Aricept).mp.	21,212
	75	(GW-1000-02 or Sativex).mp.	1,173
	76	Nomegastrol acetate.mp.	0
	77	(NU 100 or NU100).mp.	24
	78	(ADS-5102 or amantadine).mp.	23,663
	79	(EGb761 or Tanakan).mp.	911
	80	(naltrexone or Pravastatin or Apitox).mp.	59,470
	81	(stem cell and (transplantation or therapy or infusion)).mp.	488,062
	82	hsct.mp.	50,781
	83	(rituximab or blitzima or mabThera or ritemvia or rituxan or rituxin or rituzena or rixathon or riximyo or truxima or tuxella).mp.	133,516
	84	brabio.mp.	1
	85	(Monoclonal antibod* or Humani#ed monoclonal antibod* or (R 1594 or R 1594 or R-1594 or RG-1594 or "PR 070769" or PR070769 or PR-070769)).mp.	548,429
	86	(Ofatumumab or OMB157 or HYMAX-CD20 2F2 or HUMAXCD20-2F2 or Arzerra or GSK1841157 or GSK-1841157).mp.	4,511
	87	(Opicinumab or BIIB033 or BIIB-033).mp.	211
	88	((Monoclonal antibody and (human endogenous retrovirus or HERV) and envelope protein) or GNbAC1).mp.	151
	89	(Polyethylene glycol-interferon-beta- 1a or PEG IFNbeta-1a or Polyethylene glycol-interferon beta-1a).mp.	23
	90	(Elezanumab or repulsive guidance molecule A or RGMa).mp.	466
	91	(Lanalumab or VAY736).mp.	56
	92	exp Ofatumumab/	3,395
	93	exp Opicinumab/	100
	94	exp Elezanumab/	21

Facet	Search Number	Search String	Number of Hits
	95	exp fingolimod/	14,020
	96	exp glatiramer/	11,345
	97	exp alemtuzumab/	20,188
	98	exp natalizumab/	13,860
	99	exp siponimod/	652
	100	exp ocrelizumab/	2,858
	101	exp peginterferon beta1a/	606
	102	exp teriflunomide/	3,778
	103	exp fumaric acid dimethyl ester/	842
	104	exp mitoxantrone/	29,457
	105	exp cladribine/	9,718
	106	exp Methylprednisolone/	131,018
	107	exp Corticosteroid/	1,428,173
	108	exp Ozanimod/	529
	109	exp Ublituximab/	261
	110	exp Ponesimod/	238
	111	exp Laquinimod/	895
	112	exp Donepezil/	16,939
	113	exp Megestrol/	3,443
	114	exp amantadine/	23,341
	115	exp pravastatin/	25,114
	116	exp Tanakan/	7,582
	117	exp Rituximab/	111,080
	118	exp stem cell transplantation/	268,499
	119	Megestrol acetate.mp.	7,731
	120	OR/42-119	3,237,906
	121	(INV-103 or INV103 or INV 103).af.	1
	122	(IR-902 or IR902 or IR 902).af.	5
	123	(imilecleucel-T or imilecleucel T).af.	16
	124	(ATX-MS-1467 or ATX MS 1467).af.	25
	125	(NG-01 or NG01 or "NG 01").af.	148
	126	Xemys.af.	8
	127	(vafidemstat or oryzon or ORY-2001 or ORY2001 or ORY 2001).af.	258
	128	(aldesleukin or Proleukin).af.	1,973
	129	(Act-01 or Act01 or "Act 01").af.	36
	130	(SAR-441344 or SAR441344 or SAR 441344 or "INX 021" or INX-021 or INX021).af.	6
	131	(ibrigampar or AMG-131 or AMG131 or AMG 131 or CHS-131 or CHS131 or CHS 131 or INT-131 or INT131 or INT 131).af.	104
	132	(RNS-60 or RNS60 or RNS 60).af.	95
	133	(ATL-1102 or ATL1102 or ATL 1102).af.	55
	134	(GNbAC1 or temelimab).af.	136
	135	(TZLS-401 or TZLS401 or TZLS 401 or foralumab).af.	32
	136	(elezanumab or ABT-555 or ABT555 or ABT 555 or AE12-1Y-QL).af.	42

Facet	Search Number	Search String	Number of Hits
	137	(Vidofludimus or 4SC-101 or 4SC101 or 4SC 101 or SC12267).af.	115
	138	(ATA-190 or ATA190 or ATA 190).af.	2
	139	(telitacicept or RC18 or RC-18 or RC 18 or RCT-18 or RCT 18 or RCT18).af.	259
	140	orelabrutinib.af.	46
	141	(monomethyl fumarate or MMF or Bafiertam).af.	21,911
	142	Octagam.af.	515
	143	exp Evobrutinib/	126
	144	Evobrutinib.af.	201
	145	(PRN2246 or SAR442168 or Tolebrutinib).af.	70
	146	exp Tolebrutinib/	30
	147	(Fenebrutinib or GDC-0853).af.	180
	148	Orelabrutinib.af.	46
	149	exp Orelabrutinib/	35
	150	exp Fenebrutinib/	99
	151	BIIB091.af.	9
	152	(AC 0058TA or AC0058TA).af.	3
	153	BIIB068.af.	3
	154	(Poseltinib or LY3337641 or HM71224).af.	39
	155	exp poseltinib/	16
	156	exp Masitinib/	626
	157	(Masitinib or AB 1010 or AB1010 or AB-1010).af.	960
	158	exp IMATINIB/	56,369
	159	(Imatinib or Glivec or STI571 or sti-571 or sti 571).af.	66,227
	160	(MIQ-001 or MIQ001 or "MIQ 001").af.	3
	161	(GZ-402668 or GZ402668 or GZ 402668).af.	15
	162	(BCD-054 or BCD054 or "BCD 054").af.	10
	163	(CP-1050 or CP1050 or CP 1050).af.	28
	164	(TRK-560 or TRK560 or TRK 560).af.	6
	165	(rHIgM22 or M22 or sHIgM22).af.	1,306
	166	(RTL-1000 or RTL1000 or RTL 1000 or VG1000 or VG 1000 or VG-1000).af.	58
	167	(T-20-K or T20K).af.	111
	168	(ZD-03 or ZD03 or "ZD 03").af.	62
	169	(AK-119 or AK119 or AK 119).af.	10
	170	(18F-3-F4AP or 18F*3F4AP).af.	2
	171	(PIPE-307 or PIPE307 or PIPE 307).af.	1
	172	(IMS-001 or IMS001 or "IMS 001").af.	1
	173	(IPG-1094 or IPG1094 or IPG 1094).af.	1
	174	(RO-7121932 or RO7121932 or RO 7121932).af.	0
	175	(HuL-001 or HuL001 or "HuL 001").af.	1
	176	(Amilo-5MER or Amilo5MER or Amilo 5MER).af.	2
	177	(CYMS-101 or CYMS101 or CYMS 101).af.	0
	178	(BMS-986196 or BMS986196 or BMS 986196 or 11C-BMS-986196).af.	1
	179	(BIIB-061 or BIIB061 or "BIIB 061").af.	3

Facet	Search Number	Search String	Number of Hits
	180	(GSK-3888130B or GSK3888130B or GSK 3888130B).af.	1
	181	(DNL-788 or DNL788 or DNL 788 or SAR443820).af.	3
	182	(DUOC-01 or DUOC01 or "DUOC 01").af.	31
	183	(ZYIL-1 or ZYIL1 or ZYIL 1).af.	0
	184	(BIIB-107 or BIIB107 or BIIB 107).af.	1
	185	(ANK-700 or ANK700 or ANK 700).af.	1
	186	(tolerogenic dendritic cell therapy or TOIDC or Tolerogenic dendritic*).af.	1,983
	187	exp ibudilast/	689
	188	exp dapirolizumab pegol/	31
	189	exp Remibrutinib/	16
	190	exp Biotin/	37,627
	191	RPI 78M.af.	6
	192	(Divozilimab or BCD-132).af.	7
	193	CNM-Au8.af.	29
	194	(AV-411 or MN-166 or Ibudilast).af.	1,033
	195	(CDP7657 or dapirolizumab).af.	67
	196	(LOU064 or Remibrutinib).af.	44
	197	(MD1003 or Biotin or "Vitamin H").af.	75,094
	198	andrographolide.af.	3,372
	199	or/121-198	176,037
	200	199 not 120	135,920
Combine (disease, study design, and interventions)	201	11 and 41 and 200	240
Limit to English language, humans	202	limit 201 to English language, humans	182
Final after removing duplicates	203	remove duplicates from 202	134

The total number of hits from database searches was 18,937 (18,803 + 134).

Table A.3. Search strategy for hand-searching conference abstracts.

Search Number	Conference Name	Year	Link	Search Terms
1	ACTRIMS	2017	https://journals.sagepub.com/toc/msja/23/1_suppl	Whole pdf screened
		2018	https://journals.sagepub.com/toc/msja/24/1_suppl%20	Whole pdf screened
		2019	https://journals.sagepub.com/toc/msja/25/1_suppl	Whole pdf screened
		2020	https://journals.sagepub.com/toc/msja/26/1_suppl	Whole pdf screened
	ACTRIMS and ECTRIMS joint conference	2020	https://journals.sagepub.com/toc/msja/26/3_suppl	Whole pdf screened
2	ECTRIMS	2017	https://onlinelibrary.ectrims-congress.eu/ectrims/#!*menu=6*browseby=3*sortby=2 https://journals.sagepub.com/toc/msja/23/3_suppl	Whole pdf screened
		2018	https://journals.sagepub.com/toc/msja/24/2_suppl%20 https://onlinelibrary.ectrims-congress.eu/ectrims/#!*menu=6*browseby=3*sortby=2	Whole pdf screened
		2019	https://journals.sagepub.com/toc/msja/25/2_suppl https://onlinelibrary.ectrims-congress.eu/ectrims/#!*menu=6*browseby=3*sortby=2	Whole pdf screened
		2021	https://journals.sagepub.com/toc/msja/27/2_suppl	Whole pdf screened
3	AAN	2017	https://n.neurology.org/content/88/16_Supplement	MS and General Neurology sections were searched
		2018	https://n.neurology.org/content/90/15_Supplement	MS and General Neurology sections were searched
		2019	https://n.neurology.org/content/92/15_Supplement	MS and General Neurology sections were searched
		2020	https://n.neurology.org/content/94/15_Supplement	MS and General Neurology sections were searched
		2021	https://n.neurology.org/content/96/15_Supplement	MS and General Neurology sections were searched

Search Number	Conference Name	Year	Link	Search Terms
4	EAN	2017	https://www.ean.org/Archive.2880.0.html	MS and Related Disorders section was searched in the pdf
		2018	https://www.ean.org/Archive.2880.0.html	MS and Related Disorders section was searched in the pdf
		2019	https://www.ean.org/oslo2019/Abstract-Book.3928.0.html	MS and Related Disorders section was searched in the pdf
		2020	https://onlinelibrary.wiley.com/toc/14681331/2020/27/S1	MS and Related Disorders section was searched in the pdf
		2021	https://www.ean.org/congress-2021/present/abstracts/abstract-book	Whole pdf screened
5	CMSC	2017	https://cmsc.confex.com/cmsc/2017/webprogram/POSTER.html https://ijmsc.org/doi/pdf/10.7224/1537-2073-19.s1.1	Whole pdf screened
		2018	https://cmsc.confex.com/cmsc/2018/webprogram/meeting.html https://ijmsc.org/doi/pdf/10.7224/1537-2073-20.s1.1	Whole pdf screened
		2019	https://cmsc.confex.com/cmsc/2019/meetingapp.cgi/Session/1209 https://ijmsc.org/doi/pdf/10.7224/1537-2073-21.s1.1	Whole pdf screened
		2020	https://meridian.allenpress.com/ijmsc/issue/22/s2	Whole pdf screened
		2021	https://meridian.allenpress.com/ijmsc/article/23/s2/i/472175/Abstracts-from-the-35th-Annual-Meeting-of-the	Whole pdf screened
6	International MS Cognition Society	2017	https://journals.sagepub.com/toc/msja/23/8	Whole pdf screened
		2018	https://www.imscogs.com/imscogs/conferences/conference-2018-berlin/scientific-programme.html	Whole pdf screened
		2019	https://journals.sagepub.com/toc/msja/25/8	Whole pdf screened
		2020, 2021	https://www.imscogs.com/conferences/conference-2020-bordeaux.html	Event cancelled

AAN American Academy of Neurology, *ACTRIMS* Americas Committee for Treatment and Research in Multiple Sclerosis, *CMSC* Consortium of Multiple Sclerosis Centers, *EAN* European Academy of Neurology, *ECTRIMS* European Committee for Treatment and Research in Multiple Sclerosis.

Table A.4. Search strategy for ongoing, terminated, and suspended studies from ClinicalTrials.gov.

Website: https://clinicaltrials.gov/ct2/search/advanced?cond=&term=&cntry=&state=&city=&dist=				
Filters:				
Disease: Multiple sclerosis				
Age Group: Adults (18-64), Older Adult (65+)				
Study Type: Interventional (Clinical Trial)				
Search Terms (Intervention)	Initial Search on November 19, 2019	Additional Search from January 1, 2020 to March 25, 2021	Additional Search from April 1, 2021 to March 31, 2022	Remarks
Interferon beta-1b	48	4	1	Also searched for Betaseron, Betaferon, Extavia
Interferon beta-1a	131	12	3	Also searched for Rebif and Avonex
IFN	171	17	6	Also searched for Interferon and Multi
Peginterferon beta-1a	17	4	2	Also searched for Interferon
Glatiramer	68	10	3	
Copaxone	10	10	3	
Fingolimod	52	7	0	Also searched for Gilenya, FTY 720, and Multi
Natalizumab	53	11	2	Also searched for Tysabri
Teriflunomide	39	17	4	Also searched for Aubagio, HMR1726, and Multi
Alemtuzumab	24	4	1	Also searched for Lemtrada and Campath
Dimethyl fumarate	50	11	2	Also searched for Tecfidera and BG 00012
Mitoxantrone	9	5	0	
Ocrelizumab	22	34	7	Also searched for Ocrevus
Siponimod	3	4	2	Also searched for BAF132
Cladribine	11	12	1	
ATX-MS-1467	2	0	0	
ALKS 8700	3	1	1	
Diroximel fumarate	0	1	3	
Vumerity	0	1	2	
BIIB098	0	0	1	
Ofatumumab	7	7	5	
Ozanimod	6	3	1	Also searched for RPC1063
Ponesimod	5	3	0	
Ublituximab	5	2	0	Also searched for TG1101
Rituximab	21	12	2	Also searched for Mabthera and Rituxan
Laquinimod	10	5	0	
Total hits	767	197	52	

Table A.5. Search strategy for ongoing, terminated, and suspended studies from the European Union Drug Regulating Authorities Clinical Trials Database.

Website: https://www.clinicaltrialsregister.eu/ctr-search/search				
Search Terms	Population	Hits Retrieved		
		November 26, 2019	January 1, 2020 to March 25, 2021	April 1, 2021 to March 31, 2022
("Multiple sclerosis") AND (("Interferon-beta 1b") OR ("IFN beta-1b") OR ("Interferon") OR ("Betaseron") OR ("FTY 720") OR ("BG-00012") OR ("Campath") OR ("DMT") OR ("disease modifying therapy") OR ("Extavia") OR ("IFN") OR ("Interferon-beta 1a") OR ("IFN beta-1a") OR ("Rebif") OR ("Avonex") OR ("Peginterferon beta-1a") OR ("Plegridy") OR ("Glatiramer acetate") OR ("GA") OR ("Copaxone") OR ("Brabio") OR ("Fingolimod") OR ("Gilenya") OR ("Natalizumab") OR ("Tysabri") OR ("Teriflunomide") OR ("Aubagio") OR ("HMR1726") OR ("Alemtuzumab") OR ("Lemtrada") OR ("Dimethyl fumarate") OR ("Tecfidera") OR ("Mitoxantrone") OR ("Novantrone") OR ("Ocrelizumab") OR ("Ocrevus") OR ("Siponimod") OR ("Mayzent") OR ("Cladribine"))	Adults and Elderly	272	30	31
Multiple sclerosis AND (Ofatumumab OR Ozanimod OR Ponesimod OR Ublituximab OR Laquinimod OR Rituximab)	Adults and Elderly	41	5	6
Multiple sclerosis AND ("ALKS 8700" OR "Diroximel fumerate" OR "ATX-MS-1467")	Adults and Elderly	3	0	0
Total trials retrieved		316	35	37

Table A.6. Search strategy for ongoing, terminated, and suspended studies from the International Clinical Trials Registry Platform.

Search Terms	Hits Retrieved		
	December 12, 2019	January 1, 2020 to March 25, 2021	April 1, 2021 to March 31, 2022
("Multiple sclerosis") AND (("Interferon-beta 1b") OR ("IFN beta-1b") OR ("Interferon") OR "Betaseron" OR ("FTY 720") OR ("BG-00012") OR "Campath")	237	19	2
("Multiple sclerosis") AND ("DMT" OR "Extavia" OR "IFN" OR ("Interferon-beta 1a") OR ("IFN beta-1a") OR "Rebif" OR "Avonex" OR ("Peginterferon beta-1a") OR "Plegridy" OR ("Glatiramer acetate") OR "GA" OR "Copaxone" OR "Brabio")	467	96	3
("Multiple sclerosis") AND ("Fingolimod" OR "Gilenya" OR "Natalizumab" OR "Tysabri" OR "Teriflunomide" OR "Aubagio" OR ("HMR1726") OR "Alemtuzumab" OR "Lemtrada" OR ("Dimethyl fumarate"))	235	57	12
("Multiple sclerosis") AND ("Tecfidera") OR ("Mitoxantrone") OR ("Novantrone") OR ("Ocrelizumab") OR ("Ocrevus") OR ("Siponimod") OR ("Mayzent") OR ("Cladribine"))	106	64	20
("Multiple sclerosis") AND ("ATX-MS-1467" OR "ALKS 8700" OR "Diroximel fumerate" OR "Ofatumumab" OR "Ozanimod" OR "Ponesimod" OR "Ublituximab" OR "rituximab" OR "Laquinimod")	85	19	4
Total hits	1130	255	41

Table A.7. Eligibility criteria for the systematic review.

Category	Inclusion Criteria	Exclusion Criteria
Population	<ul style="list-style-type: none"> Adults (≥ 18 years) People with RMS (RRMS or SPMS with superimposed relapses) 	<ul style="list-style-type: none"> People with MS types other than RMS (CIS, PPMS, and SPMS without superimposed relapses)
Interventions	<ul style="list-style-type: none"> Alemtuzumab Cladribine Dimethyl fumarate Diroximel fumarate Fingolimod Glatiramer acetate Interferon-beta 1a Interferon-beta 1b Mitoxantrone Natalizumab Ocrelizumab Ofatumumab Ozanimod Pegylated interferon beta-1a Ponesimod Siponimod Teriflunomide Unlicensed therapies 	<ul style="list-style-type: none"> Studies assessing only unlicensed doses of approved DMTs
Comparators	<ul style="list-style-type: none"> Any of the DMTs specified in Interventions Placebo Best supportive care 	
Outcomes	<ul style="list-style-type: none"> 3-month confirmed disability progression 6-month confirmed disability progression Annualised relapse rate Proportion with relapse/relapse-free MRI outcomes Quality of life outcomes Adverse events Serious adverse events Withdrawals 	
Study Design	<ul style="list-style-type: none"> RCTs regardless of blinding status Any country English language only 	<ul style="list-style-type: none"> Any study design other than RCT Studies published in non-English languages

Note: Limiting the population to people specifically with RRMS (as opposed to RMS) was not considered as it would result in the exclusion of key trials for IFNB-1a IM, IFNB-1a SC, ocrelizumab, ofatumumab, ozanimod, ponesimod, teriflunomide, and ublituximab.

Note: Unlicensed therapies considered as interventions were ACT-01, aldesleukin, ATA-190, ATL-1102, ATX-MS-1467, dapirolizumab pegol, divozilimab, elezanumab, evobrutinib, fenebrutinib, ibrigampar, ibudilast, imatinib, imilecleucel-t, INV-103, IR-902, laquinimod, masitinib, monomethyl fumarate, NG-01, Octagam, orelabrutinib, poseltinib, remibrutinib, rituximab, RNS-60, SAR-441344, telitacicept, temelimab, tolebrutinib, ublituximab, vafidemstat, vidofludimus, and Xemys.

CIS clinically isolated syndrome, DMT disease-modifying therapy, IFNB interferon beta, IM intramuscular, MRI magnetic resonance imaging, MS multiple sclerosis, PPMS primary progressive multiple sclerosis, RCT randomised controlled trial, RMS relapsing multiple sclerosis, RRMS relapsing-remitting multiple sclerosis, SC subcutaneous, SPMS secondary progressive multiple sclerosis.

Table A.8. Relevant interventions for the network meta-analysis.

Interventions
<ul style="list-style-type: none">• Alemtuzumab (12 mg)• Cladribine (3.5 mg/kg)• Dimethyl fumarate (240 mg BID)• Fingolimod (0.5 mg)• Glatiramer acetate (20 mg QD or 40 mg TIW)• Interferon beta-1a IM (30 µg)• Interferon beta-1a SC (22 µg TIW or 44 µg TIW)• Interferon beta-1b (250 µg)• Natalizumab (300 mg)• Ocrelizumab (600 mg)• Ofatumumab (20 mg)• Ozanimod (1.0 mg)• Ponesimod (20 mg)• Pegylated interferon beta-1a (125 µg Q2W)• Teriflunomide (7 mg or 14 mg)• Ublituximab (450 mg)

Note: Interventions were considered relevant if they were approved for RMS by the FDA and/or EMA as of June 2022 or were under review by the FDA and/or EMA at this time. Drugs were included irrespective of their brand/generic name.

BID twice a day, *EMA* European Medicines Agency, *FDA* United States Food and Drug Administration, *IM* intramuscular, *Q2W* once every two weeks, *QD* once a day, *SC* subcutaneous, *TIW* three times a week.

Table A.9. List of trials included in the network meta-analysis.

Trial Name	Pivotal Publication Author (Year)	NCT Number	Relevant Treatments
ADVANCE	Calabresi (2014) [1]	NCT00906399	<ul style="list-style-type: none"> • Pegylated interferon beta-1a SC 125 µg Q2W • Placebo
AFFIRM	Polman (2006) [2]	NCT00027300	<ul style="list-style-type: none"> • Natalizumab IV 300 mg Q4W • Placebo
ASCLEPIOS I	Hauser (2020) [3]	NCT02792218	<ul style="list-style-type: none"> • Ofatumumab SC 20 mg Q4W • Teriflunomide PO 14 mg QD
ASCLEPIOS II	Hauser (2020) [3]	NCT02792231	<ul style="list-style-type: none"> • Ofatumumab SC 20 mg Q4W • Teriflunomide PO 14 mg QD
ASSESS	Cree (2021) [4]	NCT01633112	<ul style="list-style-type: none"> • Fingolimod PO 0.5 mg QD • Glatiramer acetate SC 20 mg QD
BEYOND	O'Connor (2009) [5]	NCT00099502	<ul style="list-style-type: none"> • IFNB-1b SC 250 µg Q2D • Glatiramer acetate SC 20 mg QD
Boiko et al. (2018)	Boiko (2018) [6]	NCT02753088	<ul style="list-style-type: none"> • Glatiramer acetate SC 20 mg QD • Glatiramer acetate SC 20 mg QD (Timexon) • Placebo
Bornstein et al. (1987)	Bornstein (1987) [7]	Not available	<ul style="list-style-type: none"> • Glatiramer acetate SC 20 mg QD • Placebo
BRAVO	Vollmer (2014) [8]	NCT00605215	<ul style="list-style-type: none"> • IFNB-1a IM 30 µg QW • Placebo
Calabrese et al. (2012)	Calabrese (2012) [9]	Not available	<ul style="list-style-type: none"> • IFNB-1a SC 44 µg TIW • IFNB-1a IM 30 µg QW • Glatiramer acetate SC 20 mg QD
CAMMS223	CAMMS223 Trial Investigators (2008) [10]	NCT00050778	<ul style="list-style-type: none"> • Alemtuzumab IV 12 mg (1 course every 12 months) • IFNB-1a SC 44 µg TIW
CARE-MS I	Cohen (2012) [11]	NCT00530348	<ul style="list-style-type: none"> • Alemtuzumab IV 12 mg (1 course every 12 months) • IFNB-1a SC 44 µg TIW
CARE-MS II	Coles (2012) [12]	NCT00548405	<ul style="list-style-type: none"> • Alemtuzumab IV 12 mg (1 course every 12 months) • IFNB-1a SC 44 µg TIW
CLARITY	Giovannoni (2010) [13]	NCT00213135	<ul style="list-style-type: none"> • Cladribine PO 3.5 mg/kg (2 courses over 2 years) • Placebo
CombiRx	Lublin (2013) [14]	NCT00211887	<ul style="list-style-type: none"> • IFNB-1a IM 30 µg QW • Glatiramer acetate SC 20 mg QD
CONFIRM	Fox (2012) [15]	NCT00451451	<ul style="list-style-type: none"> • Dimethyl fumarate PO 240 mg BID • Glatiramer acetate SC 20 mg QD • Placebo
Copolymer 1 MS trial	Johnson (1995) [16]	Not available	<ul style="list-style-type: none"> • Glatiramer acetate SC 20 mg QD • Placebo
DEFINE	Gold (2012) [17]	NCT00420212	<ul style="list-style-type: none"> • Dimethyl fumarate PO 240 mg BID • Placebo
Etemadifar et al. (2006)	Etemadifar (2006) [18]	Not available	<ul style="list-style-type: none"> • IFNB-1a SC 44 µg TIW • IFNB-1a IM 30 µg QW • IFNB-1b SC 250 µg Q2D
EVIDENCE	Panitch (2002) [19]	Not available	<ul style="list-style-type: none"> • IFNB-1a SC 44 µg TIW • IFNB-1a IM 30 µg QW
FREEDOMS	Kappos (2010) [20]	NCT00289978	<ul style="list-style-type: none"> • Fingolimod PO 0.5 mg QD • Placebo
FREEDOMS II	Calabresi (2014) [21]	NCT00355134	<ul style="list-style-type: none"> • Fingolimod PO 0.5 mg QD • Placebo
GALA	Khan (2013) [22]	NCT01067521	<ul style="list-style-type: none"> • Glatiramer acetate SC 40 mg TIW • Placebo
GOLDEN	Comi (2017) [23]	NCT01333501	<ul style="list-style-type: none"> • Fingolimod 0.5 mg PO QD • IFNB-1b SC 250 µg Q2D

Trial Name	Pivotal Publication Author (Year)	NCT Number	Relevant Treatments
IFNB MS	IFNB Multiple Sclerosis Study Group (1993) [24]	Not available	<ul style="list-style-type: none"> • IFNB-1b SC 250 µg Q2D • Placebo
INCOMIN	Durelli (2002) [25]	Not available	<ul style="list-style-type: none"> • IFNB-1a IM 30 µg QW • IFNB-1b SC 250 µg Q2D
MSCRG	Jacobs (1996) [26]	Not available	<ul style="list-style-type: none"> • IFNB-1a IM 30 µg QW • Placebo
OPERA I	Hauser (2017) [27]	NCT01247324	<ul style="list-style-type: none"> • Ocrelizumab IV 600 mg Q24W • IFNB-1a SC 44 µg TIW
OPERA II	Hauser (2017) [27]	NCT01412333	<ul style="list-style-type: none"> • Ocrelizumab IV 600 mg Q24W • IFNB-1a SC 44 µg TIW
OPTIMUM	Kappos (2021) [28]	NCT02425644	<ul style="list-style-type: none"> • Ponesimod PO 20 mg QD • Teriflunomide PO 14 mg QD
PRISMS	Ebers (1998) [29]	Not available	<ul style="list-style-type: none"> • IFNB-1a SC 22 µg TIW • IFNB-1a SC 44 µg TIW • Placebo
RADIANCE-B	Cohen (2019) [30]	NCT02047734	<ul style="list-style-type: none"> • Ozanimod PO 1.0 mg QD • IFNB-1a IM 30 µg QW
REGARD	Mikol (2008) [31]	NCT00078338	<ul style="list-style-type: none"> • IFNB-1a SC 44 µg TIW • Glatiramer acetate SC 20 mg QD
Stepien et al. (2013)	Stepien (2013) [32]	Not available	<ul style="list-style-type: none"> • IFNB-1a IM 30 µg QW • IFNB-1b SC 250 µg Q2D
SUNBEAM	Comi (2019) [33]	NCT02294058	<ul style="list-style-type: none"> • Ozanimod PO 1.0 mg QD • IFNB-1a IM 30 µg QW
TEMPO	O'Connor (2011) [34]	NCT00134563	<ul style="list-style-type: none"> • Teriflunomide PO 7 mg QD • Teriflunomide PO 14 mg QD • Placebo
TENERE	Vermersch (2014) [35]	NCT00883337	<ul style="list-style-type: none"> • Teriflunomide PO 7 mg QD • Teriflunomide PO 14 mg QD • IFNB-1a SC 44 µg TIW
TOWER	Confavreux (2014) [36]	NCT00751881	<ul style="list-style-type: none"> • Teriflunomide PO 7 mg QD • Teriflunomide PO 14 mg QD • Placebo
TRANSFORMS	Cohen (2010) [37]	NCT00340834	<ul style="list-style-type: none"> • Fingolimod PO 0.5 mg QD • IFNB-1a IM 30 µg QW
ULTIMATE I	Steinman (2022) [38, 39]	NCT03277261	<ul style="list-style-type: none"> • Teriflunomide PO 14 mg QD • Ublituximab IV 450 mg Q24W
ULTIMATE II	Steinman (2022) [38, 39]	NCT03277248	<ul style="list-style-type: none"> • Teriflunomide PO 14 mg QD • Ublituximab IV 450 mg Q24W

Note: Some trials included additional treatment arms not listed here that were outside of the scope of the eligibility criteria for this study.

BID twice a day, *IFNB* interferon beta, *IM* intramuscular, *IV* intravenous, *PO* oral, *Q24W* once every 24 weeks, *Q2D* once every other day, *Q2W* once every two weeks, *Q4W* once every four weeks, *QD* once a day, *QW* once a week, *SC* subcutaneous, *TIW* three times a week.

Table A.10. Risk of bias assessment results for included trials.

Trial Name	A	B	C	D	E	F	G
ADVANCE	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
AFFIRM	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
ASCLEPIOS I	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
ASCLEPIOS II	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
ASSESS	Low risk	High risk	Low risk	High risk	Low risk	Low risk	Low risk
BEYOND	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk
Boiko et al. (2018)	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk
Bornstein et al. (1987)	Unclear	Unclear	Low risk	Low risk	Unclear	Low risk	Low risk
BRAVO	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
Calabrese et al. (2012)	Low risk	Unclear	Unclear	Unclear	Unclear	Low risk	Unclear
CAMMS223	Low risk	Unclear	Low risk	High risk	Low risk	Low risk	Low risk
CARE-MS I	Low risk	High risk	Low risk	High risk	Low risk	Low risk	Low risk
CARE-MS II	Low risk	High risk	Low risk	High risk	Low risk	Low risk	Low risk
CLARITY	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
CombiRx	Low risk	Unclear	High risk	Low risk	Low risk	Low risk	Low risk
CONFIRM	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Copolymer 1 MS trial	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk
DEFINE	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Etemadifar et al. (2006)	Low risk	Unclear	Low risk	Low risk	Unclear	Low risk	Low risk
EVIDENCE	Low risk	Unclear	Unclear	Unclear	Low risk	Low risk	Low risk
FREEDOMS	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
FREEDOMS II	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
GALA	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
GOLDEN	Low risk	High risk	Low risk	High risk	Low risk	Low risk	Low risk
IFNB MS	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
INCOMIN	Low risk	Low risk	Low risk	High risk	Low risk	Low risk	Low risk
MSCRG	Low risk	Low risk	Low risk	Low risk	Unclear	Low risk	Low risk
OPERA I	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
OPERA II	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
OPTIMUM	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
PRISMS	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
RADIANCE-B	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
REGARD	Low risk	Low risk	Low risk	High risk	Low risk	Low risk	Low risk
Stepien et al. (2013)	Unclear	Unclear	Low risk	High risk	Unclear	Low risk	Unclear
SUNBEAM	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
TEMPO	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk
TENERE	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk
TOWER	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
TRANSFORMS	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
ULTIMATE I	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
ULTIMATE II	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

Risk of Bias Questions: A: Was randomization carried out appropriately?; B: Was the concealment of treatment allocation adequate?; C: Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?; D: Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?; E: Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?; F: Is there any evidence to suggest that the authors measured more outcomes than they reported?; G: Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?

NA not available.

Table A.11. List of trials excluded from the network meta-analysis.

Trial Name	Reason for Exclusion
ALLEGRO [40]	Intervention not of interest
APEX [41]	Study duration <48 weeks
APOLITOS [42]	Study duration <48 weeks
ASCEND [43]	Population not of interest (SPMS)
Barbero et al. (2004) [44]	Not RCT
Bastianello et al. (1994) [45]	Intervention not of interest
BCD-054 [46]	Study duration <48 weeks
BECOME [47]	Includes patients with CIS
Boiko et al. (2018) [48]	Did not report ARR or CDP, and ARR could not be calculated
BOLD [49]	Intervention not of interest
Cheshmavar et al. (2021) [50]	Population not of interest (SPMS)
CONCERTO [51]	Intervention not of interest
CONFIDENCE [52]	Study duration <48 weeks
De Castro et al. (1995) [53]	Intervention not of interest
EMPhASIS [54]	Study duration <48 weeks
EU SPMS [55]	Population not of interest (SPMS)
European-Canadian GA [56]	Study duration <48 weeks
EXPAND [57]	Population not of interest (SPMS)
GATE [58]	Study duration <48 weeks
GIMN [59]	Study duration <48 weeks
Gisleskog et al. (2021) [60]	Study duration <48 weeks
GLACIER [61]	Study duration <48 weeks
Gobbi et al. (2013) [62]	Pilot study
HERMES [63]	Intervention not of interest
IMPROVE [64]	Study duration <48 weeks
Kappos et al. (2011) [65]	Study duration <48 weeks
Knobler et al. (1993) [66]	Intervention not of interest
Kuhle et al. (2021) [67]	Study duration <48 weeks
LAQ5062 [68]	Intervention not of interest
Llufriu et al. (2014) [69]	Intervention not of interest
Millefiorini et al. (1997) [70]	Intervention not of interest
MIRROR [71]	Study duration <48 weeks
Mokhber et al. (2014) [72]	Did not report ARR or CDP, and ARR could not be calculated
Nabavi et al. (2013) [73]	Study duration <48 weeks
Nabavi et al. (2019) [74]	Did not report ARR or CDP, and ARR could not be calculated
Nafissi et al. (2012) [75]	Did not report ARR or CDP, and ARR could not be calculated
NOVA [76]	Intervention not of interest
O'Connor et al. (2006) [77]	Study duration <48 weeks
Olsson et al. (2014) [78]	Intervention not of interest
Pakdaman et al. (2018) [79]	Did not report ARR or CDP, and ARR could not be calculated
Polman et al. (2005) [80]	Intervention not of interest
REFINE [81]	Intervention not of interest
REFORMS [82]	Study duration <48 weeks
RESTORE [83]	Study duration <48 weeks
REVEAL [84]	Study closed early (median follow-up time was 39 weeks)
Saida et a. (2012) [85]	Study duration <48 weeks
Saida et al. (2017) [86]	Study duration <48 weeks
SPECTRIMS [87]	Population not of interest (SPMS only)
SYNERGY [88]	Intervention not of interest
Tran et al. (2014) [89]	Intervention not of interest
Wroe et al. (2005) [90]	Study duration <48 weeks
Ziemssen et al. (2017) [91]	Intervention not of interest

ARR annualised relapse rate, CDP confirmed disability progression, CIS clinically isolated syndrome, RCT randomised controlled trial, SPMS secondary progressive multiple sclerosis.

Appendix B Characteristics of Included Trials

Table B.1. Summary of general trial characteristics.

Trial Name	Sample Size ^a	Phase	Blinding ^b	MS Population	Trial Duration ^c
ADVANCE	1512	3	Double-blind	RRMS	104 weeks
AFFIRM	942	3	Double-blind	RRMS	104+ weeks
ASCLEPIOS I	927	3	Double-blind	RMS (94% RRMS)	130 weeks
ASCLEPIOS II	955	3	Double-blind	RMS (94% RRMS)	130 weeks
ASSESS	1064	3b	Single-blind (patients aware)	RRMS	52+ weeks
BEYOND	2244	3	Open label (IFN vs. GA)	RRMS	104+ weeks
Boiko et al. (2018)	158	3	Double-blind	RRMS	48 weeks
Bornstein et al. (1987)	50	NR	Double-blind	RRMS	104+ weeks
BRAVO	1331	3	Open label	RRMS	104 weeks
Calabrese et al. (2012)	165	4	NR	RRMS	104 weeks
CAMMS223	334	2	Open label	RRMS	156 weeks
CARE-MS I	581	3	Open label	RRMS	104 weeks
CARE-MS II	840	3	Open label	RRMS	104 weeks
CLARITY	1326	3	Double-blind	RRMS	96 weeks
CombiRx	1008	3	Double-blind	RRMS	156+ weeks
CONFIRM	1430	3	Double-blind (except vs. GA)	RRMS	104 weeks
Copolymer 1 MS trial	251	3	Double-blind	RRMS	104 weeks
DEFINE	1237	3	Double-blind	RRMS	104 weeks
Etemadifar et al. (2006)	90	3	Single-blind (patients aware)	RRMS	104 weeks
EVIDENCE	677	NR	Single-blind (patients aware)	RRMS	48 weeks
FREEDOMS	1272	3	Double-blind	RRMS	104 weeks
FREEDOMS II	1083	3	Double-blind	RRMS	104 weeks
GALA	1404	3	Double-blind	RRMS	52+ weeks
GOLDEN	157	4	Open label	RRMS	78 weeks
IFNB MS	372	NR	Double-blind	RRMS	104 weeks
INCOMIN	188	NR	Open label	RRMS	104 weeks
MSCRG	301	3	Double-blind	RMS	104 weeks
OPERA I	821	3	Double-blind	RMS	96 weeks
OPERA II	835	3	Double-blind	RMS	96 weeks
OPTIMUM	1133	3	Double-blind	RMS	108 weeks

Trial Name	Sample Size ^a	Phase	Blinding ^b	MS Population	Trial Duration ^c
PRISMS	560	NR	Double-blind	RRMS	104 weeks
RADIANCE-B	1313	3	Double-blind	RMS (98% RRMS)	104 weeks
REGARD	764	4	Open label	RRMS	96 weeks
Stepien et al. (2013)	68	NR	NR	RRMS	156 weeks
SUNBEAM	1346	3	Double-blind	RMS (98% RRMS)	52 weeks
TEMPO	1088	3	Double-blind	RMS (91% RRMS)	108 weeks
TENERE	324	3	Single-blind (patients aware)	RMS (99% RRMS)	48 weeks
TOWER	1169	3	Double-blind	RMS (97% RRMS)	48+ weeks
TRANSFORMS	1292	3	Double-blind	RRMS	52 weeks
ULTIMATE I	545	3	Double-blind	RMS (98% RRMS)	96+ weeks
ULTIMATE II	544	3	Double-blind	RMS (98% RRMS)	96+ weeks

^a Includes all treatment arms (i.e., may include treatment arms that do not match the eligibility criteria of the present study).

^b Patient and treating physician.

^c Where trial duration was reported in years or months, we converted using 1 year = 12 months = 52 weeks.

Note: For all trials, patients were randomly assigned to treatment arms and allocation was parallel (with one exception: CombiRx had a factorial allocation).

MS multiple sclerosis, *NR* not reported, *RMS* relapsing multiple sclerosis, *RRMS* relapsing-remitting multiple sclerosis.

Table B.2. Summary of patient inclusion/exclusion criteria.

Trial Name	Age (Years)	MS Phenotype	EDSS Score	Relapse/Lesion History	Recent Relapses	Disease Duration	Prior Corticosteroids	Prior Treatment Experience
ADVANCE	18-65	RRMS	0.0-5.0	At least 2 relapses in 3 years prior, with at least 1 relapse in 1 year prior	No relapse in 50 days prior	NR	Disallowed within 50 days	<ul style="list-style-type: none"> • No prior pegylated interferon beta-1a, total lymphoid radiation, cladribine, fingolimod, T-cell or T-cell receptor vaccine, or any therapeutic mAb • Prior Cytoxan or mitoxantrone: Disallowed within 1 year • Prior IFN: Disallowed within 6 months (or for >4 weeks of treatment) • Prior cyclosporin, plasma exchange, IVIG, azathioprine, mycophenylate, or methotrexate: Disallowed within 6 months • Prior treatment with another investigational drug or approved therapy for investigational use: Disallowed within 6 months • Prior Copaxone [GA]: Disallowed within 4 weeks
AFFIRM	18-50	RRMS	0.0-5.0	At least 1 relapse in 1 year prior	No relapse in 50 days prior	NR	NR	<ul style="list-style-type: none"> • Prior cyclophosphamide or mitoxantrone: Disallowed within 1 year • Prior IFN or GA: Disallowed within 6 months (or for >6 months of treatment) • Prior cyclosporine, azathioprine, methotrexate, or IVIG: Disallowed within 6 months
ASCLEPIOS 1	18-55	RMS	0.0-5.5	At least 1 relapse in 1 year prior, or at least 2 relapses in 2 years prior, or at least 1 Gd+ lesion in 1 year prior	Neurologically stable within 1 month prior	Disease duration ≤ 10 years if EDSS score ≤ 2.0	Disallowed within 30 days	<ul style="list-style-type: none"> • No prior mitoxantrone (with evidence of cardiotoxicity), alemtuzumab, lymphoid irradiation, bone marrow transplantation, other strongly immunosuppressive treatments (with effects potentially lasting over 6 months), ofatumumab, or teriflunomide (if discontinued for safety or lack of efficacy) • Prior highly immunosuppressive/chemotherapeutic medications (mitoxantrone, cyclophosphamide, cladribine), B-cell targeted therapies such as rituximab, ocrelizumab, or laquinimod: Disallowed within 2 years • Prior mildly to moderately immunosuppressive/chemotherapeutic medications (eg, azathioprine, methotrexate): Disallowed within 6 months • Prior daclizumab: Disallowed within 4 months • Prior teriflunomide: Disallowed within 3.5 months or 1 month if patient undergoes an accelerated elimination procedure and has documented teriflunomide plasma level below 0.02 mg/L • Prior IVIG, fingolimod, or natalizumab: Disallowed within 2 months • Prior dimethyl fumarate: Disallowed within 1 month • Prior use of other investigational drugs: Disallowed within 30 days, 5 elimination half-lives, or until the expected pharmacodynamic effect has returned to baseline, whichever is longer

Trial Name	Age (Years)	MS Phenotype	EDSS Score	Relapse/Lesion History	Recent Relapses	Disease Duration	Prior Corticosteroids	Prior Treatment Experience
ASCLEPIOS II	18-55	RMS	0.0-5.5	At least 1 relapse in 1 year prior, or at least 2 relapses in 2 years prior, or at least 1 Gd+ lesion in 1 year prior	Neurologically stable within 1 month prior	Disease duration ≤ 10 years if EDSS score ≤ 2.0	Disallowed within 30 days	<ul style="list-style-type: none"> No prior mitoxantrone (with evidence of cardiotoxicity), alemtuzumab, lymphoid irradiation, bone marrow transplantation, other strongly immunosuppressive treatments (with effects potentially lasting over 6 months), ofatumumab, or teriflunomide (if discontinued for safety or lack of efficacy) Prior highly immunosuppressive/chemotherapeutic medications (mitoxantrone, cyclophosphamide, cladribine), B-cell targeted therapies such as rituximab, ocrelizumab, or laquinimod: Disallowed within 2 years Prior mildly to moderately immunosuppressive/chemotherapeutic medications (eg, azathioprine, methotrexate): Disallowed within 6 months Prior daclizumab: Disallowed within 4 months Prior teriflunomide: Disallowed within 3.5 months or 1 month if patient undergoes an accelerated elimination procedure and has documented teriflunomide plasma level below 0.02 mg/L Prior IVIG, fingolimod, or natalizumab: Disallowed within 2 months Prior dimethyl fumarate: Disallowed within 1 month Prior use of other investigational drugs: Disallowed within 30 days, 5 elimination half-lives, or until the expected pharmacodynamic effect has returned to baseline, whichever is longer
ASSESS	18-65	RRMS	0.0-6.0	At least 1 relapse in 1 year prior, or at least 2 relapses in 2 years prior	No relapse in 30 days prior	NR	Disallowed within 30 days	<ul style="list-style-type: none"> No prior total lymphoid irradiation or bone marrow transplantation Prior lymphocyte-depleting therapies (e.g., rituximab, alemtuzumab, ofatumumab, ocrelizumab, or cladribine): Disallowed within 1 year Prior mitoxantrone: Disallowed within 6 months Prior immunosuppressive/chemotherapeutic medications (e.g., azathioprine, cyclophosphamide, methotrexate): Disallowed within 6 months Prior teriflunomide: Disallowed within 3.5 months, except if active washout (with either cholestyramine or activated charcoal) was done (in that case, plasma levels are required to be measured and be below 0.02 mg/L before randomization) Prior natalizumab: Disallowed within 2 months Prior high-dose IVIG: Disallowed within 4 weeks
BEYOND	18-55	RRMS	0.0-5.0	At least 1 relapse in 1 year prior	NR	NR	NR	<ul style="list-style-type: none"> No prior MS treatment or previous trials of drugs for MS

Trial Name	Age (Years)	MS Phenotype	EDSS Score	Relapse/Lesion History	Recent Relapses	Disease Duration	Prior Corticosteroids	Prior Treatment Experience
Boiko et al. (2018)	18-55	RRMS	0.0-5.5	At least 1 relapse in 1 year prior, or at least 1 Gd+ T1 lesion	No relapse in 4 weeks prior	Disease duration >1 year	Disallowed within 30 days	<ul style="list-style-type: none"> No prior IFN beta-1a, IFN beta-1b, GA, azathioprine, corticosteroids and immunomodulators (except for treating exacerbations), drugs and mAb, cytotoxic and/or immunosuppressive drugs Prior participation in any other clinical trial: Disallowed within 30 days
Bornstein et al. (1987)	20-35	RRMS	0.0-6.0	At least 2 relapses in 2 years prior	NR	NR	NR	NR
BRAVO	18-55	RRMS	0.0-5.5	At least 1 relapse in 1 year prior, or at least 2 relapses in 2 years prior, or at least 1 relapse in previous 1-2 years and 1 Gd+ lesion in previous 1 year	No relapse in 30 days prior	Disease duration (from first symptom) of at least 6 months	Disallowed within 30 days (disallowed within 2 months if systemic treatment of ≥ 30 consecutive days duration)	<ul style="list-style-type: none"> No prior natalizumab, laquinimod, cladribine, or any IFN beta Prior experimental drugs, investigational drugs, or immunosuppressive therapy (including mitoxantrone): Disallowed within 6 months Prior IVIG: Disallowed within 3 months Prior GA: Disallowed within 2 months
Calabrese et al. (2012)	18-55	RRMS	0.0-5.0	NR	NR	NR	NR	<ul style="list-style-type: none"> No prior treatment with immunosuppressive drugs
CAMMS223	18-50	RRMS	0.0-3.0	At least 2 clinical episodes in 2 years prior	NR	Onset of symptoms ≤ 36 months prior	NR	<ul style="list-style-type: none"> No prior DMT
CARE-MS I	18-50	RRMS	0.0-3.0	At least 2 relapses in 2 years prior, with at least 1 in 1 year prior	NR	Disease duration ≤ 5 years	NR	<ul style="list-style-type: none"> No prior MS therapy (apart from corticosteroids) No prior immunosuppressive, investigational, or mAb therapy
CARE-MS II	18-55	RRMS	0.0-5.0	At least 2 attacks in 2 years prior, with at least 1 in 1 year prior and at least 1 relapse while on IFN beta or GA after ≥ 6 months of treatment	NR	Disease duration ≤ 10 years	NR	<ul style="list-style-type: none"> No prior alemtuzumab, cytotoxic drug use, or investigational therapy Prior natalizumab, methotrexate, azathioprine, or ciclosporin: Disallowed within 6 months

Trial Name	Age (Years)	MS Phenotype	EDSS Score	Relapse/Lesion History	Recent Relapses	Disease Duration	Prior Corticosteroids	Prior Treatment Experience
CLARITY	18-65	RRMS	0.0-5.5	At least 1 relapse in 1 year prior	No relapse in 28 days prior	NR	Disallowed within 28 days	<ul style="list-style-type: none"> No more than 1 previous DMTs failed No prior cladribine, mitoxantrone, total lymphoid irradiation, myelosuppressive therapy, campath-1h, cyclophosphamide, azathioprine, methotrexate, natalizumab, or immunosuppressive therapy Prior investigational drug or experimental procedure: Disallowed within 6 months Prior DMT use: Disallowed within 3 months Prior cytokine-based therapy, IVIG, or plasmapheresis: Disallowed within 3 months
CombiRx	18-60	RRMS	0.0-5.5	At least 2 exacerbations in 3 years prior, where 1 could be an MRI change meeting 2001 McDonald criteria for dissemination in time	No acute exacerbation in 30 days prior	NR	Disallowed within 30 days	<ul style="list-style-type: none"> No prior IFN beta, GA, natalizumab, cladribine, T cell vaccine, Campath, daclizumab, rituximab, altered peptide ligand, total lymphoid irradiation, chronic systemic steroid use, or any other investigational drug unless approved by study coordinator Prior IVIG, azathioprine, methotrexate, cyclosporine, mitoxantrone, cyclophosphamide, mycophenolate, or plasma exchange: Disallowed within 12 weeks Prior 4-aminopyridines: Disallowed within 4 weeks
CONFIRM	18-55	RRMS	0.0-5.0	At least 1 relapse in 1 year prior, or at least 1 Gd+ lesion in 6 weeks prior	No relapse in 50 days prior and stabilized from previous relapse	NR	Disallowed within 50 days	<ul style="list-style-type: none"> No prior FUMADERM®, BG-12, GA, total lymphoid irradiation, cladribine, or T-cell or T-cell receptor vaccination Prior mitoxantrone or cyclophosphamide: Disallowed within 1 year Prior cyclosporine, azathioprine, methotrexate, natalizumab, IVIG, plasmapheresis, or cytapheresis: Disallowed within 6 months Prior IFN alpha or IFN beta: Disallowed within 3 months
Copolymer 1 MS trial	18-45	RRMS	0.0-5.0	At least 2 relapses in 2 year prior, with onset of 1st relapse at least 1 year prior	No relapse in 30 days prior	NR	Disallowed within 30 days	<ul style="list-style-type: none"> No prior GA, immunosuppressive therapy with cytotoxic chemotherapy (azathioprine, cyclophosphamide, or cyclosporine), or lymphoid irradiation
DEFINE	18-55	RRMS	0.0-5.0	At least 1 relapse in 1 year prior, or at least 1 Gd+ lesion in 6 weeks prior	No relapse in 50 days prior and stabilized from previous relapse	NR	Disallowed within 50 days	<ul style="list-style-type: none"> No prior Fumaderm®, BG-12, total lymphoid irradiation, cladribine, T-cell or T-cell receptor vaccination, or any therapeutic mAb except for natalizumab Prior mitoxantrone or cyclophosphamide: Disallowed within 1 year Prior cyclosporine, azathioprine, methotrexate, natalizumab, mycophenolate mofetil, IVIG, plasmapheresis, cytapheresis, or another investigational drug or approved therapy for investigational use: Disallowed within 6 months Prior subcutaneous or oral GA, IFN alpha, or IFN beta: Disallowed within 3 months

Trial Name	Age (Years)	MS Phenotype	EDSS Score	Relapse/Lesion History	Recent Relapses	Disease Duration	Prior Corticosteroids	Prior Treatment Experience
Etemadifar et al. (2006)	15-50	RRMS	0.0-5.0	At least 2 exacerbations in 2 years prior	NR	NR	NR	NR
EVIDENCE	18-55	RRMS	0.0-5.5	At least 2 exacerbations in 2 years prior	NR	NR	NR	<ul style="list-style-type: none"> • No prior IFN, cladribine, or total lymphoid irradiation • Prior other immunomodulatory agents: Disallowed within 12 months • Prior IVIG: Disallowed within 6 months • Prior GA or cytokine therapy: Disallowed within 3 months
FREEDOMS	18-55	RRMS	0.0-5.5	At least 1 relapse in 1 year prior, or at least 2 relapses in 2 years prior	No relapse in 30 days prior	NR	Disallowed within 30 days	<ul style="list-style-type: none"> • Prior IFN or GA: Disallowed within 3 months
FREEDOMS II	18-55	RRMS	0.0-5.5	At least 1 relapse in 1 year prior, or at least 2 relapses in 2 years prior	No relapse in 30 days prior	NR	Disallowed within 1 month	<ul style="list-style-type: none"> • No prior total lymphoid irradiation, bone marrow transplantation, cladribine, cyclophosphamide, mitoxantrone, or fingolimod • Prior natalizumab: Disallowed within 6 months • Prior immunosuppressive medications such as azathioprine or methotrexate: Disallowed within 6 months • Prior immunoglobulins and/or mAb: Disallowed within 6 months • Prior participation in any clinical research study evaluating another investigational drug or therapy: Disallowed within 6 months • Prior IFN-beta or GA: Disallowed within 3 months
GALA	18-55	RRMS	0.0-5.5	At least 1 relapse in 1 year prior, or at least 2 relapses in 2 years prior, or at least 1 relapse in previous 1-2 years and 1 Gd+ lesion in previous 1 year	No relapse in 30 days prior	NR	Disallowed within 6 months if chronic [>30 days] systemic corticosteroid	<ul style="list-style-type: none"> • No prior GA or any other glatiramide • Prior cladribine, natalizumab, or any other monoclonal antibody treatment: Disallowed within 2 years • Prior immunosuppressive agents, including mitoxantrone and fingolimod, or cytotoxic agents: Disallowed within 6 months • Prior immunomodulators, including IFN beta and IVIG: Disallowed within 2 months
GOLDEN	18-60	RRMS	0.0-5.0	At least 1 relapse in 1 year prior, or at least 2 relapses in 2 years prior if at least 1 Gd+ lesion on MRI performed in previous 6 months	No relapse in 30 days prior	NR	Disallowed within 1 month	<ul style="list-style-type: none"> • Unsatisfactory response with multi-weekly IFN beta-1a/b • No prior cladribine, cyclophosphamide, mitoxantrone, total lymphoid irradiation, or bone marrow transplantation • Prior immunosuppressive medications such as azathioprine or methotrexate: Disallowed within 3 months • Immunoglobulins and/or mAb: Disallowed within 3 months • Participation in any clinical research study: Disallowed within 6 months

Trial Name	Age (Years)	MS Phenotype	EDSS Score	Relapse/Lesion History	Recent Relapses	Disease Duration	Prior Corticosteroids	Prior Treatment Experience
IFNB MS	18-50	RRMS	0.0-5.5	At least 2 acute exacerbations in 2 years prior	No relapse in 30 days prior	Disease duration ≥ 1 year	Disallowed within 30 days	<ul style="list-style-type: none"> No prior azathioprine or cyclophosphamide
INCOMIN	18-50	RRMS	1.0-3.5	At least 2 relapses in 2 years prior	No relapse in 30 days prior	NR	Disallowed within 30 days	<ul style="list-style-type: none"> No prior immunosuppressive or immunomodulatory drugs except corticosteroids
MSCRG	18-55	RMS	1.0-3.5	At least 2 relapses in 3 years prior	No exacerbations in 2 months prior	Disease duration ≥ 1 year	Disallowed within 2 months	<ul style="list-style-type: none"> No prior immunosuppressive drugs or IFN
OPERA I	18-55	RMS	0.0-5.5	At least 2 relapses in 2 years prior, or at least 1 relapse in 1 year prior	No neurologic worsening in 30 days prior	Disease duration ≤ 10 years if EDSS score ≤ 2.0	NR	<ul style="list-style-type: none"> No prior B-cell-targeted therapies (i.e., rituximab, ocrelizumab, atacicept, belimumab, or ofatumumab), alemtuzumab, anti-CD4, cladribine, mitoxantrone, daclizumab, teriflunomide, laquinimod, total body irradiation, or bone marrow transplantation Prior cyclophosphamide, azathioprine, mycophenolate mofetil, cyclosporine, methotrexate, or natalizumab: Disallowed within 24 months (natalizumab allowed only if duration was < 1 year) Prior treatment with any investigational agent, fingolimod, or dimethyl fumarate: Disallowed within 6 months Prior IVIG: Disallowed within 12 weeks
OPERA II	18-55	RMS	0.0-5.5	At least 2 relapses in 2 years prior, or at least 1 relapse in 1 year prior	No neurologic worsening in 30 days prior	Disease duration ≤ 10 years if EDSS score ≤ 2.0	NR	<ul style="list-style-type: none"> No prior B-cell-targeted therapies (i.e., rituximab, ocrelizumab, atacicept, belimumab, or ofatumumab), alemtuzumab, anti-CD4, cladribine, mitoxantrone, daclizumab, teriflunomide, laquinimod, total body irradiation, or bone marrow transplantation Prior cyclophosphamide, azathioprine, mycophenolate mofetil, cyclosporine, methotrexate, or natalizumab: Disallowed within 24 months (natalizumab allowed only if duration was < 1 year) Prior treatment with any investigational agent, fingolimod, or dimethyl fumarate: Disallowed within 6 months Prior IVIG: Disallowed within 12 weeks

Trial Name	Age (Years)	MS Phenotype	EDSS Score	Relapse/Lesion History	Recent Relapses	Disease Duration	Prior Corticosteroids	Prior Treatment Experience
OPTIMUM	18-55	RMS	0.0-5.5	At least 1 relapse in 1 year prior, or at least 2 relapses in 2 years prior, or at least 1 Gd+ lesion on MRI performed in previous 6 months	No relapse in 30 days prior	NR	Disallowed within 30 days	<ul style="list-style-type: none"> • No prior alemtuzumab; mitoxantrone, leflunomide, or teriflunomide; fingolimod; ponesimod; other investigational S1P modulators; or stem-cell transplantation • Prior lymphocyte-depleting biological agents such as rituximab or ocrelizumab, or cladribine: Disallowed within 24 months • Prior azathioprine, methotrexate, or cyclophosphamide; natalizumab; other systemic immunosuppressive treatment (e.g., cyclosporine, sirolimus, mycophenolic acid); or non-lymphocyte-depleting experimental biological agents (e.g., daclizumab): Disallowed within 180 days • Prior plasmapheresis, cytapapheresis; intravenous immunoglobulin; or treatment with an investigational drug (within 90 days or five half-lives of the drug, whichever is longer), except biological agents: Disallowed within 90 days • Prior dimethyl fumarate: Disallowed within 30 days • Prior beta-blockers, diltiazem, verapamil, digoxin or any other anti-arrhythmic or HR lowering systemic therapy; or cholestyramine or activated charcoal: Disallowed within 15 days • Prior IFN beta-1a, IFN beta-1b, or GA: Disallowed within 7 days
PRISMS	NR (adults)	RRMS	0.0-5.0	At least 2 relapses in 2 years prior	NR	Disease duration ≥ 1 year	NR	<ul style="list-style-type: none"> • No prior IFN, lymphoid irradiation, or cyclophosphamide • Prior treatment with other immunosuppressive or immunomodulatory drugs: Disallowed within 12 months

Trial Name	Age (Years)	MS Phenotype	EDSS Score	Relapse/Lesion History	Recent Relapses	Disease Duration	Prior Corticosteroids	Prior Treatment Experience
RADIANCE-B	18-55	RMS	0.0-5.0	At least 1 relapse in 1 year prior, or at least 1 relapse in 2 years prior and at least 1 Gd+ lesion in 1 year prior	No relapse in 30 days prior	Disease duration ≤ 15 years if EDSS score ≤ 2.0	Disallowed within 30 days	<ul style="list-style-type: none"> No prior lymphocyte-depleting therapies (e.g., alemtuzumab, anti-CD4, cladribine, rituximab, ocrelizumab, cyclophosphamide, mitoxantrone, total body irradiation, bone marrow transplantation), lymphocyte trafficking blockers (e.g., natalizumab, fingolimod, other sphingosine 1-phosphate receptor 1 agonists), or medications with a known impact on the cardiac conduction system Prior other immunosuppressant agents such as azathioprine, cyclosporine, methotrexate, or mycophenolate, or use of any investigational agent: Disallowed within 6 months Prior IVIG or plasmapheresis, or other disease modifying therapies (e.g., dimethyl fumarate, teriflunomide, daclizumab, laquinimod): Disallowed within 3 months Prior therapies that were not allowed based on cytochrome P450 3A4 (CYP3A4) metabolism: Disallowed within 4 weeks Prior non-lymphocyte-depleting DMTs (e.g., GA, IFN): Disallowed from signing of informed consent
REGARD	18-60	RRMS	0.0-5.5	At least 1 attack in 1 year prior	Stable or neurologically improving during prior 4 weeks	NR	Disallowed within 4 weeks	<ul style="list-style-type: none"> No prior IFN beta, GA, cladribine, or total lymphoid irradiation Prior immunosuppressant use: Disallowed within 12 months Prior IVIG: Disallowed within 6 months Prior treatment with any other investigational drug or taking part in any experimental procedure: Disallowed within 6 months Prior cytokine or anticytokine therapy: Disallowed within 3 months Prior plasma exchange: Disallowed within 3 months
Stepien et al. (2013)	NR (adults)	RRMS	0.0-6.5	NR	NR	NR	Disallowed within 4 weeks	<ul style="list-style-type: none"> No prior IFN beta or other immunomodulatory drugs

Trial Name	Age (Years)	MS Phenotype	EDSS Score	Relapse/Lesion History	Recent Relapses	Disease Duration	Prior Corticosteroids	Prior Treatment Experience
SUNBEAM	18-55	RMS	0.0-5.0	At least 1 relapse in 1 year prior, or at least 1 relapse in 2 years prior and at least 1 Gd+ lesion in 1 year prior	No relapse in 30 days prior	Disease duration ≤ 15 years if EDSS score ≤ 2.0	Disallowed within 30 days	<ul style="list-style-type: none"> No prior lymphocyte-depleting therapies (e.g., alemtuzumab, anti-CD4, cladribine, rituximab, ocrelizumab, cyclophosphamide, mitoxantrone, total body irradiation, bone marrow transplantation), lymphocyte trafficking blockers (e.g., natalizumab, fingolimod, other sphingosine 1-phosphate receptor 1 agonists), or medications with a known impact on the cardiac conduction system Prior other immunosuppressant agents such as azathioprine, cyclosporine, methotrexate, or mycophenolate, or use of any investigational agent: Disallowed within 6 months Prior IVIG or plasmapheresis, or other disease modifying therapies (e.g., dimethyl fumarate, teriflunomide, daclizumab, laquinimod): Disallowed within 3 months Prior therapies that were not allowed based on cytochrome P450 3A4 (CYP3A4) metabolism: Disallowed within 4 weeks Prior non-lymphocyte-depleting DMTs (e.g., GA, IFN): Disallowed from signing of informed consent
TEMSO	18-55	RMS	0.0-5.5	At least 2 relapses in 2 years prior, or at least 1 relapse in 1 year prior	No relapse in 60 days prior, stable for 30 days prior	NR	Disallowed within 30 days	<ul style="list-style-type: none"> No prior cladribine, mitoxantrone, or other immunosuppressant agents such as azathioprine, cyclophosphamide, cyclosporin, methotrexate or mycophenolate
TENERE	≥ 18	RMS	0.0-5.5	NR	No relapse in 30 days prior	NR	Disallowed within 2 weeks	<ul style="list-style-type: none"> No prior subcutaneous IFN beta-1a, teriflunomide, leflunomide, natalizumab, cladribine, mitoxantrone, or other immunosuppressants Prior investigational agents: Disallowed within 6 months Prior other IFN, GA, IVIG, or cytokine therapy: Disallowed within 3 months
TOWER	18-55	RMS	0.0-5.5	At least 1 relapse in 1 year prior, or at least 2 relapses in 2 years prior	No relapse in 30 days prior	NR	Disallowed within 2 weeks	<ul style="list-style-type: none"> No prior natalizumab or other immunosuppressive agents, teriflunomide, leflunomide, cladribine, mitoxantrone, or other immunosuppressant agents such as azathioprine, cyclophosphamide, cyclosporin, methotrexate or mycophenolate Prior use of any investigational drug: Disallowed within 6 months Prior cytokine therapy, IVIG, IFN beta, or GA: Disallowed within 3 months
TRANSFORMS	18-55	RRMS	0.0-5.5	At least 1 relapse in 1 year prior, or at least 2 relapses in 2 years prior	No relapse in 30 days prior	NR	Disallowed within 30 days	NR

Trial Name	Age (Years)	MS Phenotype	EDSS Score	Relapse/Lesion History	Recent Relapses	Disease Duration	Prior Corticosteroids	Prior Treatment Experience
ULTIMATE I	18-55	RMS	0.0-5.5	At least 1 relapse in 1 year prior, or at least 2 relapses in 2 years prior, or at least 1 Gd+ lesion on MRI scan during 1 year prior	Neurologically stable within 30 days	Disease duration <15 years if EDSS score \leq 2.0	NR	<ul style="list-style-type: none"> • No prior anti-CD20 or other B cell directed treatment, alemtuzumab, natalizumab, teriflunomide, leflunomide, or stem cell transplantation • Cladribine: Disallowed within 24 months • Daclizumab, azathioprine, methotrexate, or cyclophosphamide: Disallowed within 6 months • Fingolimod, or experimental S1P modulators, IVIG, and plasmapheresis: Disallowed within 90 days • Glatiramer acetate, interferons, dimethyl fumarate, laquinimod or glucocorticoids: Disallowed within 30 days
ULTIMATE II	18-55	RMS	0.0-5.5	At least 1 relapse in 1 year prior, or at least 2 relapses in 2 years prior, or at least 1 Gd+ lesion on MRI scan during 1 year prior	Neurologically stable within 30 days	Disease duration <15 years if EDSS score \leq 2.0	NR	<ul style="list-style-type: none"> • No prior anti-CD20 or other B cell directed treatment, alemtuzumab, natalizumab, teriflunomide, leflunomide, or stem cell transplantation • Cladribine: Disallowed within 24 months • Daclizumab, azathioprine, methotrexate, or cyclophosphamide: Disallowed within 6 months • Fingolimod, or experimental S1P modulators, IVIG, and plasmapheresis: Disallowed within 90 days • Glatiramer acetate, interferons, dimethyl fumarate, laquinimod or glucocorticoids: Disallowed within 30 days

DMT disease-modifying therapy, *EDSS* Expanded Disability Status Scale, *GA* glatiramer acetate, *Gd+* gadolinium enhancing, *IFN* interferon, *IVIG* intravenous immunoglobulin, *mAb* monoclonal antibody, *MRI* magnetic resonance imaging, *NR* not reported, *RMS* relapsing multiple sclerosis, *RRMS* relapsing-remitting multiple sclerosis.

Table B.3. Summary of baseline patient characteristics.

Trial Name	Treatment	Sample Size	Baseline Characteristics ^a									
			Age (years)	EDSS Score	Female (%)	Previous DMT Experience (%)	Time Since First MS Symptoms (years)	Time Since MS Diagnosis (years)	Relapses Within Previous 2 Years	Relapses Within Previous 1 Year	Number of Gd+ Lesions	Volume of T2 Lesions (cm ³)
ADVANCE	PBO	500	36.3	2.4	72%	17% ^b	6.3	3.5	NR	1.6	1.6	NR
	PEG	512	36.9	2.5	71%	17% ^b	6.9	4.0	NR	1.6	1.2	NR
AFFIRM	PBO	315	36.7	2.3	67%	NR	NR	NR	NR	1.5	2.0	NR
	NAT	627	35.6	2.3	72%	NR	NR	NR	NR	1.5	2.2	NR
ASCLEPIOS I	TER 14 mg	462	37.8	2.9	69%	61%	8.2	5.6	NR	1.3	1.2	13.1
	OMB	465	38.9	3.0	68%	59%	8.4	5.8	NR	1.2	1.7	13.2
ASCLEPIOS II	TER 14 mg	474	38.2	2.9	67%	62%	8.2	5.5	NR	1.3	1.5	12.0
	OMB	481	38.0	2.9	66%	60%	8.2	5.6	NR	1.3	1.6	14.3
ASSESS	GA 20 mg	342	39.6	2.7	74%	NR	7.5	4.7	2.2	1.4	1.6	8.8
	FIN	352	40.3	2.7	75%	NR	7.4	4.3	2.2	1.4	1.7	10.3
BEYOND	IFNB-1b SC	897	35.8	2.4	70%	NR	NR	5.3	NR	1.6	2.3	9.3
	GA 20 mg	448	35.2	2.3	68%	NR	NR	5.1	NR	1.6	1.8	9.2
Boiko et al. (2018)	PBO	28	NR	NR	NR	NR	5.6	NR	NR	1.2	1.9	4.0
	GA 20 mg	61	NR	NR	NR	NR	5.0	NR	NR	1.3	1.5	4.1
	GA 20 mg (Timexon)	61	NR	NR	NR	NR	5.6	NR	NR	1.3	2.0	6.2
Bornstein et al. (1987)	PBO	23	31.1	3.1	57%	NR	NR	6.4	3.9	NR	NR	NR
	GA 20 mg	25	30.0	2.9	56%	NR	NR	4.9	3.8	NR	NR	NR
BRAVO	PBO	450	NR	NR	71%	6%	NR	NR	NR	NR	NR	NR
	IFNB-1a IM	447	NR	NR	69%	9%	NR	NR	NR	NR	NR	NR
Calabrese et al. (2012)	IFNB-1a IM	47	34.8	1.9	68%	NR	NR	5.3	NR	1.2	NR	NR
	IFNB-1a SC 44 µg	46	35.9	1.9	70%	NR	NR	5.7	NR	1.2	NR	NR
	GA 20 mg	48	38.9	2.1	73%	NR	NR	5.5	NR	1.3	NR	NR
CAMMS223	IFNB-1a SC 44 µg	111	32.8	1.9	64%	NR	NR	NR	NR	NR	NR	15.8
	ALE	112	31.9	1.9	64%	NR	NR	NR	NR	NR	NR	17.2
CARE-MS I	IFNB-1a SC 44 µg	187	33.2	2.0	65%	0%	2.0	NR	NR	1.8	2.2	7.3
	ALE	376	33.0	2.0	65%	0%	2.1	NR	NR	1.8	2.3	7.4
CARE-MS II	IFNB-1a SC 44 µg	202	35.8	2.7	65%	100%	4.7	NR	NR	1.5	2.1	9.0
	ALE	426	34.8	2.7	66%	100%	4.5	NR	NR	1.7	2.3	9.9
CLARITY	PBO	437	38.7	2.9	66%	32%	8.9	NR	NR	NR	0.8	14.3
	CLA	433	37.9	2.8	69%	26%	7.9	NR	NR	NR	1.0	14.8
CombiRx	IFNB-1a IM	250	37.6	2.0	69%	NR	NR	1.4	NR	1.7	4.1	10.1
	GA 20 mg	259	39.0	1.9	71%	NR	NR	1.0	NR	1.6	4.6	11.0
CONFIRM	PBO	363	36.9	2.6	69%	31%	NR	4.8	NR	1.4	2.7	14.6
	GA 20 mg	350	36.7	2.6	71%	29%	NR	4.4	NR	1.4	2.4	13.8
	DMF	359	37.8	2.6	68%	28%	NR	4.9	NR	1.3	2.7	13.9
Copolymer 1 MS trial	PBO	126	34.3	2.4	76%	NR	NR	6.6	2.9	NR	NR	NR
	GA 20 mg	125	34.6	2.8	70%	NR	NR	7.3	2.9	NR	NR	NR

Trial Name	Treatment	Sample Size	Baseline Characteristics ^a									
			Age (years)	EDSS Score	Female (%)	Previous DMT Experience (%)	Time Since First MS Symptoms (years)	Time Since MS Diagnosis (years)	Relapses Within Previous 2 Years	Relapses Within Previous 1 Year	Number of Gd+ Lesions	Volume of T2 Lesions (cm ³)
DEFINE	PBO	408	38.5	2.5	75%	42%	NR	5.8	NR	1.3	1.6	NR
	DMF	410	38.1	2.4	72%	40%	NR	5.6	NR	1.3	1.2	NR
Etemadifar et al. (2006)	INFB-1b SC	30	NR	1.9	70%	NR	NR	3.7	NR	2.2	NR	NR
	IFNB-1a IM	30	NR	1.9	80%	NR	NR	2.9	NR	2.0	NR	NR
	IFNB-1a SC 44 µg	30	NR	2.1	77%	NR	NR	3.0	NR	2.4	NR	NR
EVIDENCE	IFNB-1a IM	338	37.4	2.4	74% ^c	NR	6.5 ^c	NR	2.6 ^c	NR	2.7 ^c	NR
	IFNB-1a SC 44 µg	339	38.3	2.3	75% ^c	NR	6.4 ^c	NR	2.7 ^c	NR	2.0 ^c	NR
FREEDOMS	PBO	418	37.2	2.5	71%	40%	8.1	NR	2.2	1.4	1.3	6.2
	FIN	425	36.6	2.3	70%	43%	8.0	NR	2.1	1.5	1.6	6.1
FREEDOMS II	PBO	355	40.1	2.4	81%	73%	10.6	NR	2.2	1.5	1.2	5.6
	FIN	358	40.6	2.4	77%	74%	10.4	NR	2.2	1.4	1.3	5.5
GALA	PBO	461	38.1	2.7	68%	14%	7.6	NR	1.9	1.3	1.4	17.4
	GA 40 mg	943	37.4	2.8	68%	14%	7.7	NR	1.9	1.3	1.7	19.7
GOLDEN	IFNB-1b SC	28	37.6	2.1	68%	46%	NR	4.7	1.5	1.2	0.9	7.5
	FIN	80	40.2	2.8	71%	53%	NR	5.0	1.9	1.5	0.8	10.8
IFNB MS	PBO	123	36.0	2.8	72%	NR	NR	3.9	3.6	NR	NR	NR
	IFNB-1b SC	124	35.2	3.0	69%	NR	NR	4.7	3.4	NR	NR	NR
INCOMIN	IFNB-1a IM	92	34.9	2.0	62%	NR	NR	6.7	2.8	NR	NR	NR
	IFNB-1b SC	96	38.8	2.0	69%	NR	NR	5.9	3.0	NR	NR	NR
MSCRG	PBO	143	36.9	2.3	72%	NR	NR	6.4	NR	NR	2.3	NR
	IFNB-1a IM	158	36.7	2.4	75%	NR	NR	6.6	NR	NR	3.2	NR
OPERA I	IFNB-1a SC 44 µg	411	36.9	2.8	66%	NR	6.3	3.7	NR	1.3	NR	9.7
	OCR	410	37.1	2.9	66%	NR	6.7	3.8	NR	1.3	NR	10.8
OPERA II	IFNB-1a SC 44 µg	418	37.4	2.8	67%	NR	6.7	4.1	NR	1.3	NR	10.6
	OCR	417	37.2	2.8	65%	NR	6.7	4.2	NR	1.3	NR	10.7
OPTIMUM	TER 14 mg	566	36.8	2.6	66%	NR	7.7	NR	NR	1.3	NR	9.5
	PON	567	36.7	2.6	64%	NR	7.6	NR	NR	1.2	NR	8.3
PRISMS	PBO	187	NR	2.4	75%	NR	NR	NR	3.0	NR	NR	NR
	IFNB-1a SC 22 µg	189	NR	2.5	67%	NR	NR	NR	3.0	NR	NR	NR
	IFNB-1a SC 44 µg	184	NR	2.5	66%	NR	NR	NR	3.0	NR	NR	NR
RADIANCE-B	IFNB-1a IM	441	35.1	2.5	69%	29%	6.4	3.6	1.8	1.3	1.8	11.5
	OZN	433	36.0	2.6	67%	28%	6.9	4.0	1.7	1.3	1.6	11.6
REGARD	IFNB-1a SC 44 µg	386	36.7	2.4	69%	NR	NR	NR	NR	NR	1.5	7.9
	GA 20 mg	378	36.8	2.3	72%	NR	NR	NR	NR	NR	1.7	7.6

Trial Name	Treatment	Sample Size	Baseline Characteristics ^a									
			Age (years)	EDSS Score	Female (%)	Previous DMT Experience (%)	Time Since First MS Symptoms (years)	Time Since MS Diagnosis (years)	Relapses Within Previous 2 Years	Relapses Within Previous 1 Year	Number of Gd+ Lesions	Volume of T2 Lesions (cm ³)
Stepien et al. (2013)	IFNB-1a IM	20	32.6	2.3	65%	NR	NR	1.6	NR	1.2	NR	NR
	IFNB-1b SC	18	33.5	2.1	72%	NR	NR	1.9	NR	1.5	NR	NR
SUNBEAM	IFNB-1a IM	448	35.9	2.6	67%	34%	6.9	3.7	1.7	1.3	1.7	13.6
	OZN	447	34.8	2.6	63%	29%	6.9	3.6	1.8	1.3	1.8	12.5
TEMSO	PBO	363	38.4	2.7	76%	NR	8.6	NR	2.2	1.4	1.7	NR
	TER 7 mg	366	37.4	2.7	70%	NR	8.8	NR	2.3	1.4	1.5	NR
	TER 14 mg	359	37.8	2.7	71%	NR	8.7	NR	2.2	1.3	1.8	NR
TENERE	IFNB-1a SC 44 µg	104	37.0	2.0	68%	NR	7.7	NR	1.7	1.2	NR	NR
	TER 7 mg	109	35.2	2.0	64%	NR	7.0	NR	1.7	1.3	NR	NR
	TER 14 mg	111	36.8	2.3	70%	NR	6.6	NR	1.7	1.4	NR	NR
TOWER	PBO	389	38.1	2.7	70%	NR	7.6	NR	2.1	1.4	NR	NR
	TER 7 mg	408	37.4	2.7	74%	NR	8.2	NR	2.1	1.4	NR	NR
	TER 14 mg	372	38.2	2.7	69%	NR	8.2	NR	2.1	1.4	NR	NR
TRANSFORMS	IFNB-1a IM	435	36.0	2.2	68%	56%	7.4	4.9	2.3	1.5	1.1	4.9
	FIN	431	36.7	2.2	65%	55%	7.5	4.8	2.3	1.5	1.0	5.2
ULTIMATE I	TER 14 mg	274	37.0	2.9	65%	41%	6.8	4.5	2.0	1.4	1.6	14.9
	UTX	271	36.2	3.0	61%	40%	7.5	4.9	1.8	1.3	2.3	15.9
ULTIMATE II	TER 14 mg	272	36.2	3.0	65%	43%	7.4	5.0	1.8	1.2	2.5	15.7
	UTX	272	34.5	2.8	65%	49%	7.3	5.0	1.8	1.3	2.6	14.7

^a Unless otherwise stated value is the mean.

^b Overall value (not available by treatment).

^c Value is from Coyle et al. (2017) [92] because it was not reported in the pivotal publication for the trial [19].

ALE alemtuzumab, *CLA* cladribine, *DMF* dimethyl fumarate, *DMT* disease-modifying therapy, *EDSS* Expanded Disability Status Scale, *FIN* fingolimod, *GA* glatiramer acetate, *Gd+* gadolinium enhancing, *IFNB* interferon beta, *IM* intramuscular, *MS* multiple sclerosis, *NAT* natalizumab, *OCR* ocrelizumab, *OMB* ofatumumab, *OZN* ozanimod, *PBO* placebo, *PEG* pegylated interferon beta-1a, *PON* ponesimod, *SC* subcutaneous, *TER* teriflunomide, *UTX* ublituximab.

Table B.4. Summary of relapse definitions.

Definition	Trials Using Definition
New/recurrent/worsening neurological symptoms/abnormalities that lasted for at least 24 hours	ADVANCE; AFFIRM; ASCLEPIOS I/II; ASSESS; BEYOND; CLARITY; CombiRx; CONFIRM; DEFINE; Etemadifar et al. (2006); EVIDENCE; FREEDOMS; FREEDOMS II; IFNB MS; INCOMIN; OPERA I/II; OPTIMUM; PRISMS; RADIANCE-B; Stepien et al. (2013); SUNBEAM; TEMSO; TENERE; TOWER; TRANSFORMS; ULTIMATE I/II
New/recurrent/worsening neurological symptoms/abnormalities that lasted for at least 48 hours	Bornstein et al. (1987); BRAVO; CAMMS223; CARE-MS I; CARE-MS II; Copolymer 1 MS trial; GALA; MSCRG; REGARD

Note: Relapse definition not reported for Boiko et al. (2018); Calabrese et al. (2012); and GOLDEN.

Note: Trials were sorted by the required duration of relapse symptoms. Relapse definitions additionally varied between trials in numerous minor ways.

Table B.5. Summary of ARR definitions.

Definition	Trials Using Definition
Total number of relapses divided by the total number of patient-years in the study	ADVANCE; AFFIRM; CombiRx; CONFIRM; DEFINE; MSCRG; OPERA I/II
Estimated using a negative binomial model with the cumulative number of confirmed relapses by patient as the response variable and the natural log of time in study in years as an offset variable	ASCLEPIOS I/II
Total number of confirmed relapses divided by the total days in the study multiplied by 365.25	ASSESS; CLARITY; FREEDOMS II; RADIANCE-B; SUNBEAM
Estimated using a negative binomial model with the total number of confirmed relapses on-study	BRAVO
Estimated using a Poisson regression model with the number of relapses as the dependent variable and the log total amount of follow-up for each patient as an offset variable	CAMMS223
Estimated using a negative binomial model with the total number of relapses by patients as the dependent variable and the log total amount of follow-up for each patient as an offset variable	CARE-MS I; CARE-MS II
Relapses per patient per time on study	EVIDENCE
Number of confirmed relapses per year	FREEDOMS
Cumulative number of confirmed relapses divided by the number of person-years of exposure to treatment	GALA
Number of confirmed relapses per subject-year	OPTIMUM
Total number of relapses across all patients divided by the total time on study across all patients	REGARD
Total number of confirmed relapses that occurred during the treatment period divided by the sum of the treatment durations	TEMSO; TENERE; TOWER; ULTIMATE I/II
The number of confirmed relapses during a 12-month period	TRANSFORMS

Note: ARR was not reported for Boiko et al. (2018), Bornstein et al. (1987); Etemadifar et al. (2006); and PRISMS. However, ARR could be calculated for these trials using other reported data.

Note: ARR definition not reported for BEYOND; Calabrese et al. (2012); Copolymer 1 MS trial; GOLDEN; IFNB MS; INCOMIN; and Stepien et al. (2013).

ARR annualised relapse rate.

Table B.6. Summary of 3mCDP definitions.

Trial Name	Definition	Baseline EDSS Score Range	Required Increase in EDSS Score From Baseline for Progression			
			Baseline Score = 0	Baseline Score = 1 to 5	Baseline Score = 5.5	Baseline Score > 5.5
ADVANCE	≥1.0-point increase on the EDSS from a baseline EDSS ≥1.0 sustained for 12 weeks or at least a 1.5-point increase on the EDSS from a baseline EDSS of 0 sustained for 12 weeks.	0.0–5.0	1.5	1.0	NA	NA
AFFIRM	An increase of 1.0 or more on the EDSS from a baseline score of 1.0 or more or an increase of 1.5 or more from a baseline score of 0 that was sustained for 12 weeks (progression could not be confirmed during a relapse).	0.0–5.0	1.5	1.0	NA	NA
ASCLEPIOS I/II	An increase in EDSS score of at least 1.5 points if baseline score was 0, of at least 1 point if baseline score was 1–5 or of at least 0.5 points if baseline score was at least 5.5, sustained for at least 3 months. ^a	0.0–5.5	1.5	1.0	0.5	NA
BEYOND	A 1-point change in the score that was sustained for 3 months.	0.0–5.0	1.0	1.0	NA	NA
Bornstein et al. (1987)	An increase of at least 1 unit in the Kurtzke score that was maintained for at least 3 months.	0.0–6.0	1.0	1.0	1.0	1.0
BRAVO	A 1.0 point increase in EDSS score if baseline score was between 0 and 5.0, or a 0.5 point increase if baseline score was 5.5, sustained for 3 months.	0.0–5.5	1.0	1.0	0.5	NA
CAMMS223	An increase of at least 1.5 points for patients with a baseline score of 0 and of at least 1.0 point for patients with a baseline score of 1.0 or more; all scores were confirmed twice during a 6-month period. The onset of a sustained level of disability was timed to the first recorded increase in the EDSS score aside from relapse.	0.0–3.0	1.5	1.0 (baseline EDSS score = 1.0 to 3.0)	NA	NA
CLARITY	Time to a sustained increase (for at least 3 months) of at least 1 point in the EDSS score or an increase of at least 1.5 points if the baseline EDSS score was 0. ^b	0.0–5.5	1.5	1.0 (baseline EDSS score = 0.5 to 4.5)	1.0 or 0.5 (baseline EDSS score ≥5.0)	NA
CONFIRM	An increase in the EDSS score of at least 1.0 point in patients with a baseline score of 1.0 or more or an increase of at least 1.5 points in patients with a baseline score of 0, confirmed at least 12 weeks later.	0.0–5.0	1.5	1.0	NA	NA
Copolymer 1 MS trial	An increase of at least one full step on the EDSS that persisted for at least 3 months.	0.0–5.0	1.0	1.0	NA	NA
DEFINE	At least a 1.0-point increase on the EDSS in patients with a baseline score of 1.0 or higher or at least a 1.5-point increase in patients with a baseline score of 0, with the increased score sustained for at least 12 weeks.	0.0–5.0	1.5	1.0	NA	NA
EVIDENCE	Progression by one point on the EDSS scale confirmed at a visit 3 or 6 months later without an intervening EDSS value that would not meet the criteria for progression.	0.0–5.5	1.0	1.0	1.0	NA

Trial Name	Definition	Baseline EDSS Score Range	Required Increase in EDSS Score From Baseline for Progression			
			Baseline Score = 0	Baseline Score = 1 to 5	Baseline Score = 5.5	Baseline Score > 5.5
FREEDOMS	An increase of one point in the EDSS score (or half a point if the baseline EDSS score was equal to 5.5), confirmed after 3 months, with an absence of relapse at the time of assessment and with all EDSS scores measured during that time meeting the criteria for disability progression.	0.0–5.5	1.0	1.0	0.5	NA
FREEDOMS II	A 1 point EDSS increase from baseline or 0.5 point increase if baseline EDSS is ≥ 5.5 , confirmed 3 months later.	0.0–5.5	1.0	1.0	0.5	NA
IFNB MS	Two consecutive EDSS scores, separated by 90 days, that were identical, with both showing a 1.0 point increase over the baseline score.	0.0–5.5	1.0	1.0	1.0	NA
OPERA I/II	An increase from the baseline EDSS score of at least 1.0 point (or 0.5 points if the baseline EDSS score was >5.5) that was sustained for at least 12 weeks.	0.0–5.5	1.0	1.0	1.0	NA
OPTIMUM	An increase in the EDSS score, which was confirmed after 12 weeks (by an increase of at least 1.5 with a baseline EDSS score of 0.0, at least 1.0 with baseline EDSS score of 1.0 to 5.0, or at least 0.5 with a baseline EDSS score of 5.5 or more)	0.0–5.5	1.5	1.0	0.5	NA
PRISMS	An increase in EDSS of at least 1 point sustained over at least 3 months.	0.0–5.0	1.0	1.0	NA	NA
RADIANCE-B	EDSS worsening of ≥ 1 -point increase, confirmed after 3 months.	0.0–5.0	1.0	1.0	NA	NA
SUNBEAM	EDSS worsening of ≥ 1 -point increase, confirmed after 3 months.	0.0–5.0	1.0	1.0	NA	NA
TEMPO	An increase from baseline of at least 1.0 point in the EDSS score (or at least 0.5 points for patients with a baseline EDSS score greater than 5.5) that persisted for at least 12 weeks.	0.0–5.5	1.0	1.0	1.0	NA
TOWER	An increase from baseline of at least 1 EDSS point (or ≥ 0.5 points when baseline EDSS score was >5.5 points) that persisted for at least 12 weeks. For clarification, a score of 5.5 points or more could occur in patients whose EDSS score deteriorated between screening and baseline.	0.0–5.5	1.0	1.0	1.0	NA
TRANSFORMS	A 1.0-point increase in EDSS score (0.5-point increase for baseline EDSS score ≥ 5.5), confirmed 3 months later in the absence of relapse.	0.0–5.5	1.0	1.0	0.5	NA
ULTIMATE I/II	An increase in EDSS at least 1 point higher than the baseline EDSS if the baseline EDSS is ≤ 5.5 or at least 0.5 higher than the baseline EDSS if the baseline EDSS is >5.5 .	0.0–5.5	1.0	1.0	1.0	NA

^a Predefined (per-protocol) definition for ASCLEPIOS I/II.

^b Definition on ClinicalTrials.gov for the CLARITY trial differs from the pivotal publication (the trial record additionally specifies an increase of 0.5 required for baseline EDSS score 5 or greater).

3mCDP 3-month confirmed disability progression, *EDSS* Expanded Disability Status Scale, *NA* not applicable.

Table B.7. Summary of 6mCDP definitions.

Trial Name	Definition	Baseline EDSS Score Range	Required Increase in EDSS Score From Baseline for Progression			
			Baseline Score = 0	Baseline Score = 1 to 5	Baseline Score = 5.5	Baseline Score > 5.5
ADVANCE	At least a 1 point increase from baseline EDSS ≥ 1 or 1.5 point increase for patients with baseline EDSS of 0, sustained for 24 weeks. ^a	0.0–5.0	1.5	1.0	NA	NA
AFFIRM	An increase of 1.0 or more on the EDSS from a baseline score of 1.0 or more or an increase of 1.5 or more from a baseline score of 0 that was sustained for 24 weeks (progression could not be confirmed during a relapse).	0.0–5.0	1.5	1.0	NA	NA
ASCLEPIOS I/II	An increase in EDSS score of at least 1.5 points if baseline score was 0, of at least 1 point if baseline score was 1-5, or of at least 0.5 points if baseline score was at least 5.5, sustained for at least 6 months. ^b	0.0–5.5	1.5	1.0	0.5	NA
BRAVO	A 1.0 point increase in EDSS score if baseline score was between 0 and 5.0, or a 0.5 point increase if baseline score was 5.5, sustained for 6 months.	0.0–5.5	1.0	1.0	0.5	NA
CAMMS223	An increase of at least 1.5 points for patients with a baseline score of 0 and of at least 1.0 point for patients with a baseline score of 1.0 or more; all scores were confirmed twice during a 6-month period. The onset of a sustained level of disability was timed to the first recorded increase in the EDSS score aside from relapse.	0.0–3.0	1.5	1.0 (baseline EDSS score = 1.0 to 3.0)	NA	NA
CARE-MS I	An increase from baseline of at least one EDSS point (or ≥ 1.5 points if baseline EDSS score was 0) confirmed over 6 months.	0.0–3.0	1.5	1.0 (baseline EDSS score = 1.0 to 3.0)	NA	NA
CARE-MS II	An increase from baseline of at least one EDSS point (or ≥ 1.5 points if the baseline EDSS score was 0) confirmed over 6 months.	0.0–5.0	1.5	1.0	NA	NA
CLARITY	Definition for 6-month CDP was not reported, so definition was assumed to match that reported for time to 3mCDP with regards to required increase in EDSS score: Time to a sustained increase (for at least 3 months) of at least 1 point in the EDSS score or an increase of at least 1.5 points if the baseline EDSS score was 0. ^c	0.0–5.5	1.5	1.0 (baseline EDSS score = 0.5 to 4.5)	1.0 or 0.5 (baseline EDSS score ≥ 5.0)	NA
CombiRx	A 1.0 increase in the EDSS from baseline, when baseline ≤ 5.0 ; or an increase of 0.5 from baseline, when baseline ≥ 5.5 , sustained for 6 months (2 successive quarterly visits) as assessed by the blinded EDSS examiner and confirmed centrally.	0.0–5.5	1.0	1.0	0.5	NA
CONFIRM	A ≥ 1.0 point increase on the EDSS from a baseline EDSS score ≥ 1.0 that was confirmed at least 24 weeks later, or a ≥ 1.5 point increase on the EDSS from a baseline EDSS score = 0 that was confirmed at least 24 weeks later. ^a	0.0–5.0	1.5	1.0	NA	NA

Trial Name	Definition	Baseline EDSS Score Range	Required Increase in EDSS Score From Baseline for Progression			
			Baseline Score = 0	Baseline Score = 1 to 5	Baseline Score = 5.5	Baseline Score > 5.5
DEFINE	A ≥ 1.0 point increase on the EDSS from a baseline EDSS score ≥ 1.0 that was confirmed at least 24 weeks later, or a ≥ 1.5 point increase on the EDSS from a baseline EDSS score = 0 that was confirmed at least 24 weeks later. ^a	0.0–5.0	1.5	1.0	NA	NA
EVIDENCE	Progression by one point on the EDSS scale confirmed at a visit 3 or 6 months later without an intervening EDSS value that would not meet the criteria for progression.	0.0–5.5	1.0	1.0	1.0	NA
FREEDOMS	An increase of one point in the EDSS score (or half a point if the baseline EDSS score was equal to 5.5), confirmed after 6 months, with an absence of relapse at the time of assessment and with all EDSS scores measured during that time meeting the criteria for disability progression.	0.0–5.5	1.0	1.0	0.5	NA
FREEDOMS II	A 1 point EDSS increase from baseline or 0.5 point increase if baseline EDSS is ≥ 5.5 , confirmed 6 months later.	0.0–5.5	1.0	1.0	0.5	NA
INCOMIN	An increase in EDSS of at least one point sustained for at least 6 months and confirmed at the end of follow-up.	1.0–3.5	NA	1.0 (baseline EDSS score = 1.0 to 3.5)	NA	NA
MSCRG	Deterioration from baseline by at least 1.0 point on the EDSS persisting for at least 6 months.	1.0–3.5	NA	1.0 (baseline EDSS score = 1.0 to 3.5)	NA	NA
OPERA I/II	An increase from the baseline EDSS score of at least 1.0 point (or 0.5 points if the baseline EDSS score was >5.5) that was sustained for at least 24 weeks.	0.0–5.5	1.0	1.0	1.0	NA
OPTIMUM	An increase in the EDSS score, which was confirmed after 24 weeks (by an increase of at least 1.5 with a baseline EDSS score of 0.0, at least 1.0 with baseline EDSS score of 1.0 to 5.0, or at least 0.5 with a baseline EDSS score of 5.5 or more)	0.0–5.5	1.5	1.0	0.5	NA
RADIANCE-B	EDSS worsening of ≥ 1 -point increase, confirmed after 6 months.	0.0–5.0	1.0	1.0	NA	NA
REGARD	Disability progression at the 6-month follow-up visit was confirmed as follows: if the EDSS score at baseline was 0, then a change of 1.5 points or more was required; if the EDSS was 0.5–4.5 at baseline, then a change of 1.0 point or more was required; and if the EDSS at baseline was 5 points or more, then the change required was 0.5 points or more.	0.0–5.5	1.5	1.0 (baseline EDSS score = 0.5 to 4.5)	0.5	NA
SUNBEAM	EDSS worsening of ≥ 1 -point increase, confirmed after 6 months.	0.0–5.0	1.0	1.0	NA	NA

Trial Name	Definition	Baseline EDSS Score Range	Required Increase in EDSS Score From Baseline for Progression			
			Baseline Score = 0	Baseline Score = 1 to 5	Baseline Score = 5.5	Baseline Score > 5.5
TEMPO	At least 1 point increase on EDSS score from baseline, if the baseline EDSS score was ≤ 5.5 , or time to at least 0.5 increase on EDSS score from baseline, if the baseline EDSS score was > 5.5 ; this increase in EDSS score was to be persistent for at least 24 weeks. ^a	0.0–5.5	1.0	1.0	1.0	NA
TOWER	At least 1 point increase on EDSS score from baseline, if the baseline EDSS score was ≤ 5.5 , or time to at least 0.5 increase on EDSS score from baseline, if the baseline EDSS score was > 5.5 ; this increase in EDSS score was to be persistent for at least 24 weeks. ^a	0.0–5.5	1.0	1.0	1.0	NA
ULTIMATE I/II	An increase in EDSS at least 1 point higher than the baseline EDSS if the baseline EDSS is ≤ 5.5 or at least 0.5 higher than the baseline EDSS if the baseline EDSS is > 5.5 .	0.0–5.5	1.0	1.0	1.0	NA

^a Definition not found in the pivotal trial publication, so referred to a Summary of Product Characteristics or EMA assessment report associated with the trial.

^b Predefined (per-protocol) definition for ASCLEPIOS I/II.

^c Definition on ClinicalTrials.gov for the CLARITY trial differs from the pivotal publication (the trial record additionally specifies an increase of 0.5 required for baseline EDSS score 5 or greater).

6mCDP 6-month confirmed disability progression, *EDSS* Expanded Disability Status Scale, *EMA* European Medicines Agency, *NA* not applicable.

Placebo Arm ARR

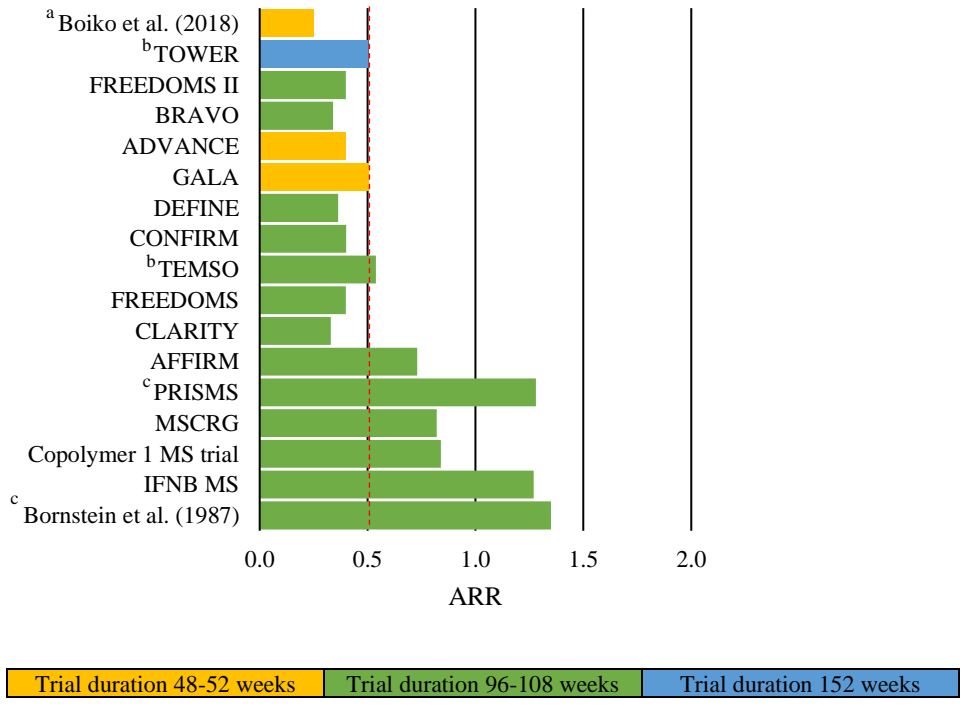


Figure B.1. Placebo response by trial for ARR.

^a Calculated by dividing total exacerbations by number of patients multiplied by trial duration in years.

^b Value to three decimal places obtained from an European Medicines Agency report [93].

^c Calculated by dividing relapses per patient (over 2 years) by 2.

Note: Trials are ordered by pivotal publication year with the most recent at the top.

Note: Where bars are not shown, data was not reported.

Note: Red dashed line is the mean weighted by sample size (ARR: 0.51).

ARR annualised relapse rate.

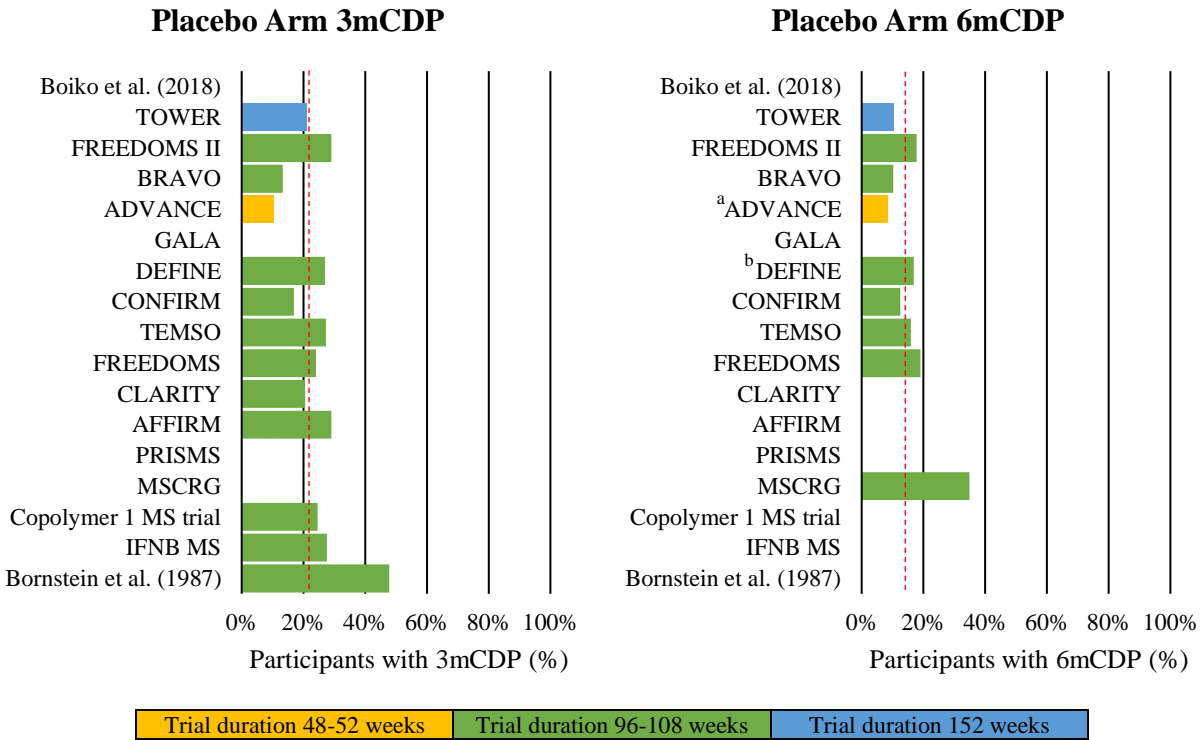


Figure B.2. Placebo response by trial for proportion of patients with 3mCDP and 6mCDP.

^a Obtained from the Summary of Product Characteristics for pegylated interferon beta-1a [94] since it was not reported by the pivotal trial publication [1].

^b Obtained from a European Medicines Agency report [95] since it was not reported by the pivotal trial publication [17].

Note: It was not possible to compare placebo response for time to 3mCDP and time to 6mCDP across trials as these outcomes were extracted as relative measures (i.e., hazard ratio [HR] between a treatment arm and comparator arm). Instead, the proportion of patients with 3mCDP and the proportion with 6mCDP were calculated and compared across trials.

Note: Trials are ordered by pivotal publication year with the most recent at the top.

Note: Where bars are not shown, data was not reported.

Note: Red dashed line is the mean weighted by sample size (proportion with 3mCDP: 22%, proportion with 6mCDP: 15%).
 3mCDP 3-month confirmed disability progression, 6mCDP 6-month confirmed disability progression.

Appendix C Input Data for Network Meta-analyses

Table C.1. Input data for the ARR network meta-analysis.

Trial Name	Treatment	ARR (mean)	Sample Size	Trial Duration (weeks) ^a
AFFIRM	PBO	0.73	315	104
	NAT	0.23	627	104
ASCLEPIOS I	TER 14 mg	0.22	452	130
	OMB	0.11	454	130
ASCLEPIOS II	TER 14 mg	0.25	469	130
	OMB	0.10	469	130
ASSESS	GA 20 mg	0.258	324	52
	FIN	0.153	345	52
BEYOND	IFNB-1b SC	0.36	888 ^b	182
	GA 20 mg	0.34	445 ^b	182
Boiko et al. (2018) ^c	PBO	0.271 ^d	28	48
	GA 20 mg	0.195 ^d	122	48
Bornstein et al. (1987)	PBO	1.35 ^e	23	104
	GA 20 mg	0.3 ^e	25	104
BRAVO	PBO	0.34	450	104
	IFNB-1a IM	0.26	447	104
Calabrese et al. (2012)	IFNB-1a IM	0.5	47	104
	IFNB-1a SC 44 µg	0.4	46	104
	GA 20 mg	0.5	48	104
CAMMS223	IFNB-1a SC 44 µg	0.36	111	156
	ALE	0.11	112	156
CARE-MS I	IFNB-1a SC 44 µg	0.39	187	104
	ALE	0.18	376	104
CARE-MS II	IFNB-1a SC 44 µg	0.52	202	104
	ALE	0.26	426	104
CLARITY	PBO	0.33	437	96
	CLA	0.14	433	96
CombiRx ^f	IFNB-1a IM	0.16	250	156
	GA 20 mg	0.11	259	156
CONFIRM	PBO	0.401	363	104
	GA 20 mg	0.286	350	104
	DMF	0.224	359	104
Copolymer 1 MS trial	PBO	0.84	126	104
	GA 20 mg	0.59	125	104
DEFINE	PBO	0.364	408	96
	DMF	0.172	410	96
Etemadifar et al. (2006)	IFNB-1a IM	0.950 ^d	30	104
	IFNB-1b SC	1.083 ^d	30	104
	IFNB-1a SC 44 µg	1.100 ^d	30	104
EVIDENCE	IFNB-1a IM	0.64	338	48
	IFNB-1a SC 44 µg	0.54	339	48
FREEDOMS	PBO	0.40	418	104
	FIN	0.18	425	104

Trial Name	Treatment	ARR (mean)	Sample Size	Trial Duration (weeks) ^a
FREEDOMS II	PBO	0.40	355	104
	FIN	0.21	358	104
GALA	PBO	0.505	461	52
	GA 40 mg	0.331	943	52
GOLDEN	IFNB-1b SC	0.39	47	78
	FIN	0.12	104	78
IFNB MS	PBO	1.27	123	104
	IFNB-1b SC	0.84	124	104
MSCRG	PBO	0.82	143	104
	IFNB-1a IM	0.67	158	104
OPERA I	IFNB-1a SC 44 µg	0.292 ^g	411	96
	OCR	0.156 ^g	410	96
OPERA II	IFNB-1a SC 44 µg	0.290 ^g	418	96
	OCR	0.155 ^g	417	96
OPTIMUM	TER 14 mg	0.290	566	108
	PON	0.202	567	108
PRISMS	PBO	1.28 ^e	187	104
	IFNB-1a SC 22 µg	0.91 ^e	189	104
	IFNB-1a SC 44 µg	0.87 ^e	184	104
RADIANCE-B	IFNB-1a IM	0.28	441	104
	OZN	0.17	433	104
REGARD	IFNB-1a SC 44 µg	0.30	386	96
	GA 20 mg	0.29	378	96
Stepien et al. (2013)	IFNB-1b SC	0.43	18	156
	IFNB-1a IM	0.35	20	156
SUNBEAM	IFNB-1a IM	0.35	448	52
	OZN	0.18	447	52
TEMZO	PBO	0.539 ^h	363	108
	TER 7 mg	0.370 ^h	365	108
	TER 14 mg	0.369 ^h	358	108
TENERE	IFNB-1a SC 44 µg	0.22	104	115
	TER 7 mg	0.41	109	115
	TER 14 mg	0.26	111	115
TOWER	PBO	0.501 ^h	388	152 ⁱ
	TER 7 mg	0.389 ^h	407	152 ⁱ
	TER 14 mg	0.319 ^h	370	152 ⁱ
TRANSFORMS	IFNB-1a IM	0.33	431	52
	FIN	0.16	429	52
ULTIMATE I	TER 14 mg	0.188 ^j	274	96
	UTX	0.076 ^j	271	96
ULTIMATE II	TER 14 mg	0.178 ^j	272	96
	UTX	0.091 ^j	272	96

^a Where trial duration was reported in years or months, it was assumed that 1 year = 12 months and 1 year = 52 weeks.

^b Sample size was not reported and so was assumed based on reported safety results.

^c Non-inferiority trial for GA 20 mg, so the two GA 20 mg arms were pooled (the ARR was the same for both arms).

^d ARR calculated by dividing total relapses by number of patients multiplied by trial duration in years.

^e ARR calculated by dividing relapses per patient (over 2 years) by 2.

^f Each treatment arm for the CombiRx trial included a placebo for the other treatment.

^g Value to three decimal places obtained from a European Medicines Agency report [96].

^h Value to three decimal places obtained from a European Medicines Agency report [93].

ⁱ Based on the ClinicalTrials.gov record for this trial (NCT00751881).

^j Value to three decimal places obtained from a conference poster [38].

ALE alemtuzumab, *ARR* annualised relapse rate, *CLA* cladribine, *DMF* dimethyl fumarate, *FIN* fingolimod, *GA* glatiramer acetate, *IFNB* interferon beta, *IM* intramuscular, *NAT* natalizumab, *OCR* ocrelizumab, *OMB* ofatumumab, *OZN* ozanimod, *PBO* placebo, *PON* ponesimod, *SC* subcutaneous, *TER* teriflunomide, *UTX* ublituximab.

Table C.2. Input data for the time to 3mCDP network meta-analysis.

Trial Name	Treatment	HR for time to 3mCDP (95% CI)	Ln(HR)	Ln(HR SE)
AFFIRM	PBO	-	NA	NA
	NAT	0.58 (0.43-0.77)	-0.55267	0.14862
ASCLEPIOS I (predefined)	TER 14 mg	-	NA	NA
	OMB	0.652 (0.445-0.957)	-0.42682	0.19534
ASCLEPIOS I (EDSS-aligned)	TER 14 mg	-	NA	NA
	OMB	0.578 (0.388-0.862)	-0.54762	0.20364
ASCLEPIOS II (predefined)	TER 14 mg	-	NA	NA
	OMB	0.660 (0.447-0.947)	-0.42983	0.19152
ASCLEPIOS II (EDSS-aligned)	TER 14 mg	-	NA	NA
	OMB	0.615 (0.405-0.936)	-0.48500	0.21371
BEYOND	IFNB-1b SC	-	NA	NA
	GA 20 mg	NR	-0.05484 ^a	0.12911 ^a
Bornstein et al. (1987)	PBO	-	NA	NA
	GA 20 mg	NR	-1.07006 ^a	0.54313 ^a
BRAVO	PBO	-	NA	NA
	IFNB-1a IM	0.74 (0.51-1.09)	-0.29358	0.19376
CLARITY	PBO	-	NA	NA
	CLA	0.67 (0.48-0.93)	-0.40327	0.16872
CONFIRM	PBO	-	NA	NA
	GA 20 mg	0.93 (0.63-1.37)	-0.07361	0.19818
	DMF	0.79 (0.52-1.19)	-0.23999	0.21119
Copolymer 1 MS trial	PBO	-	NA	NA
	GA 20 mg	NR	-0.14871 ^a	0.26400 ^a
DEFINE	PBO	-	NA	NA
	DMF	0.62 (0.44-0.87)	-0.48012	0.17391
EVIDENCE	IFNB-1a IM	-	NA	NA
	IFNB-1a SC 44 µg	0.87 (0.58-1.31)	-0.13735	0.20785
FREEDOMS	PBO	-	NA	NA
	FIN	0.70 (0.52-0.96)	-0.34737	0.15640
FREEDOMS II	PBO	-	NA	NA
	FIN	0.83 (0.61-1.12)	-0.19048	0.15501
HAS meta-analysis ^b	IFNB-1a SC 44 µg	-	NA	NA
	ALE	0.66 (0.49-0.87)	-0.42631	0.14645
IFNB MS	PBO	-	NA	NA
	IFNB-1b SC	NR	-0.36253 ^a	0.26427 ^a
OPERA I	IFNB-1a SC 44 µg	-	NA	NA
	OCR	0.57 (0.37-0.90)	-0.54981	0.22676
OPERA II	IFNB-1a SC 44 µg	-	NA	NA
	OCR	0.63 (0.42-0.92)	-0.47544	0.20003
OPTIMUM	TER 14 mg	-	NA	NA
	PON	0.83 (0.58-1.18)	-0.18961	0.18118

Trial Name	Treatment	HR for time to 3mCDP (95% CI)	Ln(HR)	Ln(HR SE)
PRISMS	PBO	-	NA	NA
	IFNB-1a SC 22 µg	0.68 (0.48-0.98)	-0.37709	0.18208
	IFNB-1a SC 44 µg	0.62 (0.43-0.91)	-0.46914	0.19124
RADIANCE-B and SUNBEAM ^c	INF-1a IM	-	NA	NA
	OZN	0.95 (0.68-1.33)	-0.05024	0.17113
TEMSO	PBO	-	NA	NA
	TER 7 mg	0.763 (0.555-1.049) ^d	-0.27047	0.16240
	TER 14 mg	0.702 (0.506-0.973) ^d	-0.35429	0.16680
TOWER	PBO	-	NA	NA
	TER 7 mg	0.955 (0.677-1.347) ^d	-0.04610	0.17550
	TER 14 mg	0.685 (0.467-1.004) ^d	-0.37872	0.19526
TRANSFORMS	IFNB-1a IM	-	NA	NA
	FIN	NR	-0.30252 ^a	0.26250 ^a
ULTIMATE I/II ^e	TER 14 mg	-	NA	NA
	UTX	0.843 (0.504-1.407) ^f	-0.17186	0.26190

^a Derived from the reported proportion of patients who progressed over the trial duration using formulae described by Watkins and Bennett (2018) [97].

^b A pooled time to 3mCDP estimate derived from CAMMS223, CARE-MS I, and CARE-MS II was reported in a 2016 HAS meta-analysis [98]. Because CARE-MS I and CARE-MS II do not publicly report the result for the outcome of time to 3mCDP, the decision was made to use the HAS meta-analysis value to include these trials in the time to 3mCDP network. This HAS value was also used by McCool et al. (2019) [99] and Samjoo et al. (2020) [100].

^c Disability progression was assessed as a prespecified pooled analysis of the RADIANCE-B and SUNBEAM trials; values are for the pooled analysis as reported in the RADIANCE pivotal trial publication (Cohen et al. [2019] [30]).

^d Value to three decimal places obtained from a European Medicines Agency report [93].

^e Disability progression was assessed as a prespecified pooled analysis of ULTIMATE I and ULTIMATE II.

^f Value to three decimal places obtained from a conference poster [38].

3mCDP 3-month confirmed disability progression, *ALE* alemtuzumab, *CLA* cladribine, *DMF* dimethyl fumarate, *FIN* fingolimod, *GA* glatiramer acetate, *HAS* Haute Autorité de Santé, *HR* hazard ratio, *IFNB* interferon beta, *IM* intramuscular, *NA* not applicable, *NAT* natalizumab, *NR* not reported, *OCR* ocrelizumab, *OMB* ofatumumab, *OZN* ozanimod, *PBO* placebo, *PON* ponesimod, *SC* subcutaneous, *SE* standard error, *TER* teriflunomide, *UTX* ublituximab.

Table C.3. Input data for the time to 6mCDP network meta-analysis.

Trial Name	Treatment	HR for time to 6mCDP (95% CI)	Ln(HR)	Ln(HR SE)
AFFIRM	PBO	-	NA	NA
	NAT	0.46 (0.33-0.64)	-0.77747	0.16897
ASCLEPIOS I (predefined)	TER 14 mg	-	NA	NA
	OMB	0.607 (0.396-0.930)	-0.49946	0.21780
ASCLEPIOS I (EDSS-aligned)	TER 14 mg	-	NA	NA
	OMB	0.564 (0.361-0.880)	-0.57336	0.22731
ASCLEPIOS II (predefined)	TER 14 mg	-	NA	NA
	OMB	0.756 (0.489-1.170)	-0.27919	0.22255
ASCLEPIOS II (EDSS-aligned)	TER 14 mg	-	NA	NA
	OMB	0.671 (0.418-1.077)	-0.39905	0.24144
BRAVO	PBO	-	NA	NA
	IFNB-1a IM	0.73 (0.47-1.14)	-0.31200	0.22603
CAMMS223	IFNB-1a SC 44 µg	-	NA	NA
	ALE	0.25 (0.11-0.57)	-1.38470	0.00000
CARE-MS I	IFNB-1a SC 44 µg	-	NA	NA
	ALE	0.70 (0.40-1.23)	-0.35464	0.28656
CARE-MS II	IFNB-1a SC 44 µg	-	NA	NA
	ALE	0.58 (0.38-0.87)	-0.55342	0.21131
CLARITY	PBO	-	NA	NA
	CLA	0.53 (0.36-0.79) ^a	-0.62869	0.20049
CombiRx ^b	IFNB-1a IM	-	NA	NA
	GA 20 mg	NR	0.15914 ^c	0.18929 ^c
CONFIRM	PBO	-	NA	NA
	GA 20 mg	0.87 (0.55-1.38)	-0.13788	0.23467
	DMF	0.62 (0.37-1.03)	-0.48235	0.26118
DEFINE	PBO	-	NA	NA
	DMF	0.77 (0.52-1.14) ^d	-0.26145	0.20024
EVIDENCE	IFNB-1a IM	-	NA	NA
	IFNB-1a SC 44 µg	0.70 (0.39-1.25)	-0.35923	0.29713
FREEDOMS	PBO	-	NA	NA
	FIN	0.63 (0.44-0.90)	-0.46317	0.18256
FREEDOMS II	PBO	-	NA	NA
	FIN	0.72 (0.48-1.07)	-0.33316	0.20450
MSCRG	PBO	-	NA	NA
	IFNB-1a IM	NR	-0.55191 ^c	0.22225 ^c
OPERA I	IFNB-1a SC 44 µg	-	NA	NA
	OCR	0.57 (0.34-0.95)	-0.56505	0.26212
OPERA II	IFNB-1a SC 44 µg	-	NA	NA
	OCR	0.63 (0.40-0.98)	-0.46825	0.22859
OPTIMUM	TER 14 mg	-	NA	NA
	PON	0.84 (0.57-1.24)	-0.17350	0.19827
RADIANCE-B and SUNBEAM ^e	IFNB-1a IM	-	NA	NA
	OZN	1.41 (0.92-2.17)	0.34567	0.21891
REGARD	IFNB-1a SC 44 µg	-	NA	NA
	GA 20 mg	NR	-0.30522 ^c	0.22929 ^c

Trial Name	Treatment	HR for time to 6mCDP (95% CI)	Ln(HR)	Ln(HR SE)
TEMISO	PBO	-	NA	NA
	TERI 7 mg	0.750 (0.507-1.110) ^f	-0.28744	0.19990
	TERI 14 mg	0.749 (0.505-1.111) ^f	-0.28897	0.20114
TOWER	PBO	-	NA	NA
	TERI 7 mg	1.054 (0.690-1.610) ^f	0.05259	0.21615
	TERI 14 mg	0.843 (0.533-1.334) ^f	-0.17053	0.23403
ULTIMATE I/II ^g	TER 14 mg	-	NA	NA
	UTX	0.657 (0.358-1.205) ^h	-0.42037	0.30962

^a Obtained from a European Medicines Agency report [101] since not reported by the pivotal trial publication [13].

^b Each treatment arm for the CombiRx trial included a placebo for the other treatment.

^c Derived from the reported proportion of patients who progressed over the trial duration using formulae described by Watkins and Bennett (2018) [97].

^d Obtained from a European Medicines Agency report [95] since not reported by the pivotal trial publication [17].

^e Disability progression was assessed as a prespecified pooled analysis of the RADIANCE-B and SUNBEAM trials; values are for the pooled analysis as reported in the RADIANCE pivotal trial publication [30].

^f Value to three decimal places obtained from a European Medicines Agency report [93].

^g Disability progression was assessed as a prespecified pooled analysis of ULTIMATE I and ULTIMATE II.

^h Value to three decimal places obtained from a conference poster [38].

6mCDP 6-month confirmed disability progression, ALE alemtuzumab, CLA cladribine, DMF dimethyl fumarate, FIN fingolimod, GA glatiramer acetate, HR hazard ratio, IFNB interferon beta, IM intramuscular, NA not applicable, NAT natalizumab, NR not reported, OCR ocrelizumab, OMB ofatumumab, OZN ozanimod, PBO placebo, PON ponesimod, SC subcutaneous, SE standard error, TER teriflunomide, UTX ublituximab.

Table D.1. SUCRA and p-best for the ARR network meta-analysis.

Treatment	Mean SUCRA (%)	Mean p-best (%)	Trial Name(s)
Alemtuzumab	94	39	CAMMS223; CARE-MS I; CARE-MS II
Cladribine	66	1	CLARITY
Dimethyl fumarate	54	0	CONFIRM; DEFINE
Fingolimod	66	0	ASSESS; FREEDOMS; FREEDOMS II; GOLDEN; TRANSFORMS
Glatiramer acetate 20 mg	36	0	ASSESS; BEYOND; Boiko et al. (2018); Bornstein et al. (1987); Calabrese et al. (2012); CombiRx; CONFIRM; Copolymer 1 MS trial; REGARD
Glatiramer acetate 40 mg	32	0	GALA
IFNB-1a IM	14	0	BRAVO; Calabrese et al. (2012); CombiRx; Etemadifar et al. (2006); EVIDENCE; MSCRG; RADIANCE-B; Stepien et al. (2013); SUNBEAM; TRANSFORMS
IFNB-1a SC 22 µg	25	0	PRISMS
IFNB-1a SC 44 µg	35	0	Calabrese et al. (2012); CAMMS223; CARE-MS I; CARE-MS II; Etemadifar et al. (2006); EVIDENCE; OPERA I; OPERA II; PRISMS; REGARD; TENERE
IFNB-1b SC	20	0	BEYOND; Etemadifar et al. (2006); GOLDEN; IFNB MS; Stepien et al. (2013)
Natalizumab	86	14	AFFIRM
Ocrelizumab	81	3	OPERA I; OPERA II
Ofatumumab	90	23	ASCLEPIOS I; ASCLEPIOS II
Ozanimod	65	0	RADIANCE-B; SUNBEAM
Placebo	0	0	AFFIRM; Boiko et al. (2018); Bornstein et al. (1987); BRAVO; CLARITY; CONFIRM; Copolymer 1 MS trial; DEFINE; FREEDOMS; FREEDOMS II; GALA; IFNB MS; MSCRG; PRISMS; TEMSO; TOWER
Ponesimod	58	0	OPTIMUM
Teriflunomide 7 mg	11	0	TEMSO; TENERE; TOWER
Teriflunomide 14 mg	30	0	ASCLEPIOS I; ASCLEPIOS II; OPTIMUM; TEMSO; TENERE; TOWER; ULTIMATE I; ULTIMATE II
Ublituximab	87	21	ULTIMATE I; ULTIMATE II

ARR annualised relapse rate, IFNB interferon beta, IM intramuscular, NMA network meta-analysis, p-best probability of being the best treatment, SC subcutaneous, SUCRA surface under the cumulative ranking curve.

Table D.2. SUCRA and p-best for the time to 3mCDP network meta-analysis (predefined).

Treatment	Mean SUCRA (%)	Mean p-best (%)	Trial Name(s)
Alemtuzumab	89	24	CAMMS223; CARE-MS I; CARE-MS II
Cladribine 3.5 mg/kg	50	1	CLARITY
Dimethyl fumarate	53	0	CONFIRM; DEFINE
Fingolimod	39	0	FREEDOMS; FREEDOMS II; TRANSFORMS
Glatiramer acetate 20 mg	33	0	BEYOND; Bornstein et al. (1987); CONFIRM; Copolymer 1 MS trial
IFNB-1a IM	26	0	BRAVO; EVIDENCE; RADIANCE-B; SUNBEAM; TRANSFORMS
IFNB-1a SC 22 µg	44	0	PRISMS
IFNB-1a SC 44 µg	54	0	CAMMS223; CARE-MS I; CARE-MS II; EVIDENCE; OPERA I; OPERA II; PRISMS
IFNB-1b SC	31	0	BEYOND; IFNB MS
Natalizumab	69	2	AFFIRM
Ocrelizumab	93	43	OPERA I; OPERA II
Ofatumumab	87	20	ASCLEPIOS I; ASCLEPIOS II
Ozanimod	34	0	RADIANCE-B; SUNBEAM
Placebo	3	0	AFFIRM; Bornstein et al. (1987); BRAVO; CLARITY; CONFIRM; Copolymer 1 MS trial; DEFINE; FREEDOMS; FREEDOMS II; IFNB MS; PRISMS; TEMSO; TOWER
Ponesimod	66	3	OPTIMUM
Teriflunomide 7 mg	20	0	TEMSO; TOWER
Teriflunomide 14 mg	46	0	ASCLEPIOS I; ASCLEPIOS II; OPTIMUM; TEMSO; TOWER; ULTIMATE I; ULTIMATE II
Ublituximab	63	7	ULTIMATE I; ULTIMATE II

3mCDP 3-month confirmed disability progression, IFNB interferon beta, IM intramuscular, p-best probability of being the best treatment, SC subcutaneous, SUCRA surface under the cumulative ranking curve.

Table D.3. SUCRA and p-best for the time to 3mCDP network meta-analysis (EDSS-aligned).

Treatment	Mean SUCRA (%)	Mean p-best (%)	Trial Name(s)
Alemtuzumab	88	21	CAMMS223; CARE-MS I; CARE-MS II
Cladribine 3.5 mg/kg	52	1	CLARITY
Dimethyl fumarate	53	0	CONFIRM; DEFINE
Fingolimod	40	0	FREEDOMS; FREEDOMS II; TRANSFORMS
Glatiramer acetate 20 mg	32	0	BEYOND; Bornstein et al. (1987); CONFIRM; Copolymer 1 MS trial
IFNB-1a IM	27	0	BRAVO; EVIDENCE; RADIANCE-B; SUNBEAM; TRANSFORMS
IFNB-1a SC 22 µg	45	0	PRISMS
IFNB-1a SC 44 µg	52	0	CAMMS223; CARE-MS I; CARE-MS II; EVIDENCE; OPERA I; OPERA II; PRISMS
IFNB-1b SC	31	0	BEYOND; IFNB MS
Natalizumab	69	2	AFFIRM
Ocrelizumab	92	37	OPERA I; OPERA II
Ofatumumab	90	30	ASCLEPIOS I; ASCLEPIOS II
Ozanimod	35	0	RADIANCE-B; SUNBEAM
Placebo	3	0	AFFIRM; Bornstein et al. (1987); BRAVO; CLARITY; CONFIRM; Copolymer 1 MS trial; DEFINE; FREEDOMS; FREEDOMS II; IFNB MS; PRISMS; TEMSO; TOWER
Ponesimod	65	3	OPTIMUM
Teriflunomide 7 mg	20	0	TEMSO; TOWER
Teriflunomide 14 mg	45	0	ASCLEPIOS I; ASCLEPIOS II; OPTIMUM; TEMSO; TOWER; ULTIMATE I; ULTIMATE II
Ublituximab	63	6	ULTIMATE I; ULTIMATE II

3mCDP 3-month confirmed disability progression, IFNB interferon beta, IM intramuscular, p-best probability of being the best treatment, SC subcutaneous, SUCRA surface under the cumulative ranking curve.

Table D.4. SUCRA and p-best for the time to 6mCDP network meta-analysis (predefined).

Treatment	Mean SUCRA (%)	Mean p-best (%)	Trial Name(s)
Alemtuzumab	87	34	CAMMS223; CARE-MS I; CARE-MS II
Cladribine 3.5 mg/kg	70	8	CLARITY
Dimethyl fumarate	50	0	CONFIRM; DEFINE
Fingolimod	51	0	FREEDOMS; FREEDOMS II
Glatiramer acetate 20 mg	34	0	CombiRx; CONFIRM; REGARD
IFNB-1a IM	44	0	BRAVO; CombiRx; EVIDENCE; MSCRG; RADIANCE-B; SUNBEAM
IFNB-1a SC 44 µg	34	0	CAMMS223; CARE-MS I; CARE-MS II; EVIDENCE; OPERA I; OPERA II; REGARD
Natalizumab	83	18	AFFIRM
Ocrelizumab	79	15	OPERA I; OPERA II
Ofatumumab	72	6	ASCLEPIOS I; ASCLEPIOS II
Ozanimod	15	0	RADIANCE-B; SUNBEAM
Placebo	8	0	AFFIRM; BRAVO; CLARITY; CONFIRM; DEFINE; FREEDOMS; FREEDOMS II; MSCRG; TEMSO; TOWER
Ponesimod	50	2	OPTIMUM
Teriflunomide 7 mg	21	0	TEMSO; TOWER
Teriflunomide 14 mg	32	0	ASCLEPIOS I; ASCLEPIOS II; OPTIMUM; TEMSO; TOWER; ULTIMATE I; ULTIMATE II
Ublituximab	70	17	ULTIMATE I; ULTIMATE II

6mCDP 6-month confirmed disability progression, IFNB interferon beta, IM intramuscular, p-best probability of being the best treatment, SC subcutaneous, SUCRA surface under the cumulative ranking curve.

Table D.5. SUCRA and p-best for the time to 6mCDP network meta-analysis (EDSS-aligned).

Treatment	Mean SUCRA (%)	Mean p-best (%)	Trial Name(s)
Alemtuzumab	85	28	CAMMS223; CARE-MS I; CARE-MS II
Cladribine 3.5 mg/kg	70	6	CLARITY
Dimethyl fumarate	49	0	CONFIRM; DEFINE
Fingolimod	51	0	FREEDOMS; FREEDOMS II
Glatiramer acetate 20 mg	32	0	CombiRx; CONFIRM; REGARD
IFNB-1a IM	43	0	BRAVO; CombiRx; EVIDENCE; MSCRG; RADIANCE-B; SUNBEAM
IFNB-1a SC 44 µg	30	0	CAMMS223; CARE-MS I; CARE-MS II; EVIDENCE; OPERA I; OPERA II; REGARD
Natalizumab	82	17	AFFIRM
Ocrelizumab	77	12	OPERA I; OPERA II
Ofatumumab	80	15	ASCLEPIOS I; ASCLEPIOS II
Ozanimod	14	0	RADIANCE-B; SUNBEAM
Placebo	8	0	AFFIRM; BRAVO; CLARITY; CONFIRM; DEFINE; FREEDOMS; FREEDOMS II; MSCRG; TEMSO; TOWER
Ponesimod	51	2	OPTIMUM
Teriflunomide 7 mg	22	0	TEMSO; TOWER
Teriflunomide 14 mg	33	0	ASCLEPIOS I; ASCLEPIOS II; OPTIMUM; TEMSO; TOWER; ULTIMATE I; ULTIMATE II
Ublituximab	72	19	ULTIMATE I; ULTIMATE II

6mCDP 6-month confirmed disability progression, IFNB interferon beta, IM intramuscular, p-best probability of being the best treatment, SC subcutaneous, SUCRA surface under the cumulative ranking curve.

Appendix E Summary of Direct Evidence and NMA Estimates

Table E.1. Comparison of direct evidence and NMA estimates for ARR.

Comparison	Direct Evidence RR (95% CrI)	Network Meta-analysis RR (95% CrI)
Alemtuzumab vs. IFNB-1a SC 44	CAMMS223: 0.31 ^a CARE-MS I: 0.45 (0.32 to 0.63) CARE-MS II: 0.51 (0.39 to 0.65)	0.44 (0.35 to 0.53)
Cladribine vs. placebo	CLARITY: 0.42 ^a	0.42 (0.30 to 0.59)
Dimethyl fumarate vs. glatiramer acetate 20 mg	CONFIRM: 0.78 ^a	0.79 (0.62 to 1.01)
Dimethyl fumarate vs. placebo	CONFIRM: 0.56 ^a DEFINE: 0.47 (0.37 to 0.61)	0.50 (0.40 to 0.62)
Fingolimod vs. glatiramer acetate 20 mg	ASSESS: 0.59 ^a	0.66 (0.54 to 0.81)
Fingolimod vs. IFNB-1a IM	TRANSFORMS: 0.48 ^a	0.55 (0.45 to 0.67)
Fingolimod vs. IFNB-1b SC	GOLDEN: 0.31 ^a	0.59 (0.44 to 0.73)
Fingolimod vs. placebo	FREEDOMS: 0.45 ^a FREEDOMS II: 0.52 (0.40 to 0.66)	0.42 (0.35 to 0.50)
Glatiramer acetate 20 mg vs. placebo	Boiko et al. (2018): 0.72 ^a Bornstein et al. (1987): 0.22 ^a CONFIRM: 0.71 ^a Copolymer 1 MS trial: 0.70 ^a	0.64 (0.55 to 0.73)
Glatiramer acetate 40 mg vs. placebo	GALA: 0.66 (0.54 to 0.80)	0.65 (0.48 to 0.90)
IFNB-1a IM vs. glatiramer acetate 20 mg	Calabrese et al. (2012): 1.00 ^a CombiRx: 1.46 ^a	1.20 (1.02 to 1.43)
IFNB-1a IM vs. IFNB-1b SC	Etemadifar et al. (2006): 0.88 ^a Stepien et al. (2013): 0.81 ^a	1.06 (0.84 to 1.28)
IFNB-1a IM vs. placebo	BRAVO: 0.74 (0.60 to 0.92) MSCRG: 0.82 ^a	0.77 (0.65 to 0.89)
IFNB-1a SC 22 µg vs. placebo	PRISMS: 0.71 ^a	0.69 (0.53 to 0.90)
IFNB-1a SC 44 µg vs. glatiramer acetate 20 mg	Calabrese et al. (2012): 0.80 ^a REGARD: 1.03 ^a	1.01 (0.85 to 1.20)
IFNB-1a SC 44 µg vs. IFNB-1a IM	Calabrese et al. (2012): 0.80 ^a Etemadifar et al. (2006): 1.16 ^a EVIDENCE: 0.84 ^a	0.84 (0.71 to 1.00)
IFNB-1a SC 44 µg vs. IFNB-1a SC 22 µg	PRISMS: 0.96 ^a	0.92 (0.70 to 1.21)
IFNB-1a SC 44 µg vs. IFNB-1b SC	Etemadifar et al. (2006): 1.02 ^a	0.89 (0.70 to 1.08)
IFNB-1a SC 44 µg vs. placebo	PRISMS: 0.68 ^a	0.64 (0.54 to 0.75)
IFNB-1a SC 44 µg vs. teriflunomide 7 mg	TENERE: 0.54 ^a	0.81 (0.62 to 0.99)
IFNB-1a SC 44 µg vs. teriflunomide 14 mg	TENERE: 0.85 ^a	0.96 (0.75 to 1.18)
IFNB-1b SC vs. glatiramer acetate 20 mg	BEYOND: 1.06 ^a	1.13 (0.96 to 1.41)
IFNB-1b SC vs. placebo	IFNB MS: 0.66 ^a	0.72 (0.61 to 0.89)
Natalizumab vs. placebo	AFFIRM: 0.32 ^a	0.32 (0.23 to 0.42)
Ocrelizumab vs. IFNB-1a SC 44	OPERA I: 0.54 (0.40 to 0.72) OPERA II: 0.53 (0.40 to 0.71)	0.53 (0.42 to 0.68)
Ofatumumab vs. teriflunomide 14 mg	ASCLEPIOS I: 0.50 (0.37 to 0.65) ASCLEPIOS II: 0.42 (0.31 to 0.56)	0.45 (0.35 to 0.57)
Ozanimod vs. IFNB-1a IM	RADIANCE-B: 0.62 (0.51 to 0.77) SUNBEAM: 0.52 (0.41 to 0.66)	0.56 (0.44 to 0.72)
Ponesimod vs. teriflunomide 14 mg	OPTIMUM: 0.70 (0.54 to 0.90)	0.70 (0.51 to 0.95)
Teriflunomide 7 mg vs. placebo	TEMSO: 0.69 ^a TOWER: 0.78 ^a	0.79 (0.67 to 0.99)
Teriflunomide 14 mg vs. placebo	TEMSO: 0.68 ^a TOWER: 0.64 ^a	0.67 (0.56 to 0.82)
Teriflunomide 7 mg vs. teriflunomide 14 mg	TEMSO: 1.00 ^a TENERE: 1.58 ^a TOWER: 1.22 ^a	1.19 (1.00 to 1.45)
Ublituximab vs. teriflunomide 14 mg	ULTIMATE I: 0.41 (0.27 to 0.62) ULTIMATE II: 0.51 (0.33 to 0.78)	0.46 (0.33 to 0.63)

^a RR was not reported by the specified RCT, so an RR was estimated based on the reported ARR values for each arm.

ARR annualised relapse rate, CrI credible interval, IFNB interferon beta, IM intramuscular, RCT randomised controlled trial, RR rate ratio, SC subcutaneous.

Table E.2. Comparison of direct evidence and NMA estimates for time to 3mCDP.

Comparison	Direct Evidence HR (95% CrI)	Network Meta-analysis HR (95% CrI) (Predefined)	Network Meta-analysis HR (95% CrI) (EDSS-aligned)
Alemtuzumab vs. IFNB-1a SC 44	HAS meta-analysis: 0.66 (0.49-0.87) ^a	0.65 (0.46 to 0.91)	0.55 (0.31 to 0.97)
Cladribine vs. placebo	CLARITY: 0.67 (0.48-0.93)	0.67 (0.46 to 0.98)	0.67 (0.45 to 0.98)
Dimethyl fumarate vs. placebo	CONFIRM: 0.79 (0.52-1.19) DEFINE: 0.62 (0.44-0.87)	0.66 (0.51 to 0.89)	0.66 (0.50 to 0.89)
Fingolimod vs. placebo	FREEDOMS: 0.70 (0.52-0.96) FREEDOMS II: 0.83 (0.61-1.12)	0.74 (0.58 to 0.92)	0.73 (0.58 to 0.93)
Fingolimod vs. IFNB-1a IM	TRANSFORMS: 0.74 ^b	0.91 (0.66 to 1.27)	0.91 (0.64 to 1.29)
Glatiramer acetate 20 mg vs. IFNB-1b SC	BEYOND: 0.95 ^b	0.98 (0.74 to 1.30)	0.98 (0.75 to 1.30)
Glatiramer acetate 20 mg vs. placebo	Bornstein et al., 1987: 0.34 ^b Copolymer 1 MS trial: 0.86 ^b CONFIRM: 0.93 (0.63-1.37)	0.77 (0.58 to 1.02)	0.78 (0.59 to 1.01)
IFNB-1a IM vs. placebo	BRAVO: 0.74 (0.51-1.09)	0.81 (0.60 to 1.08)	0.81 (0.59 to 1.09)
IFNB-1a SC 22 µg vs. placebo	PRISMS: 0.68 (0.48-0.98)	0.70 (0.48 to 1.04)	0.71 (0.47 to 1.03)
IFNB-1a SC 44 µg vs. IFNB-1a IM	EVIDENCE: 0.87 (0.58-1.31)	0.82 (0.58 to 1.15)	0.83 (0.59 to 1.17)
IFNB-1a SC 44 µg vs. placebo	PRISMS: 0.62 (0.43-0.91)	0.66 (0.48 to 0.91)	0.67 (0.47 to 0.93)
IFNB-1b SC vs. placebo	INFB MS: 0.70 ^b	0.79 (0.56 to 1.11)	0.79 (0.56 to 1.09)
Natalizumab vs. placebo	AFFIRM: 0.58 (0.43-0.77)	0.57 (0.41 to 0.81)	0.57 (0.40 to 0.81)
Ocrelizumab vs. IFNB-1a SC 44	OPERA I: 0.57 (0.37-0.90) OPERA II: 0.63 (0.42-0.92)	0.60 (0.44 to 0.82)	0.60 (0.44 to 0.84)
Ofatumumab vs. teriflunomide 14 mg	ASCLEPIOS I (predefined): 0.652 (0.445-0.957) ASCLEPIOS I (EDSS-aligned): 0.578 (0.388-0.862) ASCLEPIOS II (predefined): 0.660 (0.447-0.947) ASCLEPIOS II (EDSS-aligned): 0.615 (0.405-0.936)	0.65 (0.48 to 0.87)	0.60 (0.44 to 0.82)
Ozanimod vs. IFNB-1a IM	RADIANCE-B and SUNBEAM: 0.95 (0.68-1.33) ^c	0.96 (0.65 to 1.40)	0.96 (0.65 to 1.39)
Ponesimod vs. teriflunomide 14 mg	OPTIMUM: 0.83 (0.58-1.18)	0.83 (0.55 to 1.24)	0.83 (0.55 to 1.24)
Teriflunomide 7 mg vs. placebo	TEMPO: 0.763 (0.555-1.049) ^d TOWER: 0.955 (0.677-1.347) ^d	0.85 (0.66 to 1.11)	0.85 (0.65 to 1.12)
Teriflunomide 14 mg vs. placebo	TEMPO: 0.702 (0.506-0.973) ^d TOWER: 0.685 (0.467-1.004) ^d	0.70 (0.52 to 0.93)	0.71 (0.53 to 0.93)
Ublituximab vs. teriflunomide 14 mg	ULTIMATE I/II: 0.843 (0.504-1.407) ^{e,f}	0.84 (0.48 to 1.45)	0.83 (0.48 to 1.45)

^a A pooled time to 3mCDP estimate derived from CAMMS223, CARE-MS I, and CARE-MS II was reported in a 2016 HAS meta-analysis [98]. Because CARE-MS I and CARE-MS II do not publicly report the result for the outcome of time to 3mCDP, the decision was made to use the HAS meta-analysis value to include these trials in the time to 3mCDP network. This HAS value was also used by McCool et al. (2019) [99] and Samjoo et al. (2020) [100].

^b HR was not reported by the specified RCT, so an HR was derived from the reported proportion of patients who progressed over the trial duration for each arm using formulae described by Watkins and Bennett (2018) [97].

^c Disability progression was assessed as a prespecified pooled analysis of the RADIANCE-B and SUNBEAM trials; values are for the pooled analysis as reported in the RADIANCE pivotal trial publication (Cohen et al. [2019] [30]).

^d Value to three decimal places obtained from a European Medicines Agency report [93].

^e Disability progression was assessed as a prespecified pooled analysis of ULTIMATE I and ULTIMATE II.

^f Value to three decimal places obtained from a conference poster [38].

3mCDP 3-month confirmed disability progression, CrI credible interval, EDSS Expanded Disability Status Scale, HR hazard ratio, IFNB interferon beta, IM intramuscular, RCT randomised controlled trial, SC subcutaneous.

Table E.3. Comparison of direct evidence and NMA estimates for time to 6mCDP.

Comparison	Direct Evidence HR (95% CrI)	Network Meta-analysis HR (95% CrI) (Predefined)	Network Meta-analysis HR (95% CrI) (EDSS-aligned)
Alemtuzumab vs. IFNB-1a SC 44	CAMMS223: 0.25 (0.11 to 0.57) CARE-MS I: 0.70 (0.40 to 1.23) CARE-MS II: 0.58 (0.38 to 0.87)	0.53 (0.38 to 0.75)	0.54 (0.38 to 0.75)
Cladribine vs. placebo	CLARITY: 0.53 (0.36 to 0.79) ^a	0.54 (0.33 to 0.85)	0.54 (0.34 to 0.85)
Dimethyl fumarate vs. placebo	CONFIRM: 0.62 (0.37 to 1.03) DEFINE: 0.77 (0.52 to 1.14) ^b	0.68 (0.47 to 0.95)	0.68 (0.48 to 0.96)
Fingolimod vs. placebo	FREEDOMS: 0.63 (0.44 to 0.90) FREEDOMS II: 0.72 (0.48 to 1.07)	0.66 (0.48 to 0.91)	0.67 (0.49 to 0.92)
Glatiramer acetate 20 mg vs. IFNB-1a IM	CombiRx: 1.17 ^c	1.08 (0.79 to 1.48)	1.09 (0.78 to 1.52)
Glatiramer acetate 20 mg vs. IFNB 1b SC 44 µg	REGARD: 0.74 ^c	0.99 (0.65 to 1.52)	0.98 (0.65 to 1.48)
Glatiramer acetate 20 mg vs. placebo	CONFIRM: 0.87 (0.55 to 1.38)	0.77 (0.53 to 1.11)	0.79 (0.55 to 1.12)
IFNB-1a IM vs. placebo	BRAVO: 0.73 (0.47 to 1.14) MSCRG: 0.58 ^c	0.71 (0.52 to 0.98)	0.72 (0.54 to 0.98)
IFNB-1a SC 44 µg vs. IFNB-1a IM	EVIDENCE: 0.70 (0.39 to 1.25)	1.09 (0.69 to 1.71)	1.12 (0.72 to 1.70)
Natalizumab vs. placebo	AFFIRM: 0.46 (0.33 to 0.64)	0.46 (0.30 to 0.68)	0.46 (0.31 to 0.69)
Ocrelizumab vs. IFNB-1a SC 44	OPERA-I: 0.57 (0.34 to 0.95) OPERA-II: 0.63 (0.40 to 0.98)	0.60 (0.41 to 0.88)	0.60 (0.41 to 0.87)
Ofatumumab vs. teriflunomide 14 mg	ASCLEPIOS I (predefined): 0.607 (0.396 to 0.930) ASCLEPIOS I (EDSS-aligned): 0.564 (0.361 to 0.880) ASCLEPIOS II (predefined): 0.756 (0.489 to 1.170) ASCLEPIOS II (EDSS-aligned): 0.671 (0.418 to 1.077)	0.67 (0.47 to 0.96)	0.61 (0.42 to 0.89)
Ozanimod vs. IFNB-1a IM	RADIANCE-B and SUNBEAM: 1.41 (0.92 to 2.17) ^d	1.42 (0.86 to 2.34)	1.40 (0.86 to 2.28)
Ponesimod vs. teriflunomide 14 mg	OPTIMUM: 0.84 (0.57 to 1.24)	0.84 (0.53 to 1.33)	0.85 (0.53 to 1.33)
Teriflunomide 7 mg vs. placebo	TEMSO: 0.750 (0.507 to 1.110) ^e TOWER: 1.054 (0.690 to 1.610) ^e	0.88 (0.63 to 1.24)	0.88 (0.62 to 1.23)
Teriflunomide 14 mg vs. placebo	TEMSO: 0.749 (0.505 to 1.111) ^e TOWER: 0.843 (0.533 to 1.334) ^e	0.79 (0.56 to 1.12)	0.78 (0.56 to 1.12)
Ublituximab vs. teriflunomide 14 mg	ULTIMATE I/II: 0.657 (0.358 to 1.205) ^{f,g}	0.66 (0.34 to 1.26)	0.65 (0.34 to 1.23)

^a Obtained from a European Medicines Agency report [101] since not reported by the pivotal trial publication [13].

^b Obtained from a European Medicines Agency report [95] since not reported by the pivotal trial publication [17].

^c HR was not reported by the specified RCT, so an HR was derived from the reported proportion of patients who progressed over the trial duration for each arm using formulae described by Watkins and Bennett (2018) [97].

^d Disability progression was assessed as a prespecified pooled analysis of the RADIANCE-B and SUNBEAM trials; values are for the pooled analysis as reported in the RADIANCE pivotal trial publication [30].

^e Value to three decimal places obtained from a European Medicines Agency report [93].

^f Disability progression was assessed as a prespecified pooled analysis of ULTIMATE I and ULTIMATE II.

^g Value to three decimal places obtained from a conference poster [38].

6mCDP 6-month confirmed disability progression, CrI credible interval, EDSS Expanded Disability Status Scale, HR hazard ratio, IFNB interferon beta, IM intramuscular, RCT randomised controlled trial, SC subcutaneous.

Appendix F Inconsistency Analysis

Table F.1. Model fit parameters for the ARR inconsistency analysis.

Model	DIC	Total Residual Deviance	SD (95% CrI)
Consistency (i.e., main analysis)	671.97	98.04 (vs. 85 data points)	0.114 (0.014 to 0.226)
Inconsistency	667.58	94.80 (vs. 85 data points)	0.095 (0.003 to 0.239)

ARR annualised relapse rate, CrI credible interval, DIC deviance information criterion, SD standard deviation.

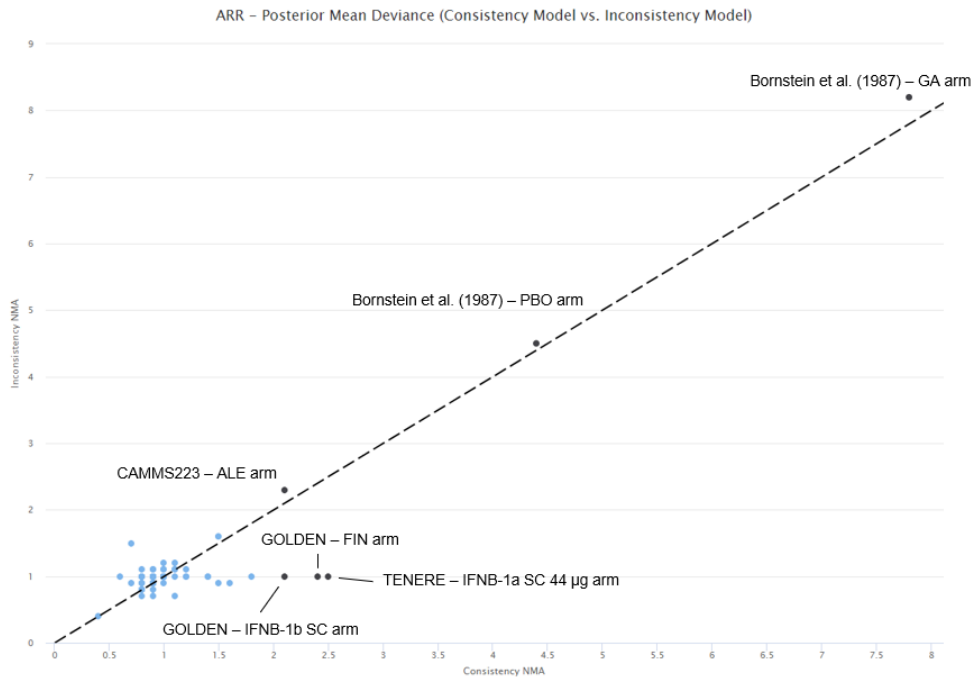


Figure F.1. Unrelated mean effects scatter plot for the ARR inconsistency analysis.

Note: Labeled trials had a posterior mean deviance >2 for the consistency model and/or the inconsistency model, and so were identified as potentially contributing to inconsistency.

ALE alemtuzumab, ARR annualised relapse rate, GA glatiramer acetate, IFNB interferon beta, NMA network meta-analysis, PBO placebo, SC subcutaneous.

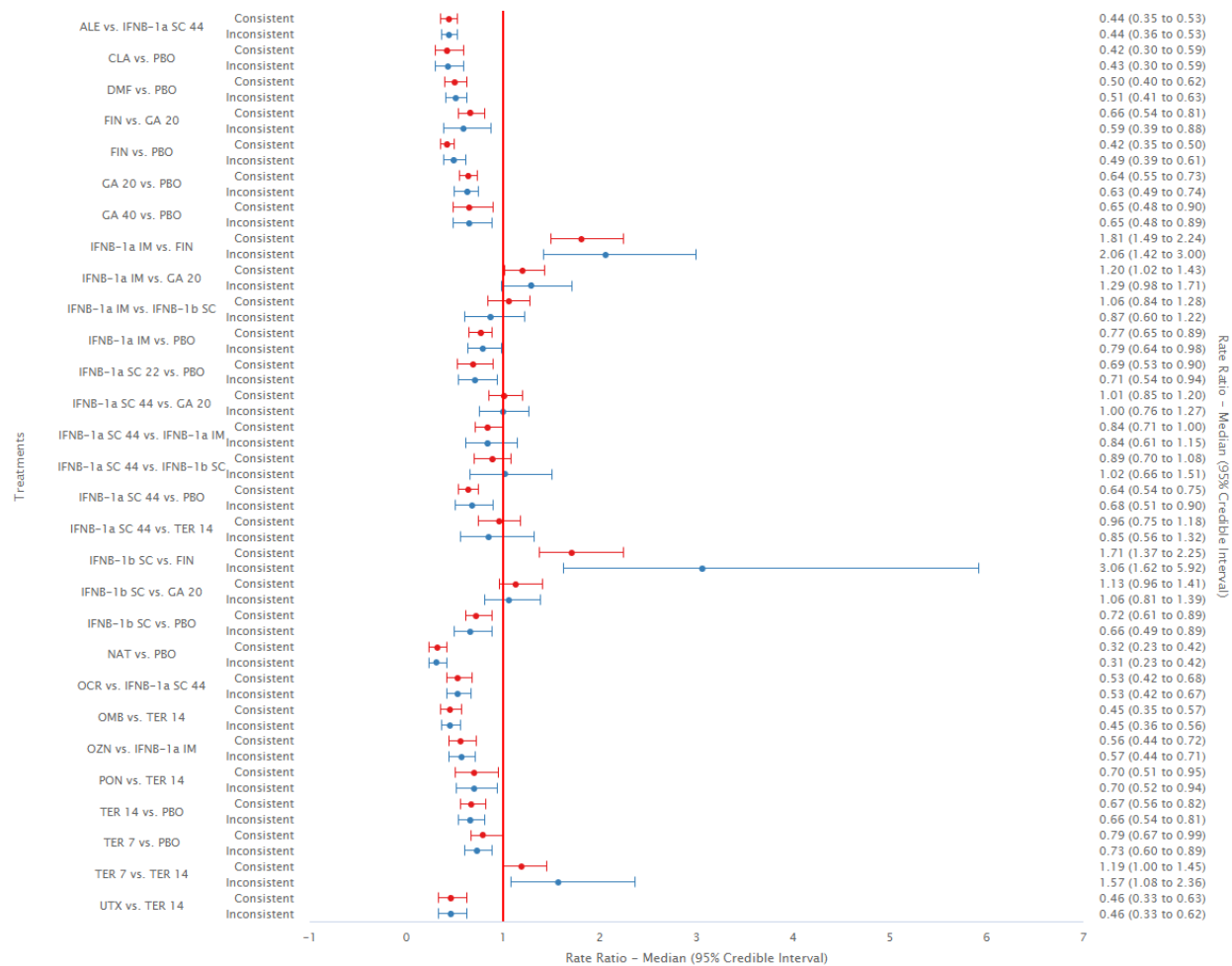


Figure F.2. Forest plot for ARR inconsistency analysis.

Note: Results for the consistency model (i.e., main analysis) are red. Results for the inconsistency model are blue. ARR annualised relapse rate.

Table F.2. Model fit parameters for the time to 3mCDP inconsistency analysis (predefined).

Model	DIC	Total Residual Deviance	SD (95% CrI)
Consistency (i.e., main analysis)	-16.76	24.01 (vs. 28 data points)	0.068 (0.017 to 0.188)
Inconsistency	-15.46	25.56 (vs. 28 data points)	0.073 (0.017 to 0.223)

3mCDP 3-month confirmed disability progression, CrI credible interval, DIC deviance information criterion, SD standard deviation.

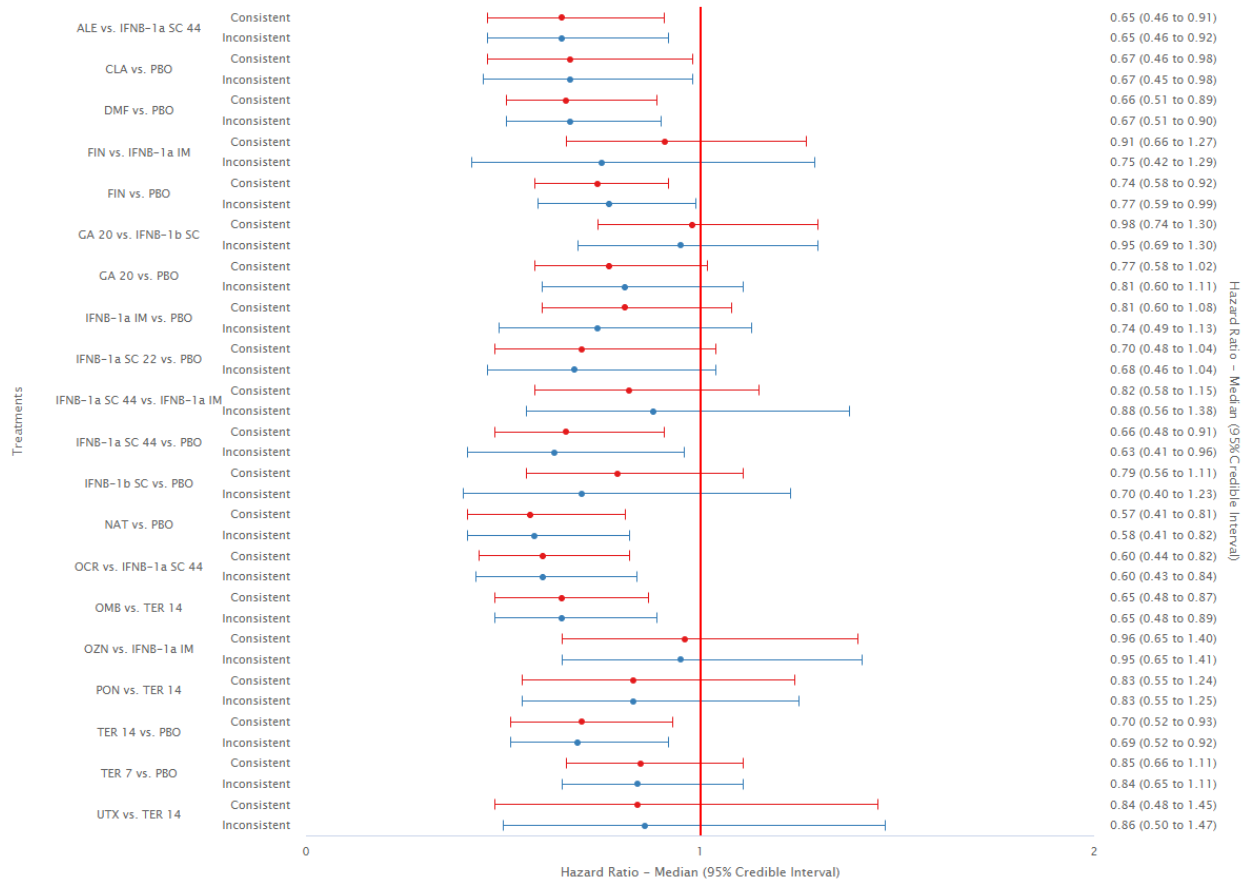


Figure F.3. Forest plot for the time to 3mCDP inconsistency analysis (predefined).

Note: Results for the consistency model (i.e., main analysis) are red. Results for the inconsistency model are blue. 3mCDP 3-month confirmed disability progression.

Table F.3. Model fit parameters for the time to 6mCDP inconsistency analysis (predefined).

Model	DIC	Total Residual Deviance	SD (95% CrI)
Consistency (i.e., main analysis)	-3.55	26.91 (vs. 26 data points)	0.088 (0.020 to 0.264)
Inconsistency	-5.48	24.21 (vs. 26 data points)	0.084 (0.020 to 0.263)

6mCDP 6-month confirmed disability progression, CrI credible interval, DIC deviance information criterion, SD standard deviation.

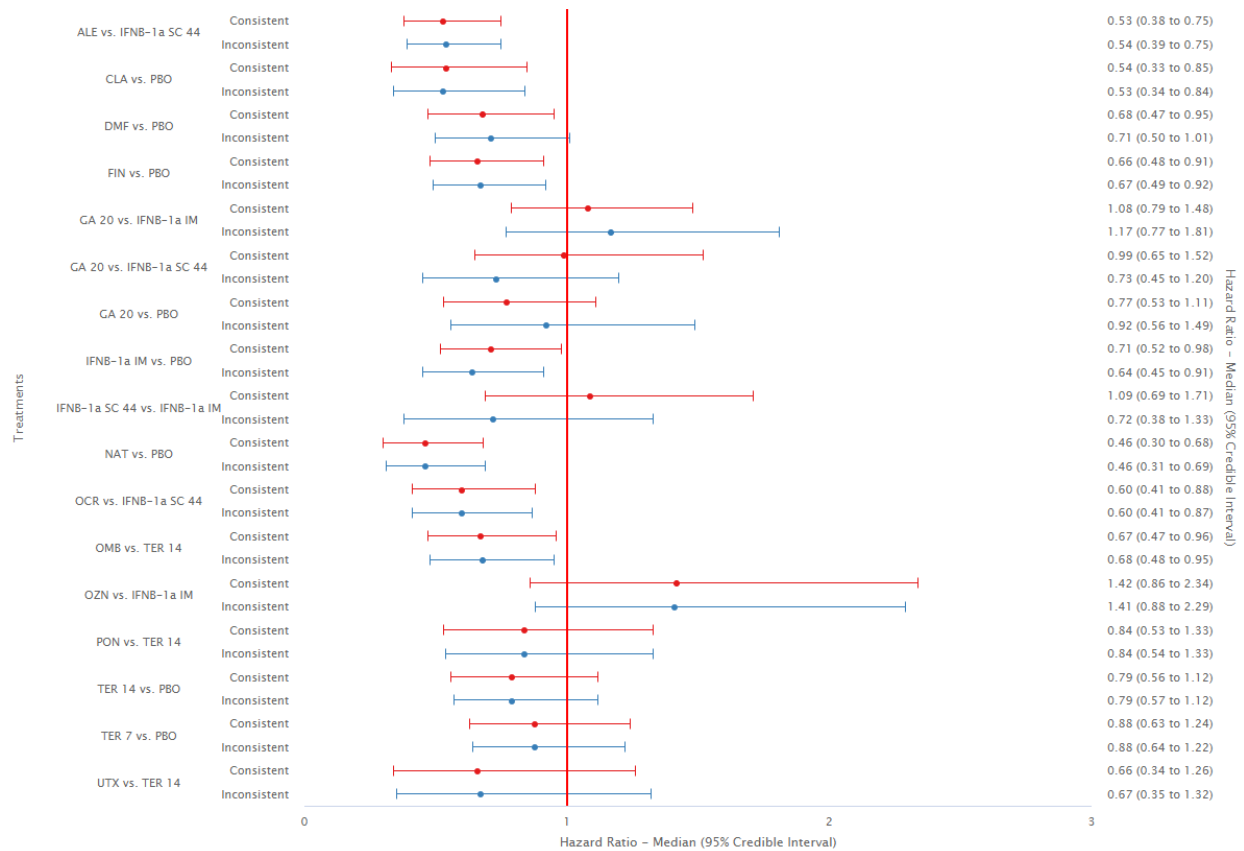


Figure F.4. Forest plot for the time to 6mCDP inconsistency analysis (predefined).

Note: Results for the consistency model (i.e., main analysis) are red. Results for the inconsistency model are blue. 6mCDP 6-month confirmed disability progression.

Appendix G

Sensitivity Analyses

Sensitivity analysis #1: Fixed effects models instead of random effects models

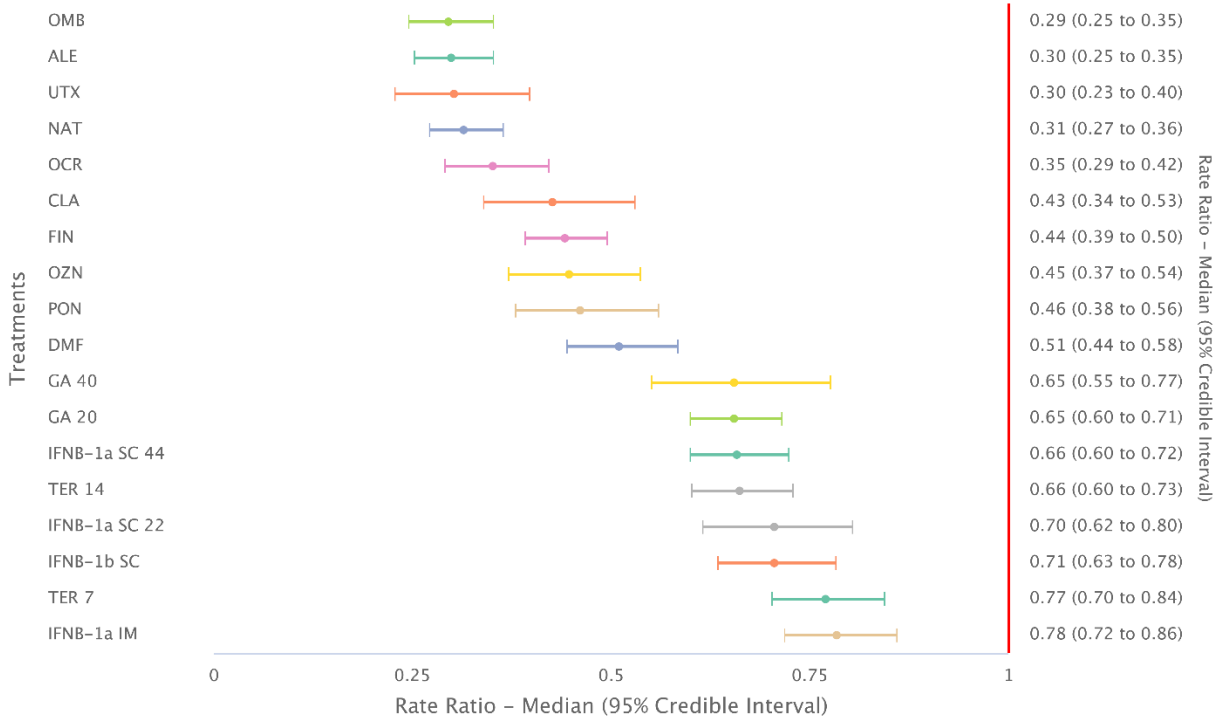


Figure G.1. ARR network meta-analysis results (treatment vs. placebo) for sensitivity analysis #1 (fixed effects model).

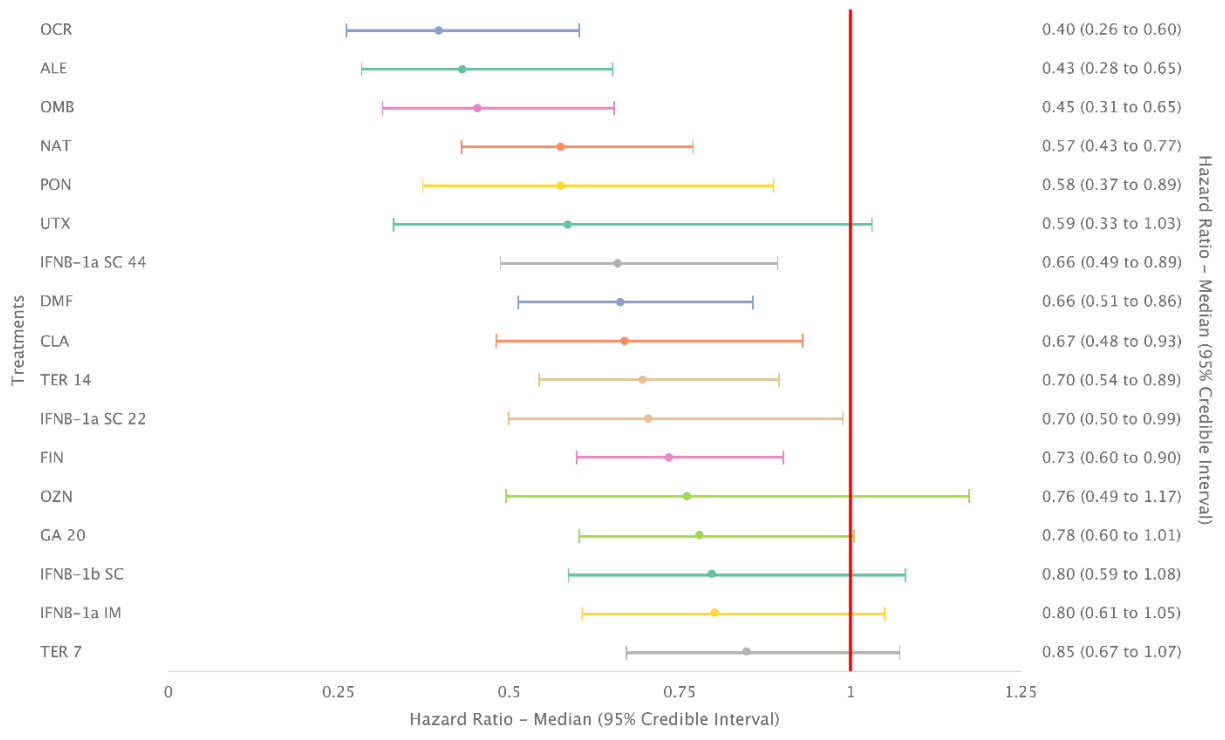


Figure G.2. Time to 3mCDP network meta-analysis results (treatment vs. placebo) for sensitivity analysis #1 (fixed effects model) (predefined).

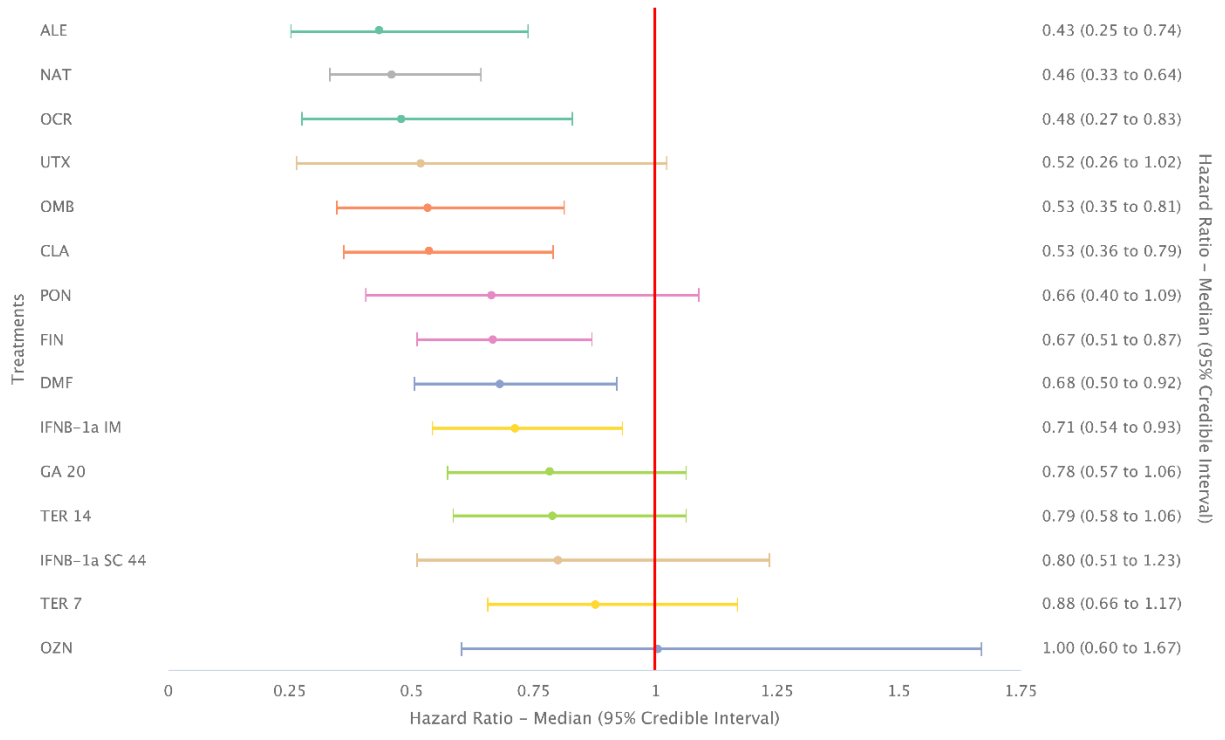


Figure G.3. Time to 6mCDP network meta-analysis results (treatment vs. placebo) for sensitivity analysis #1 (fixed effects model) (predefined).

Sensitivity analysis #2: Inclusion of the ADVANCE trial

Table G.1. Input data additions for sensitivity analysis #2 (inclusion of the ADVANCE trial).

Trial Name	Treatment	ARR			3mCDP				6mCDP			
		ARR (mean)	Sample Size	Trial Duration (weeks) ^a	HR for Time to Event (95% CI)	Proportion with CDP (%)	Ln(HR)	Ln(HR SE)	HR for Time to Event (95% CI)	Proportion with CDP (%)	Ln(HR)	Ln(HR SE)
ADVANCE	PBO	0.397	500	48	-	11%	NA	NA	-	8% ^b	NA	NA
	PEG	0.256	512	48	0.62 (0.40-0.97)	7%	-0.47337	0.22598	0.46 (0.26-0.81) ^b	4% ^b	-0.77890	0.28989

^a Where trial duration was reported in years or months, it was assumed that 1 year = 12 months and 1 year = 52 weeks.

^b Obtained from the Summary of Product Characteristics for pegylated interferon beta-1a [94] since not reported by the pivotal trial publication [1].

3mCDP 3-month confirmed disability progression, *6mCDP* 6-month confirmed disability progression, *ARR* annualised relapse rate, *CI* confidence interval, *HR* hazard ratio, *NA* not applicable, *PEG* pegylated interferon beta-1a, *PBO* placebo, *SE* standard error.

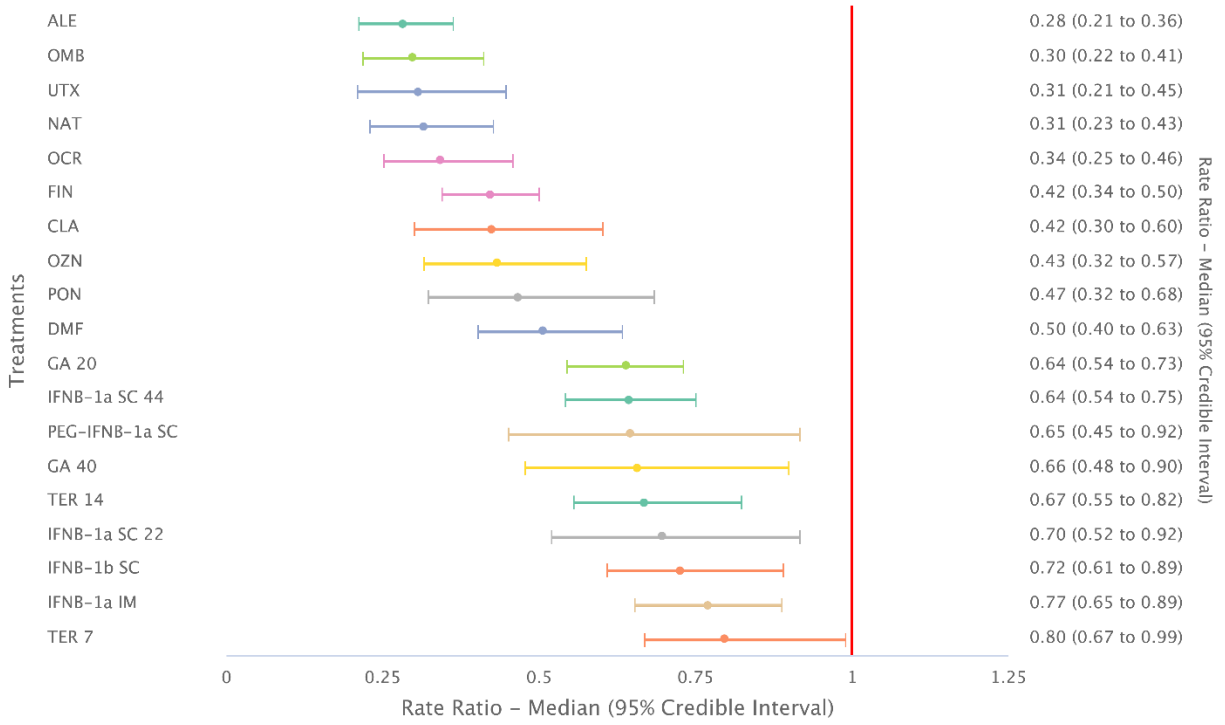


Figure G.4. ARR network meta-analysis results (treatment vs. placebo) for sensitivity analysis #2 (inclusion of the ADVANCE trial).

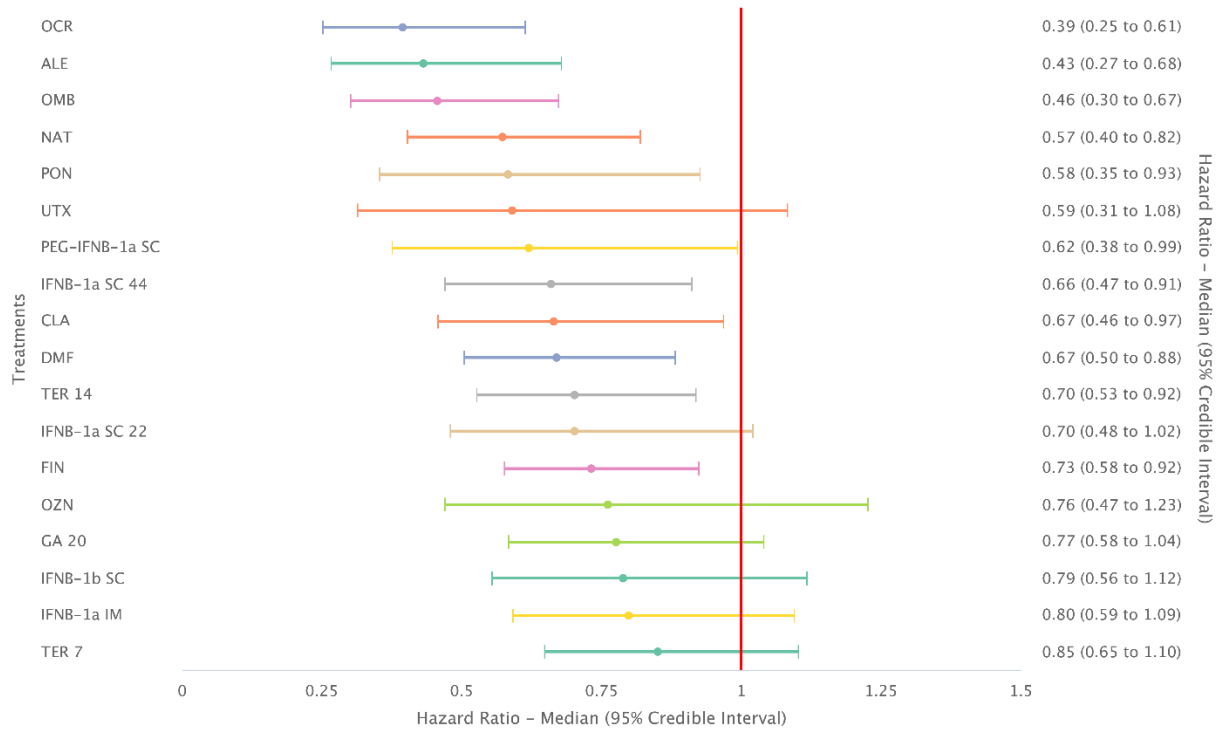


Figure G.5. Time to 3mCDP network meta-analysis results (treatment vs. placebo) for sensitivity analysis #2 (inclusion of the ADVANCE trial) (predefined).

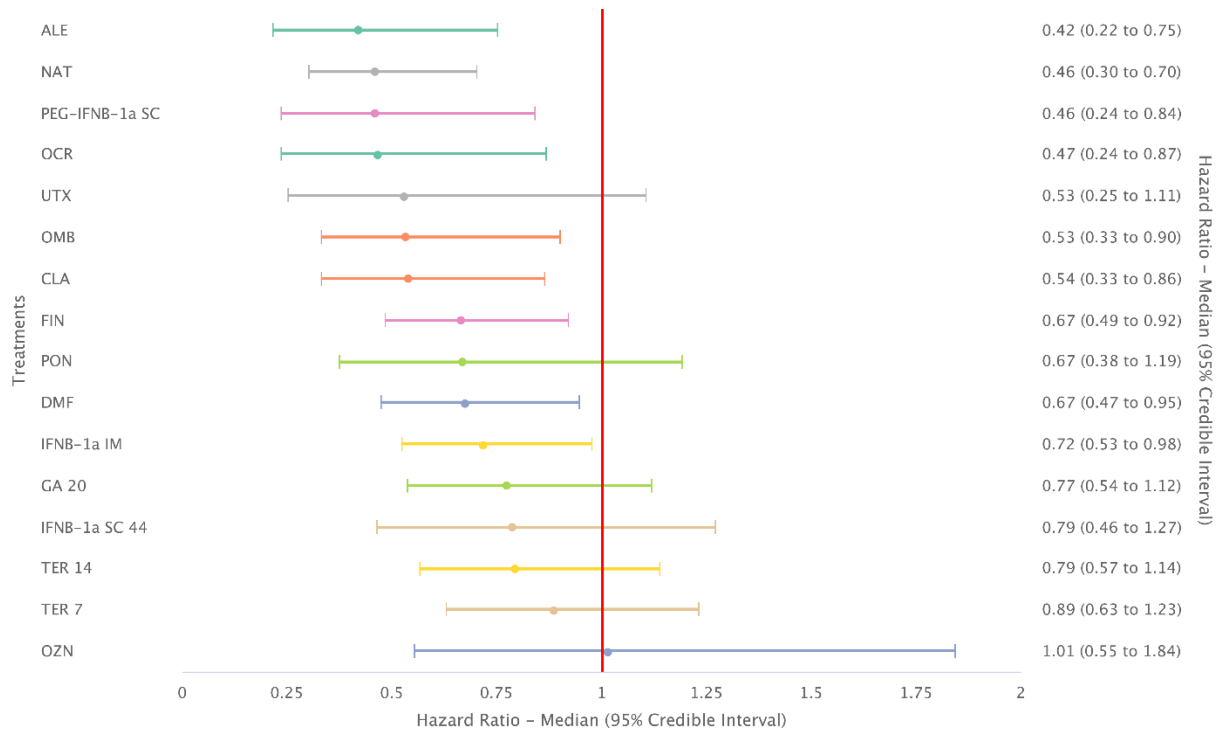


Figure G.6. Time to 6mCDP network meta-analysis results (treatment vs. placebo) for sensitivity analysis #2 (inclusion of the ADVANCE trial) (predefined).

Sensitivity analysis #3: Inclusion of the INCOMIN trial

Table G.2. Input data additions for sensitivity analysis #3 (inclusion of the INCOMIN trial).

Trial Name	Treatment	ARR			6mCDP			
		ARR (mean)	Sample Size	Trial Duration (weeks) ^a	HR for Time to Event (95% CI)	Proportion with CDP (%)	Ln(HR)	Ln(HR SE)
INCOMIN	IFNB-1a IM	0.7	92	104	-	30%	NA	NA
	IFNB-1b SC	0.5	96	104	NR	14%	-0.91391 ^b	0.33640 ^b

^a Where trial duration was reported in years or months, it was assumed that 1 year = 12 months and 1 year = 52 weeks.

^b Derived from the proportion of patients who progressed over the trial duration as per McCool et al. (2019) [99] using the formulae by Watkins and Bennett (2018) [97].
6mCDP 6-month confirmed disability progression, *ARR* annualised relapse rate, *CI* confidence interval, *HR* hazard ratio, *IFNB* interferon beta, *IM* intramuscular, *NA* not applicable, *NR* not reported, *SC* subcutaneous, *SE* standard error.

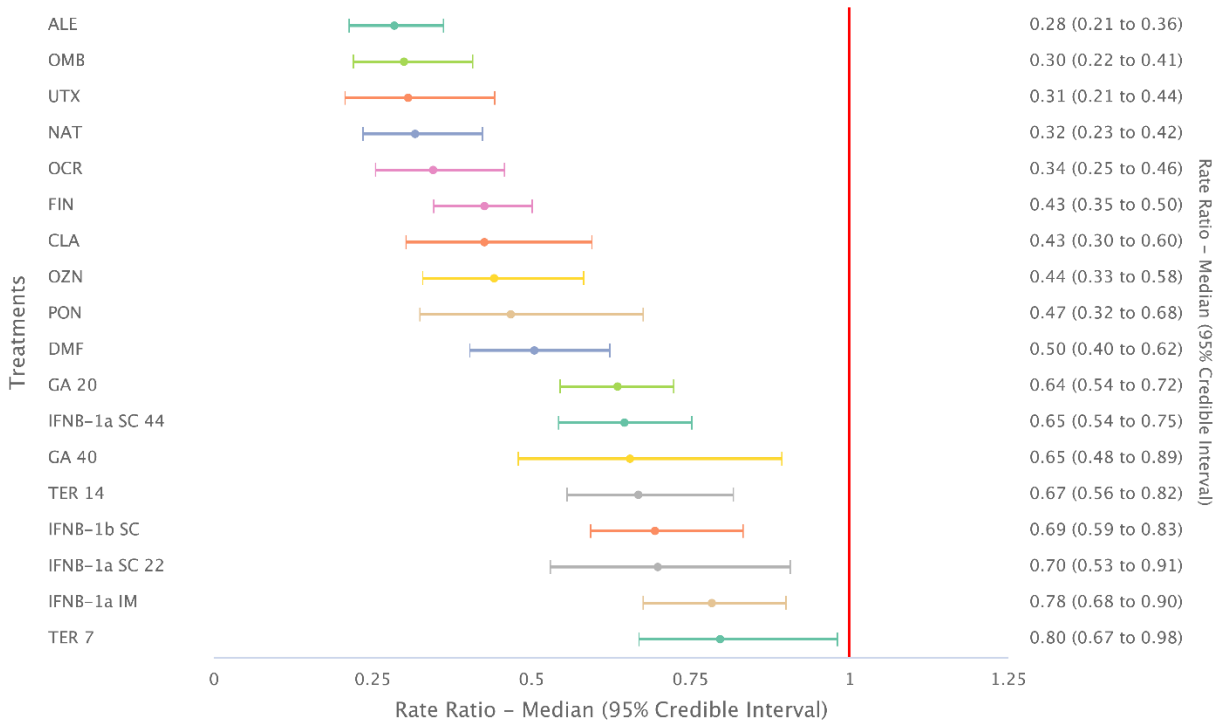


Figure G.7. ARR network meta-analysis results (treatment vs. placebo) for sensitivity analysis #3 (inclusion of the INCOMIN trial).

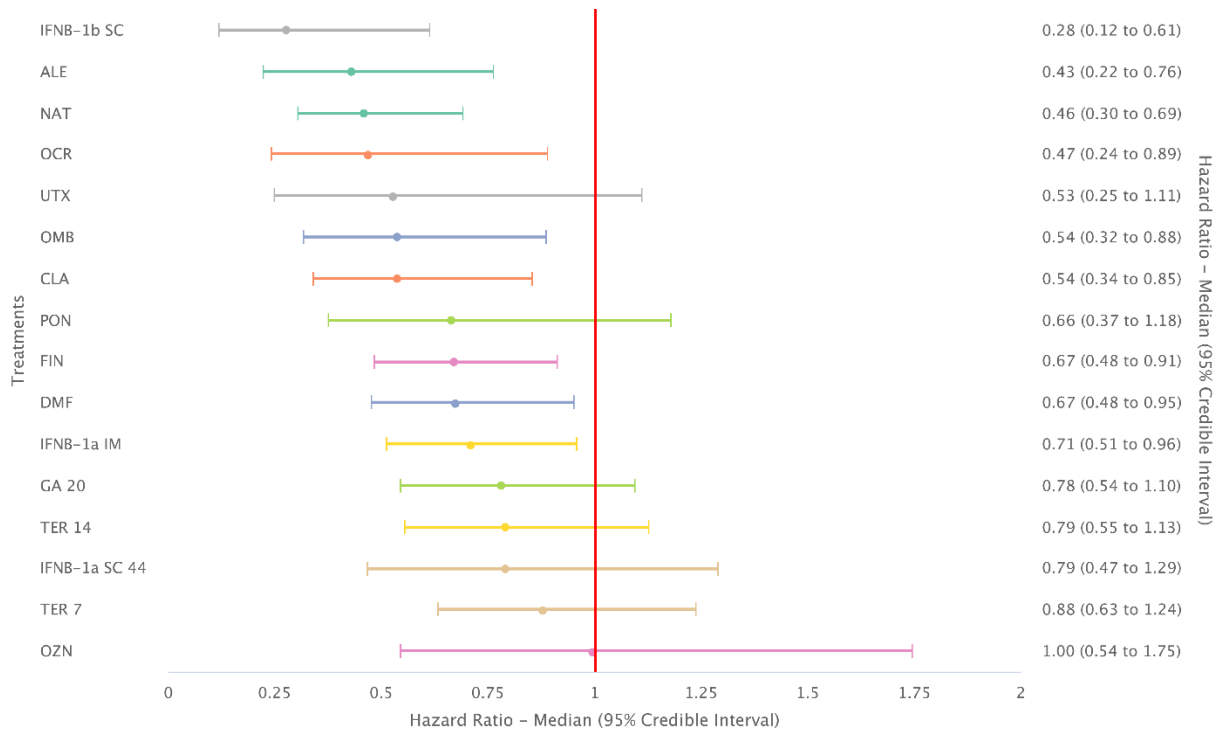


Figure G.8. Time to 6mCDP network meta-analysis results (treatment vs. placebo) for sensitivity analysis #3 (inclusion of the INCOMIN trial) (predefined).

Sensitivity analysis #4: Exclusion of trials identified as potential contributors to ARR analysis inconsistency

Table G.3. Trials iteratively excluded in sensitivity analysis #4.

Trial Name	Pivotal Publication Author (Year)	NCT Number	Relevant Treatments
TENERE	Vermersch (2014) [35]	NCT00883337	Teriflunomide PO 7 mg QD Teriflunomide PO 14 mg QD IFNB-1a SC 44 µg TIW
GOLDEN	Comi (2017) [23]	NCT01333501	Fingolimod 0.5 mg PO QD IFNB-1b SC 250 µg Q2D
Bornstein et al. (1987)	Bornstein (1987) [7]	Not available	Glatiramer acetate SC 20 mg QD Placebo

Note: These trials were excluded one by one in iterative analyses to assess their contribution to inconsistency. CAMMS223 also had a posterior mean deviance >2 for the consistency model and/or the inconsistency model but did not need to be excluded to address the inconsistency for ARR (i.e., excluding TENERE, GOLDEN, and Bornstein et al. (1987) was sufficient to decrease the DIC to less than 3).

DIC deviance information criterion, *IFNB* interferon beta, *PO* oral, *Q2D* once every other day, *QD* once a day, *QW* once a week, *SC* subcutaneous, *TIW* three times a week.

Table G.4. Model fit parameters for ARR inconsistency analysis for sensitivity analysis #4.

Analysis	DIC for Consistency Model	DIC for Inconsistency Model
Main analysis	671.97	667.58
Exclusion of TENERE trial	653.27	647.02
Exclusion of TENERE and GOLDEN trials	638.54	634.67
Exclusion of TENERE, GOLDEN, and Bornstein et al. (1987) trials	614.47	612.86

ARR annualised relapse rate, *CrI* credible interval, *DIC* deviance information criterion.

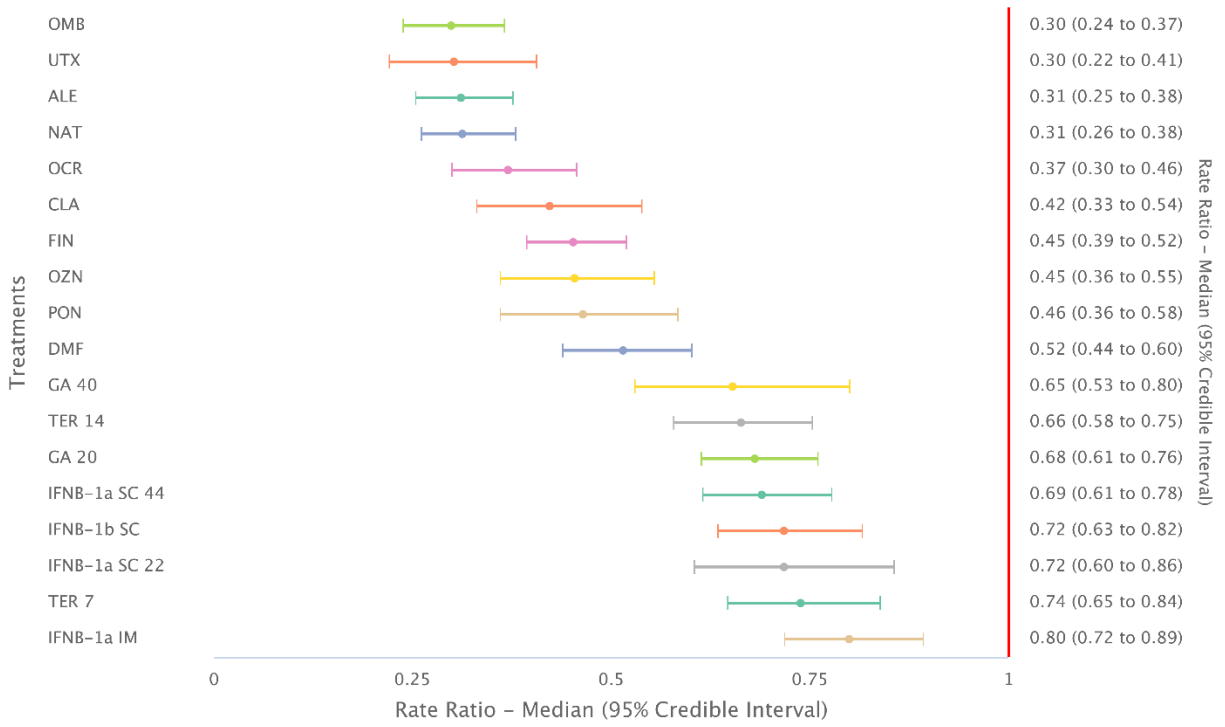


Figure G.9. ARR network meta-analysis results (treatment vs. placebo) for sensitivity analysis #4 (exclusion of TENERE, GOLDEN, and Bornstein et al. [1987] trials).

Sensitivity analysis #5: Only trials published in 2004 or later

Table G.5. Trials excluded for sensitivity analysis #5 (only trials published in 2004 or later).

Trial Name	Pivotal Publication Author (Year)	NCT Number	Relevant Treatments
Bornstein et al. (1987)	Bornstein (1987) [7]	Not available	Glatiramer acetate SC 20 mg QD Placebo
Copolymer 1 MS trial	Johnson (1995) [16]	Not available	Glatiramer acetate SC 20 mg QD Placebo
EVIDENCE	Panitch (2002) [19]	Not available	IFNB-1a SC 44 µg TIW IFNB-1a IM 30 µg QW
IFNB MS	IFNB Multiple Sclerosis Study Group (1993) [24]	Not available	IFNB-1b SC 250 µg Q2D Placebo
MSCRG	Jacobs (1996) [26]	Not available	IFNB-1a IM 30 µg QW Placebo
PRISMS	Ebers (1998) [29]	Not available	IFNB-1a SC 22 µg TIW IFNB-1a SC 44 µg TIW Placebo

Note: Some trials included additional treatment arms not listed here that were outside of the scope of the eligibility criteria for this study.

IFNB interferon beta, IM intramuscular, Q2D once every other day, QD once a day, QW once a week, SC subcutaneous, TIW three times a week.

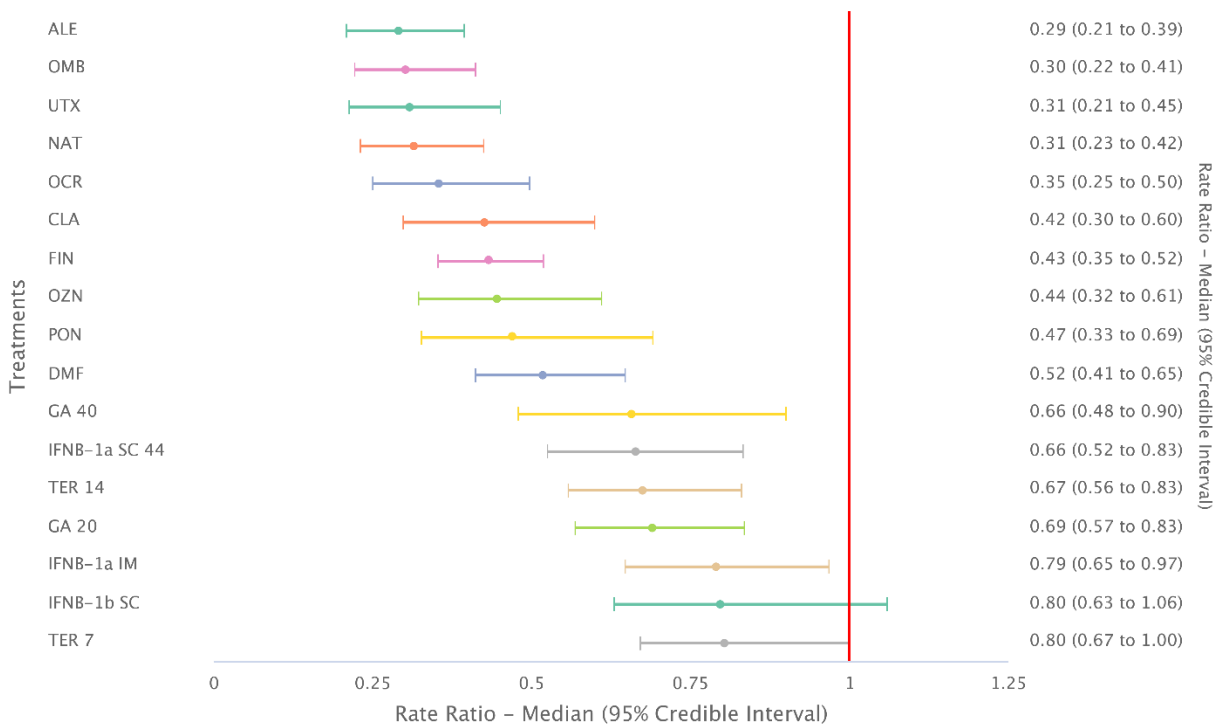


Figure G.10. ARR network meta-analysis results (treatment vs. placebo) for sensitivity analysis #5 (only trials published in 2004 or later).

Reference List

1. 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. *Lancet Neurology*. 2014;13(7):657-65.
2. Polman CH, O'Connor PW, Havrdova E *et al.* A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. *New England Journal of Medicine*. 2006;354(9):899-910.
3. Hauser SL, Bar-Or A, Cohen JA *et al.* Ofatumumab versus teriflunomide in multiple sclerosis. *New England Journal of Medicine*. 2020;383(6):546-57.
4. 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 Neurology*. 2021;78(1):48-60.
5. O'Connor P, Filippi M, Arnason B *et al.* 250 microg or microg interferon beta-1b versus 20 mg glatiramer acetate in relapsing-remitting multiple sclerosis: a prospective, randomised, multicentre study. *Lancet Neurology*. 2009;8(10):889-97.
6. Boiko AN, Lashch NY, Sharanova SN *et al.* A comparative placebo-controlled clinical trial of the efficacy and safety of glatiramer acetate 20 mg in patients with relapsing multiple sclerosis: first-year study results. *Neuroscience and Behavioral Physiology*. 2018;48(3):351-7.
7. Bornstein MB, Miller A, Slagle S *et al.* A pilot trial of Cop 1 in exacerbating-remitting multiple sclerosis. *New England Journal of Medicine*. 1987;317(7):408-14.
8. Vollmer TL, Sorensen PS, Selmaj K *et al.* A randomized placebo-controlled phase III trial of oral laquinimod for multiple sclerosis. *Journal of Neurology*. 2014;261(4):773-83.
9. Calabrese M, Bernardi V, Atzori M *et al.* Effect of disease-modifying drugs on cortical lesions and atrophy in relapsing-remitting multiple sclerosis. *Multiple Sclerosis Journal*. 2012;18(4):418-24.
10. CAMMS223 Trial Investigators. Alemtuzumab vs. interferon beta-1a in early multiple sclerosis. *New England Journal of Medicine*. 2008;359(17):1786-801.
11. 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*. 2012;380(9856):1819-28.
12. 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*. 2012;380(9856):1829-39.
13. 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):416-26.
14. Lublin FD, Cofield SS, Cutter GR *et al.* Randomized study combining interferon and glatiramer acetate in multiple sclerosis. *Annals of Neurology*. 2013;73(3):327-40.
15. Fox RJ, Miller DH, Phillips JT *et al.* Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis. *New England Journal of Medicine*. 2012;367(12):1087-97.
16. 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. *Neurology*. 1995;45(7):1268-76.
17. Gold R, Kappos L, Arnold DL *et al.* Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis. *New England Journal of Medicine*. 2012;367(12):1098-107.
18. Etemadifar M, Janghorbani M, Shaygannejad V. Comparison of Betaferon, Avonex, and Rebif in treatment of relapsing-remitting multiple sclerosis. *Acta Neurologica Scandinavica*. 2006;113(5):283-7.
19. 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):1496-506.
20. Kappos L, Radue E-W, O'Connor P *et al.* A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. *New England Journal of Medicine*. 2010;362(5):387-401.

21. Calabresi PA, Radue E-W, 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. *Lancet Neurology*. 2014;13(6):545-56.
22. Khan O, Rieckmann P, Boyko A, Selmaj K, Zivadinov R, GALA Study Group. Three times weekly glatiramer acetate in relapsing-remitting multiple sclerosis. *Annals of Neurology*. 2013;73(6):705-13.
23. Comi G, Patti F, Rocca MA *et al.* Efficacy of fingolimod and interferon beta-1b on cognitive, MRI, and clinical outcomes in relapsing-remitting multiple sclerosis: an 18-month, open-label, rater-blinded, randomised, multicentre study (the GOLDEN study). *Journal of Neurology*. 2017;264(12):2436-49.
24. IFNB Multiple Sclerosis Study Group. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. I. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. *Neurology*. 1993;43(4):655-.
25. 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*. 2002;359(9316):1453-60.
26. Jacobs LD, Cookfair DL, Rudick RA *et al.* Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis. *Annals of Neurology*. 1996;39(3):285-94.
27. 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):221-34.
28. 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 Neurology*. 2021;78(5):558-67.
29. Ebers GC, PRISMS Study Group. Randomised double-blind placebo-controlled study of interferon beta-1a in relapsing/remitting multiple sclerosis. *Lancet*. 1998;352(9139):1498-504.
30. 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 Neurology*. 2019;18(11):1021-33.
31. 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. *Lancet Neurology*. 2008;7(10):903-14.
32. Stępień A, Chalimoniuk M, Lubina-Dąbrowska N, Chrapusta SJ, Galbo H, Langfort J. Effects of interferon beta-1a and interferon beta-1b monotherapies on selected serum cytokines and nitrite levels in patients with relapsing-remitting multiple sclerosis: a 3-year longitudinal study. *Neuroimmunomodulation*. 2013;20(4):213-22.
33. 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. *Lancet Neurology*. 2019;18(11):1009-20.
34. O'Connor P, Wolinsky JS, Confavreux C *et al.* Randomized trial of oral teriflunomide for relapsing multiple sclerosis. *New England Journal of Medicine*. 2011;365(14):1293-303.
35. Vermersch P, Czonkowska A, Grimaldi LM *et al.* Teriflunomide versus subcutaneous interferon beta-1a in patients with relapsing multiple sclerosis: a randomised, controlled phase 3 trial. *Multiple Sclerosis Journal*. 2014;20(6):705-16.
36. 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. *Lancet Neurology*. 2014;13(3):247-56.
37. Cohen JA, Barkhof F, Comi G *et al.* Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. *New England Journal of Medicine*. 2010;362(5):402-15.
38. Steinman L, Fox E, Hartung H-P *et al.* Efficacy and safety of ublituximab vs teriflunomide in patients with relapsing multiple sclerosis: results from two phase 3 studies ULTIMATE I & ULTIMATE II. 2021. [Poster]. American Academy of Neurology Virtual Annual Meeting, April 17–22.

39. Steinman L, Fox E, Hartung H-P *et al.* Ublituximab versus teriflunomide in relapsing multiple sclerosis. *New England Journal of Medicine.* 2022;387(8):704-14.
40. Comi G, Jeffery D, Kappos L *et al.* Placebo-controlled trial of oral laquinimod for multiple sclerosis. *New England Journal of Medicine.* 2012;366(11):1000-9.
41. Saida T, Yamamura T, Kondo T *et al.* A randomized placebo-controlled trial of delayed-release dimethyl fumarate in patients with relapsing-remitting multiple sclerosis from East Asia and other countries. *BMC Neurology.* 2019;19(1):5.
42. Kira JI, Nakahara J, Sazonov D *et al.* Efficacy and safety of ofatumumab versus placebo in relapsing multiple sclerosis patients in Japan and Russia: results from the phase 2 APOLITOS study. *Multiple Sclerosis Journal.* 2020;26(S3):219.
43. Kapoor R, Ho P-R, Campbell N *et al.* Effect of natalizumab on disease progression in secondary progressive multiple sclerosis (ASCEND): a phase 3, randomised, double-blind, placebo-controlled trial with an open-label extension. *The Lancet Neurology.* 2018;17(5):405-15.
44. Barbero P, Verdun E, Bergui M *et al.* High-dose, frequently administered interferon beta therapy for relapsing-remitting multiple sclerosis must be maintained over the long term: the interferon beta dose-reduction study. *Journal of the Neurological Sciences.* 2004;222(1):13-9.
45. Bastianello S, Pozzilli C, D'Andrea F *et al.* A controlled trial of mitoxantrone in multiple sclerosis: serial MRI evaluation at one year. *Canadian Journal of Neurological Sciences.* 1994;21(3):266-70.
46. Boyko A, Zinkina-Orikhan A, Linkova Y. 20-week results of the phase 3, multicenter, double-blind, placebo-controlled study of the original pegylated interferon beta-1a drug in patients with relapsing multiple sclerosis. *Multiple Sclerosis Journal.* 2019;25(S2):863.
47. Cadavid D, Wolansky LJ, Skurnick J *et al.* Efficacy of treatment of MS with IFN β -1b or glatiramer acetate by monthly brain MRI in the BECOME study. *Neurology.* 2009;72(23):1976-83.
48. Boiko AN, Bosenko LP, Vasilovskii VV *et al.* A comparative placebo-controlled clinical trial of the efficacy and safety of interferon beta-1a formulations for subcutaneous administration in patients with relapsing multiple sclerosis: first-year results. *Neuroscience and Behavioral Physiology.* 2018;48(7):883-9.
49. Selmaj K, Li DKB, Hartung H-P *et al.* Siponimod for patients with relapsing-remitting multiple sclerosis (BOLD): an adaptive, dose-ranging, randomised, phase 2 study. *Lancet Neurology.* 2013;12(8):756-67.
50. Cheshmavar M, Mirmosayyeb O, Badihian N, Badihian S, Shaygannejad V. Rituximab and glatiramer acetate in secondary progressive multiple sclerosis: a randomized clinical trial. *Acta Neurologica Scandinavica.* 2021;143(2):178-87.
51. Comi G, Vollmer T, Boyko A *et al.* CONCERTO: A placebo-controlled trial of oral laquinimod in patients with relapsing-remitting multiple sclerosis. *Multiple Sclerosis Journal.* 2017;23(S3):74-5.
52. Cutter G, Veneziano A, Grinspan A *et al.* Higher satisfaction and adherence with glatiramer acetate 40 mg/mL TIW vs 20 mg/mL QD in RRMS. *Multiple Sclerosis and Related Disorders.* 2019;33:13-21.
53. De Castro S, Cartoni D, Millefiorini E *et al.* Noninvasive assessment of mitoxantrone cardiotoxicity in relapsing remitting multiple sclerosis. *Journal of Clinical Pharmacology.* 1995;35(6):627-32.
54. Fox RJ, Wiendl H, Wolf C *et al.* A double-blind, randomized, placebo-controlled phase 2 trial evaluating the selective dihydroorotate dehydrogenase inhibitor vidofludimus calcium in relapsing-remitting multiple sclerosis. *Annals of Clinical and Translational Neurology.* 2022;9(7):977-87.
55. Kappos L, European Study Group on Interferon β -1b in Secondary Progressive MS. Placebo-controlled multicentre randomised trial of interferon β -1b in treatment of secondary progressive multiple sclerosis. *Lancet.* 1998;352(9139):1491-7.
56. Comi G, Filippi M, Wolinsky JS, European/Canadian Glatiramer Acetate Study Group. European/Canadian multicenter, double-blind, randomized, placebo-controlled study of the effects of glatiramer acetate on magnetic resonance imaging-measured disease activity and burden in patients with relapsing multiple sclerosis. *Annals of Neurology.* 2001;49(3):290-7.
57. Kappos L, Bar-Or A, Cree BAC *et al.* Siponimod versus placebo in secondary progressive multiple sclerosis (EXPAND): a double-blind, randomised, phase 3 study. *Lancet.* 2018;391(10127):1263-73.

58. Cohen J, Belova A, Selmaj K *et al.* Equivalence of generic glatiramer acetate in multiple sclerosis: a randomized clinical trial. *JAMA Neurology*. 2015;72(12):1433-41.
59. Popova EV, Boiko AN, Boiko OV *et al.* Results of a randomized open multicenter comparative study of the tolerability and safety of Gilenya (fingolimod) in patients with relapsing multiple sclerosis (the GIMN study). *Neuroscience and Behavioral Physiology*. 2017;47(1):102-6.
60. Gisleskog PO, Valenzuela B, Scherz T, Burcklen M, Pérez-Ruixo JJ, Poggesi I. An exposure-response analysis of the clinical efficacy of ponesimod in a randomized phase II study in patients with multiple sclerosis. *Clinical Pharmacokinetics*. 2021;60(9):1227-37.
61. Wolinsky JS, Borresen TE, Dietrich DW *et al.* 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-relapsing multiple sclerosis. *Multiple Sclerosis and Related Disorders*. 2015;4(4):370-6.
62. Gobbi C, Meier DS, Cotton F *et al.* Interferon beta 1b following natalizumab discontinuation: one year, randomized, prospective, pilot trial. *BMC Neurology*. 2013;13(1):101.
63. Hauser SL, Waubant E, Arnold DL *et al.* B-cell depletion with rituximab in relapsing-relapsing multiple sclerosis. *New England Journal of Medicine*. 2008;358(7):676-88.
64. De Stefano N, Curtin F, Stubinski B *et al.* Rapid benefits of a new formulation of subcutaneous interferon beta-1a in relapsing-relapsing multiple sclerosis. *Multiple Sclerosis Journal*. 2010;16(7):888-92.
65. Kappos L, Li D, Calabresi PA *et al.* Ocrelizumab in relapsing-relapsing multiple sclerosis: a phase 2, randomised, placebo-controlled, multicentre trial. *Lancet*. 2011;378(9805):1779-87.
66. Knobler R, Greenstein J, Johnson K *et al.* Systemic recombinant human interferon- β treatment of relapsing-relapsing multiple sclerosis: pilot study analysis and six-year follow-up. *Journal of Interferon Research*. 1993;13(5):333-40.
67. Kuhle J, Kappos L, Montalban X *et al.* The effect of evobrutinib, a Bruton's tyrosine kinase inhibitor, on blood neurofilament light chain levels in relapsing multiple sclerosis. 2021.
68. Comi G, Pulizzi A, Rovaris M *et al.* Effect of laquinimod on MRI-monitored disease activity in patients with relapsing-relapsing multiple sclerosis: a multicentre, randomised, double-blind, placebo-controlled phase IIb study. *Lancet*. 2008;371(9630):2085-92.
69. Llufriu S, Sepúlveda M, Blanco Y *et al.* Randomized placebo-controlled phase II trial of autologous mesenchymal stem cells in multiple sclerosis. *PLOS ONE*. 2014;9(12):e113936.
70. Millefiorini E, Gasperini C, Pozzilli C *et al.* Randomized placebo-controlled trial of mitoxantrone in relapsing-relapsing multiple sclerosis: 24-month clinical and MRI outcome. *Journal of Neurology*. 1997;244(3):153-9.
71. Sorensen PS, Lisby S, Grove R *et al.* Safety and efficacy of ofatumumab in relapsing-relapsing multiple sclerosis: a phase 2 study. *Neurology*. 2014;82(7):573-81.
72. Mokhber N, Azarpazhooh A, Orouji E *et al.* Cognitive dysfunction in patients with multiple sclerosis treated with different types of interferon beta: a randomized clinical trial. *Journal of the Neurological Sciences*. 2014;342(1):16-20.
73. Nabavi M, Abolfazli R, Beladimoghadam N *et al.* A randomized double blind non-inferiority study of efficacy, safety and tolerability of Actorif versus Rebif in patients with relapsing-relapsing MS. *Neuroepidemiology*. 2013;41(3-4):259.
74. Nabavi SM, Abolfazli R, Etemadrezaei A *et al.* A comparison study of efficacy and safety of a biosimilar form of intramuscular beta-interferon 1-a versus the reference product: a randomized controlled clinical trial in Iran. *Iranian Journal of Pharmaceutical Research*. 2019;18(3):1632-8.
75. Nafissi S, Azimi A, Amini-Harandi A, Salami S, Shahkarami MA, Heshmat R. Comparing efficacy and side effects of a weekly intramuscular biogeneric/biosimilar interferon beta-1a with Avonex in relapsing-relapsing multiple sclerosis: a double blind randomized clinical trial. *Clinical Neurology and Neurosurgery*. 2012;114(7):986-9.
76. Foley J, Defer G, Ryerson LZ *et al.* Primary results of NOVA: a randomized controlled study of the efficacy of 6 week dosing of natalizumab versus continued 4-week treatment 2021.

77. O'Connor PW, Li D, Freedman MS *et al.* A phase II study of the safety and efficacy of teriflunomide in multiple sclerosis with relapses. *Neurology*. 2006;66(6):894-900.
78. Olsson T, Boster A, Fernández Ó *et al.* Oral ponesimod in relapsing-remitting multiple sclerosis: a randomised phase II trial. *Journal of Neurology, Neurosurgery and Psychiatry*. 2014;85(11):1198-208.
79. Pakdaman H, Abbasi M, Gharagozli K, Ashrafi F, Kasmaei H, Harandi A. A randomized double-blind trial of comparative efficacy and safety of Avonex and CinnoVex for treatment of relapsing-remitting multiple sclerosis. *Neurological Sciences*. 2018;39(12):2107-13.
80. Polman C, Barkhof F, Sandberg-Wollheim M, Linde A, Nordle O, Nederman T. Treatment with laquinimod reduces development of active MRI lesions in relapsing MS. *Neurology*. 2005;64(6):987-91.
81. Trojano M, Ramio-Torrenta L, Grimaldi L *et al.* Subcutaneous natalizumab 300mg every 4 weeks is comparable to standard intravenous dosing in REFINO: a study exploring the safety, tolerability, and efficacy of multiple natalizumab treatment regimens in patients with relapsing multiple sclerosis. *Neurology*. 2015;85(4):e46.
82. Singer B, Bandari D, Cascione M *et al.* Comparative injection-site pain and tolerability of subcutaneous serum-free formulation of interferon β -1a versus subcutaneous interferon β -1b: results of the randomized, multicenter, phase IIIb REFORMS study. *BMC Neurology*. 2012;12(1):154.
83. Fox RJ, Cree BAC, De Sèze J *et al.* MS disease activity in RESTORE: a randomized 24-week natalizumab treatment interruption study. *Neurology*. 2014;82(17):1491-8.
84. Butzkueven H, Jeffery D, Arnold DL *et al.* The rapid efficacy of natalizumab vs fingolimod in patients with active relapsing-remitting multiple sclerosis (RRMS): results from reveal, a randomised, head-to-head study. *Journal of Neurology, Neurosurgery and Psychiatry*. 2018;89(6):A35-A.
85. Saida T, Kikuchi S, Itoyama Y *et al.* A randomized, controlled trial of fingolimod (FTY720) in Japanese patients with multiple sclerosis. *Multiple Sclerosis Journal*. 2012;18(9):1269-77.
86. Saida T, Kira J-i, Kishida S *et al.* Efficacy, safety, and pharmacokinetics of natalizumab in Japanese multiple sclerosis patients: a double-blind, randomized controlled trial and open-label pharmacokinetic study. *Multiple Sclerosis and Related Disorders*. 2017;11:25-31.
87. SPECTRIMS Study Group. Randomized controlled trial of interferon beta-1a in secondary progressive MS. *Neurology*. 2001;56(11):1496-504.
88. Cadavid D, Mellion M, Hupperts R *et al.* Safety and efficacy of opicinumab in patients with relapsing multiple sclerosis (SYNERGY): a randomised, placebo-controlled, phase 2 trial. *Lancet Neurology*. 2019;18(9):845-56.
89. Tran JQ, Rana J, Barkhof F *et al.* Randomized phase I trials of the safety/tolerability of anti-LINGO-1 monoclonal antibody BIIB033. *Neurology Neuroimmunology & Neuroinflammation*. 2014;1(2):e18.
90. Wroe S. Effects of dose titration on tolerability and efficacy of interferon beta-1b in people with multiple sclerosis. *Journal of International Medical Research*. 2005;33(3):309-18.
91. Ziemssen T, Tumani H, Sehr T *et al.* Safety and in vivo immune assessment of escalating doses of oral laquinimod in patients with RRMS. *Journal of Neuroinflammation*. 2017;14(1):172.
92. Coyle PK, Reder AT, Freedman MS, Fang J, Dangond F. Early MRI results and odds of attaining 'no evidence of disease activity' status in MS patients treated with interferon beta-1a in the EVIDENCE study. *Journal of the Neurological Sciences*. 2017;379:151-6.
93. European Medicines Agency. Assessment report: Aubagio. 2013.
94. Biogen Netherlands B.V. Summary of product characteristics: Plegridy. 2014.
95. European Medicines Agency. Assessment report: Tecfidera. 2013.
96. European Medicines Agency. Assessment report: Ocrevus. 2017.
97. Watkins C, Bennett I. A simple method for combining binomial counts or proportions with hazard ratios for evidence synthesis of time-to-event data. *Research Synthesis Methods*. 2018;9(3):352-60.
98. Haute Autorité de Santé. Commission de la Transparence: Alemtuzumab. 2016.
99. McCool R, Wilson K, Arber M *et al.* Systematic review and network meta-analysis comparing ocrelizumab with other treatments for relapsing multiple sclerosis. *Multiple Sclerosis and Related Disorders*. 2019;29:55-61.

100. Samjoo IA, Worthington E, Drudge C *et al.* Comparison of ofatumumab and other disease-modifying therapies for relapsing multiple sclerosis: a network meta-analysis. *Journal of Comparative Effectiveness Research.* 2020;9(18):1255-74.
101. European Medicines Agency. Assessment report: Mavenclad. 2017.