Appendix e-5. Evidence tables (summary of findings) for disease-modifying therapies for multiple sclerosis

SAFETY NOTE: After US Food and Drug Administration approval was received, daclizumab (ZINBRYTA) was voluntarily removed from the market on March 2, 2018, by its manufacturers, Biogen and AbbVie, due to serious adverse events in relapsing multiple sclerosis.[e22a]

Table e-1. Azathioprine vs placebo in relapsing−remitting multiple sclerosis: outcomes of interest

Outcomes	Study	Placebo	Azathioprine	Relative effect	Number of participants	Number and class of studies
Main outcomes						
Proportion of patients with at least one relapse at 1 y	Goodkin 1991	17/25	16/27	Relative risk 0.872 (0.572, 1.321)	52	Class II
Proportion of patients with at least one relapse at 2 y	Goodkin 1991	20/25	16/27	Relative risk 0.741 (0.499, 1.067)	52	Class II
Mean number of relapses at 1 y	Goodkin 1991	1.17±1.3	0.74±1.3	SMD 0.331 (-0.217, 0.878)	52	Class II
Mean number of relapses at 2 y	Goodkin 1991	0.79±0.77	0.3±0.77	SMD 0.636 (0.079, 1.194)	52	Class II
Change in EDSS disability score at 1 y	Goodkin 1991	0.04±1.05	0.04±1.13	SMD 0.0 (-0.544, 0.544)	52	Class II
Change in EDSS disability score at 2 y	Goodkin 1991	0.42±1.36	0.17±1.38	SMD 0.182 (-0.363, 0.728)	52	Class II
Proportion of patients with disability progression over 2 y	Goodkin 1991	8/25	5/27	Relative risk 0.579 (0.227, 1.462)	52	Class II
Proportion of patients with adverse event−related discontinuation at 2 y	Goodkin 1991	1/25	6/29	Risk difference 16.69% (-2.26, 34.69)	54	Class II
Other outcomes						
Proportion of patients with gastrointestinal adverse effects	Goodkin 1991	0/25	1/29	Relative risk 1.724 (0.107, 25.971)	54	Class II
Proportion of patients with cutaneous rash	Goodkin 1991	0/25	5/29	Relative risk 8.621 (0.838, 87.017)	54	Class II
Proportion of patients with abnormal liver enzymes	Goodkin 1991	0/25	5/29	Relative risk 8.621 (0.838, 87.017)	54	Class II
Proportion of patients with leucopenia	Goodkin 1991	0/25	7/29	Relative risk 12.069 (1.24, 119.025)	54	Class II

Abbreviations: SMD = standardized mean difference; EDSS = Expanded Disability Status Scale.

Table e-2. Azathioprine vs placebo in relapsing−remitting multiple sclerosis: outcomes of interest

Outcomes	Study	Placebo	Azathioprine	Relative effect	Number of participants	Number and class of studies
Main outcomes						
Proportion of patients with at least one relapse at 1 y	Ellison 1989	11/34	7/31	Relative risk 0.6979 (0.315, 1.515)	65	Class II
Proportion of patients with at least one relapse at 2 y	Ellison 1989	14/33	7/31	Relative risk 0.532 (0.2506, 1.0974)	64	Class II
Proportion of patients with at least one relapse at 3 y	Ellison 1989	19/28	10/26	Relative risk 0.5668 (0.3211, 0.9481)	54	Class II
Mean number of relapses at 1 y	Ellison 1989	0.44±0.75	0.35±0.84	SMD 0.113 (0.374, 0.600)	65	Class II
Mean number of relapses at 2 y	Ellison 1989	0.44±0.75	0.13±0.43	SMD 0.501 (0.007, 0.995)	65	Class II
Mean number of relapses at 3 y	Ellison 1989	0.61±0.99	0.22±0.64	SMD 0.463 (-0.03, 0.957)	54	Class II
Proportion of patients with disability progression over 3 y	Ellison 1989	13/28	8/27	Relative risk 0.6382 (0.3175, 1.2472)	55	Class II
Change in EDSS disability score at 1 y	Ellison 1989	0.12±0.82	0.03±0.77	SMD 0.113 (-0.374, 0.6)	63	Class II
Change in EDSS disability score at 2 y	Ellison 1989	0.45±1.12	0.2±1.1	SMD 0.225 (-0.263, 0.713)	62	Class II
Change in EDSS disability score at 3 y	Ellison 1989	0.46±1.06	0.35±1.02	SMD 0.106 (-0.381, 0.593)	54	Class II
Proportion of patients with malignancy	Ellison 1989	1/34	1/31	Risk difference 0.28% (-11.98, 13.48)	65	Class II
Other outcomes						
Proportion of patients with cutaneous rash	Ellison 1989	0/34	3/31	Relative risk 6.581 (0.555, 70.969)	65	Class II
Proportion of patients with viral or bacterial infection	Ellison 1989	12/34	13/31	Relative risk 1.188 (0.651, 2.168)	65	Class II
Proportion of patients with leucopenia	Ellison 1989	0/34	2/31	Relative risk 4.387 (0.333, 51.608)	65	Class II

Abbreviations: SMD = standardized mean difference; EDSS = Expanded Disability Status Scale.

Table e-3. Azathioprine vs beta interferons in relapsing−remitting multiple sclerosis: outcomes of interest

Main outcomes of interest						
Outcomes	**Study**	**Beta interferons**	**Azathioprine**	**Relative effect**	**Number of participants**	**Number and class of studies**
Annualized relapse rate	Massacesi 2014 (noninferiority design)	0.39 (0.30, 0.51	0.26 (0.19, 0.37)	Rate ratio 0.67 (0.43, 1.03) One-sided 95% CI 0.96; below noninferiority margin M=1.23, $p<0.01$ Conclusion: Azathioprine is not inferior to beta interferons	150	Class III
Proportion of patients with no relapses at 1 y	Etemadifar 2007	27/47	36/47	Relative risk 1.333 (1.0022, 1.8115)	94	Class II
Proportion of patients with no relapses at 2 y	Massacesi 2014	31/65	39/62	Relative risk 1.319 (0.964, 1.82)	127	
Change from baseline in EDSS score at 2 y	Massacesi 2014	0.22 (-0.03, 0.47) SD 1.03	-0.08(-0.31, 0.16) SD 0.94	SMD 0.304 (-0.046, 0.654)	127	Class III
Change from baseline in EDSS score at 1 y	Etemadifar 2007	0.30 (0.05, 0.4) SD 0.61	0.46 (0.35, 0.56) SD 0.37	SMD 0.317 (-0.090, 0.724)	94	Class II
Annualized new T2 lesion rate	Massacesi 2014	0.69 (0.54, 0.88)	0.76 (0.61, 0.95)	Rate ratio 1.10 One-sided 95% CI 1.45; below noninferiority margin M=1.84	97	Class II
Proportion of patients with no new T2 lesions at 2 y	Massacesi 2014	21/47	27/50	Relative risk 1.209 (0.811, 1.824)	97	Class II
Proportion of patients with no new gadolinium enhanced lesions at 2 y	Massacesi	43/47	41/50	Relative risk 0.896 (0.750, 1.056)		
Proportion of patients discontinuing treatment because of adverse effects						
	Massacesi 2014	6/68	14/65	Risk difference 12.71% (0.4, 25.08)	133	Class III
	Etemadifar 2007	3/47	3/47	Risk difference 0% (-11.57, 11.57)	94	Class II

Abbreviations: EDSS = Expanded Disability Status Scale; SMD = standardized mean difference.

Table e-4. Azathioprine plus Avonex vs Avonex alone in relapsing−remitting multiple sclerosis: main outcomes of interest

Outcomes	**Study**	**Avonex alone**	**Avonex plus azathioprine**	**Relative effect**	**Number of participants**	**Number and class of studies**
Annualized relapse rate	Havrdova 2009	1.05 (0.79, 1.36) SD 1.11	0.91 (0.6, 1.2) SD 1.17	SMD 0.123 (-0.242, 0.487)	116	Class II
Proportion of patients with no relapses at 2 y	Havrdova 2009	41/58	38/58	Relative risk 0.927 (0.718, 1.191)	116	Class II

Abbreviation: SMD = standardized mean difference.

Table e-5. Betaseron vs placebo in relapsing−remitting multiple sclerosis

Outcomes	Study	Placebo	Betaseron 250 micrograms	Relative effect	Number of participants	Study class
Proportion of patients with at least one relapse at 24 wk	Knobler 1993	4/7	2/6	Risk ratio 0.5833 (0.162, 1.764)	13	Class III
Proportion of patients with at least one relapse at 2 y	IFNB MS Group 1993	94/112	79/115	Risk ratio 0.819 (0.702, 0.947)	227	Class II
Proportion of patients with at least one relapse at 3 y	IFNB MS Group 1993	106/123	97/124	Risk ratio 0.908 (0.803, 1.021)	247	Class III
Exacerbation rate over 2 y	IFNB MS Group 1993	1.27 SD 0.837	0.84 SD 0.684	SMD 0.563 (0.298, 0.829)	227	Class II
Proportion of patients with disability progression over 3 y	IFNB MS 1993	34/123	25/124	Risk ratio 0.729 (0.466, 1.140)	227	Class III
Proportion of patients with adverse event−related discontinuation at 2 y	IFNB MS 1993	1/123	10/124	Risk difference 7.25% (2.11, 13.43)	227	Class II
Injection site reactions	IFNB MS 1993	7/123	86/124	Risk difference 63.66% (53.41, 71.64)	227	Class II

Abbreviations: SD = standard deviation; SMD = standardized mean difference.

Table e-6. Betaseron 250 micrograms vs Betaseron 375 micrograms in individuals with relaxing−remitting multiple sclerosis who suboptimally respond to Betaseron 250 micrograms

Outcomes	Study	Betaseron 250 micrograms	Betaseron 375 micrograms	Relative effect	Number of participants	Study class
Proportion of patients with no MRI activity at mo 9 to 12	OPTIMS 2008	16/40	30/36	Risk ratio 2.08 (1.41, 3.20)	76	Class I
Proportion of patients with at least one relapse at 6 mo	OPTIMS 2008	7/40	3/36	Risk ratio 0.476 (0.143, 1.581)	76	Class IV
Proportion of patients with confirmed EDSS progression at 6 mo	OPTIMS 2008	3/40	2/36	Risk ratio 0.741 (0.150, 3.679)	76	Class IV
Injection site reactions	OPTIMS 2008	9/40	13/36	Risk difference 13.61% (-6.67, 32.84)	76	Class IV
Proportion of patients with adverse event−related discontinuation at 6 mo	OPTIMS 2008	0/40	3/36	Risk difference 8.33% (-1.99, 21.83)	76	Class IV

Abbreviations: SD = standard deviation; SMD = standardized mean difference.

Table e-7. Betaseron 500 micrograms vs Betaseron 250 micrograms in relaxing−remitting multiple sclerosis

Outcomes	Study	Interferon beta-1b 500 micrograms	Interferon beta-1b 250 micrograms	Relative effect	Number of participants	Study class
Proportion of patients with at least one relapse at 2 y	O'Connor 2009	360/899	377/897	Risk ratio 0.9528 (0.8528, 1.0644)	1796	Class II
Proportion of patients with confirmed EDSS progression at 2 y	O'Connor 2009	200/899	244/897	Risk ratio 0.8178 (0.6953, 0.9618)	1796	Class II
Any injection site reaction	O'Connor 2009	485/887	427/888	Risk difference 6.59% (1.94, 11.20)	1775	Class II
Influenza-like illness	O'Connor 2009	401/887	359/888	Risk difference 4.78% (0.18, 9.36)	1775	Class II

Abbreviation: EDSS = Expanded Disability Status Scale.

Table e-8. Betaseron vs placebo in secondary progressive multiple sclerosis

Outcomes	Study	Placebo	Betaseron	Relative effect	Number of participants	Study class
Annualized relapse rate				SMD 0.125 (0.018, 0.232)		
	European Study Group 1998	0.64 SD 1.4	0.44 SD 1.4	SMD 0.143 (-0.004, 0.289)	718	Class II
	NASG 2004	0.28 SD 1.15	0.16 SD 1.15	SMD 0.104 (-0.053, 0.261)	625	Class II
Proportion of patients with at least one relapse over 3 y				Risk ratio 0.837 (0.75, 0.933)		
	European Study Group 1998	224/358	194/360	Risk ratio 0.861 (0.760, 0.975)	718	Class II
	NASG 2004	116/308	91/317	Risk ratio 0.762 (0.609, 0.954)		
Proportion of patients with disability progression over 3 y				Risk ratio 0.846 (0.705, 1.015)		
	European Study Group 1998	178/358	140/360	Risk ratio 0.782 (0.662, 0.923)	718	Class II
	NASG 2004	104/308	101/317	Risk ratio 0.944 (0.754, 1.180)	939	Class II
Proportion of patients with adverse event−related discontinuation	European Study Group 1998	15/368	45/360	Risk difference 8.42% (4.47, 12.56)	718	Class II
Injection site reaction	NASG 2004	43/308	165/317	Risk difference 38.09% (31.1, 44.52)	625	Class II
Flulike syndrome	NASG 2004	102/308	137/317	Risk difference 10.1% (2.48, 17.55)	625	Class II
Leukopenia	NASG 2004	25/308	78/317	Risk difference 16.49% (10.8, 22.13)	625	Class II

Abbreviation: SMD = standardized mean difference.

Table e-9. Betaseron vs placebo for primary progressive multiple sclerosis

Outcomes	Study	Placebo	Betaseron	Relative effect	Number of participants	Study class
Proportion of patients with disability progression over 2 y	Montalban 2009	12/37	8/36	Risk ratio 0.685 (0.324, 1.433)	73	Class II
Proportion of patients with active MRI lesions at 2 y	Montalban 2009	19/37	8/36	Risk ratio 0.433 (0.218, 0.83)	73	Class II
Flulike syndrome	Montalban 2009	2/37	15/36	Risk difference 36.26% (17.23, 52.86)	73	Class II
Leukopenia	Montalban 2009	3/37	10/36	Risk difference 19.67% (1.88, 36.73)	73	Class II
Injection site reaction	Montalban 2009	0/37	28/36	Risk difference 77.78% (59.34, 88.28)	73	Class II

Table e-10. Cyclophosphamide vs placebo relapsing-remitting multiple sclerosis

Outcomes	Study	Placebo	Cyclophosphamide IV once a mo	Relative effect	Number of participants	Study class
Proportion of patients with	Killian	6/8	3/6	Risk ratio 0.667 (0.246, 1.444)	14	Class III

at least one relapse at 1 y	1988					
Annualized relapse rate	Killian 1988	2.3 SD 1.7	0.5 SD 0.5	SMD 1.345 (0.175, 2.515)	14	Class III
Proportion of patients with gadolinium-enhanced lesions at 6 mo	Smith 2005	11/29	4/30	Risk ratio 0.352 (0.131, 0.9190)	59	Class II
Proportion of patients with alopecia	Smith 2005	1/29	5/30	Risk difference 13.22% (-3.38, 30.35)	59	Class II
Proportion of patients with adverse event−related discontinuation at 1 y	Killian 1988	1/8	0/6	Risk difference -12.5% (-47.09, 27.86)	14	Class III

Abbreviations: SMD = standardized mean difference.

Table e-11. Cyclophosphamide vs placebo in progressive multiple sclerosis

Outcomes	Study	Placebo	Cyclophosphamide	Relative effect	Number of participants	Study class
Proportion of patients with disability progression over 1 y				Risk ratio 0.909 (0.587, 1.409)		
	CCMSSG 1991	12/48	7/48	Risk ratio 0.583 (0.257, 1.314)	86	Class II
	Likosky 1991	14/20	14/22	Risk ratio 0.909 (0.587, 1.410)	42	Class II
Proportion of patients with disability progression over 2 y				Risk ratio 1.192 (0.697, 2.039)		
	Likosky 1991	9/17	9/19	Risk ratio 0.895 (0.473, 1.706)	36	Class II
	CCMSSG 1991	10/30	16/31	Risk ratio 1.548 (0.864, 2.852)	61	Class II
Proportion of patients with alopecia	Likosky 1991	0/20	22/22	Risk difference 100% (78.1, 100)	42	Class II
Proportion of patients with hemorrhagic cystitis	CCMSSG 1991	0/54	2/54	Risk difference 3.7% (-3.46, 12.54)	108	Class II

Table e-12: Daclizumab 150 mg every 4 wk vs placebo in relaxing-remitting multiple sclerosis

Outcomes	Study	Daclizumab 150 mg	Placebo	Relative effect	Number of participants	Study class
Patients with relapse at 52 wk	Gold 2013 (SELECT)	38/201	69/196	Risk ratio 0.537 (0.381, 0.754)	397	Class I
Annualized relapse rate over 52 wk	Gold 2013 (SELECT)	0.21 (0.16-0.29) SD 0.47	0.46 (0.37-0.57) SD 0.714	SMD 0.415 (0.216, 0.614)	397	Class I
Confirmed disability progression at 52 wk	Gold 2013 (SELECT)	11/201	25/196	Risk ratio 0.429 (0.220, 0.841)	397	Class I
Changes in EDSS from baseline to wk 52	Gold 2013 (SELECT)	-0.08 (0.52)	0.09 (0.71)	SMD 0.274 (0.076, 0.471)	397	Class I
Mean number of new gadolinium-enhanced lesions at wk 52	Gold 2013 (SELECT)	0.3 (0.9)	1.4 (2.3)	SMD 0.633 (0.431, 0.834)	397	Class I

Mean number of new or newly enlarging T2 hyperintense lesions at wk 52	Gold 2013 (SELECT)	2.4 (2.0-3.0) SD 2.6	8.1 (6.7-9.9) SD 8.2	SMD 0.942 (0.735, 1.149)	397	Class I
Multiple Sclerosis Impact Scale, Physical Impact Score, change from baseline to wk 52	Gold 2013 (SELECT)	-1.0 (11.8)	3.0 (13.5)	SMD 0.316 (0.118, 0.514)	397	Class I
Multiple Sclerosis Impact Scale, Psychological Impact Score, change from baseline to wk 52	Gold 2013 (SELECT)	-1.8 (15.8)	0.6 (14.4)	SMD 0.159 (-0.038, 0.356)	397	Class I
Any adverse effect	Gold 2013 (SELECT)	151/208	161/204	Risk difference -6.3% (-14.49, 1.97)	412	Class I
Any “serious” adverse effect	Gold 2013 (SELECT)	32/208	53/204	Risk difference -10.6% (-18.3, -2.77)	412	Class I
Death	Gold 2013 (SELECT)	1/208	0/204	Risk difference 0.48% (-1.41, 2.67)	412	Class I
Serious infections	Gold 2013 (SELECT)	6/208	0/204	Risk difference 2.88% (0.47, 6.15)	412	Class I
ALT/AST 5 times upper limit of normal	Gold 2013 (SELECT)	9/208	1/204	Risk difference 3.84% (0.82, 7.55)	412	Class I
Malignancy	Gold 2013 (SELECT)	1/208	1/204	Risk difference 0.01% (-2.28, 2.22)	412	Class I

Abbreviations: SMD = standardized mean difference; EDSS = Expanded Disability Status Scale.

Table e-13. Daclizumab 150 mg or 300 mg every 4 wk vs placebo in relapsing-remitting multiple sclerosis

Outcomes	Study	Daclizumab 150mg or 300 mg	Placebo	Relative effect	Number of participants	Quality of evidence
Annualized relapse rate at 52 wk	Giovannoni 2014 (SELECTION)	0.179 (0.123-0.261) SD 0.449	0.434 (0.347-0.544) SD 0.642	SMD 0.453 (0.243, 0.664)	163	1 Class II
Confirmed disability progression at 52 wk	Giovannoni 2014 (SELECTION)	8/163	18/163	Risk ratio 0.444 (0.203, 0.98)	163	1 Class II
Mean n1umber of new gadolinium-enhancing lesions at wk 52	Giovannoni 2014 (SELECTION)	0.2 (0.8)	1.4 (2.40)	SMD 0.647 (0.434, 0.860)	163	1 Class II
Mean number of new or newly-enlarging T2 hyperintense lesions at wk 52	Giovannoni 2014 (SELECTION)	2.1 (3.7)	8.0 (9.5)	SMD 0.792 (0.576, 1.008)	163	1 Class II

Abbreviations: SD = standard deviation; SMD = standardized mean difference.

Table e-14. Daclizumab 1 or 2 mg/kg every 4 wk plus interferon beta vs placebo plus interferon beta in relapsing-remitting multiple sclerosis

Outcomes	Study	Low-dose daclizumab and interferon beta	High-dose daclizumab and interferon beta	Placebo and interferon beta	Number of participants	Quality of evidence
Patients with relapse between 8 and 24 wk	Wynn 2010 (CHOICE)	19/78 Risk ratio 0.987 (0.573, 1.701)	16/75 Risk ratio 0.8646 (0.4864, 1.533)	19/77	230	1 Class II
Mean number of new or enlarged T2 lesions at wk 24	Wynn 2010 (CHOICE)	2.2 (4.0) SMD 0.225 (-0.091, 0.541)	1.1 (2.3) SMD 0.476 (0.153, 0.798)	3.4 (6.4)	230	1 Class II
Any adverse effect	Wynn 2010 (CHOICE)	78/78 Risk difference 2.6% (-2.46, 8.98)	71/75 Risk difference -2.74% (-10.56, 4.43)	75/77	230	1 Class II
Infections	Wynn 2010 (CHOICE)	54/78 Risk difference 1.7% (-12.73, 16.06)	51/75 Risk difference 0.4% (-14.17, 15.03)	52/77	230	1 Class II

Abbreviation: SMD = standardized mean difference.

Table e-15. Daclizumab 150 mg every 4 wk vs Interferon Beta-1a, RRMS

Outcomes	Study	Daclizumab 150 mg	Interferon beta-1a	Relative effect	Number of participants	Study class
Annualized relapse rate	Kappos 2015 (DECIDE)	0.22 SD 0.387	0.39 SD 0.697	SMD 0.301 (0.210, 0.393)	1841	Class II
Proportion of patients with at least one relapse at wk 144	Kappos 2015 (DECIDE)	303/919	452/922	Risk ratio 0.673 (0.600, 0.752)	1841	Class II
Confirmed disability progression at wk 144	Kappos 2015 (DECIDE)	147/919	184/922	Risk ratio 0.802 (0.659, 0.975)	1841	Class II
Mean number of new or newly enlarging T2 hyperintense lesions over 96 wk	Kappos 2015 (DECIDE)	4.3 SD 6.96	9.4 SD 15.49	SMD 0.424 (0.332, 0.517)	1841	Class II
Treatment discontinuation due to adverse effect	Kappos 2015 (DECIDE)	142/919	112/922	Risk difference 3.3% (0.1, 6.46)	1841	Class II
Serious infection	Kappos 2015 (DECIDE)	40/919	15/922	Risk difference 2.73% (1.18, 4.37)	1841	Class II
Serious hepatobiliary disorder	Kappos 2015 (DECIDE)	7/919	4/922	Risk difference 0.33% (-0.45, 1.17)	1841	Class II
Serious hepatic event	Kappos 2015 (DECIDE)	6/919	4/922	Risk difference 0.22% (-0.54, 1.03)	1841	Class II

Abbreviation: SMD = standardized mean difference.

Table e-16. Daclizumab in relapsing-remitting multiple sclerosis

Patients: Relapsing remitting multiple sclerosis
Intervention: Daclizumab
Comparison: Placebo or other disease-modifying therapy

Outcomes	Daclizumab 150 mg	Daclizumab 300 mg	Placebo	Number of participants	Number of studies and class
Patients with relapse at 52 wk	38/201	40/203	69/196	621	1 Class I
Hazard ratio	0.45 (0.30-0.67) $p<0.0001$	0.49 (0.33-0.72) $p=0.00032$			
Annualized relapse rate over 52 wk	0.21 (0.16-0.29)	0.23 (0.17-0.31)	0.46 (0.37-0.57)	621	1 Class I
Rate ratio	0.46 (0.32-0.67) $p<0.0001$	0.50 (0.35-0.72) $p=0.00015$			
Confirmed disability progression at 52 wk	11/201	15/203	25/196	621	1 Class I
Hazard ratio	0.43 (0.21-0.88) $p=0.021$	0.57 (0.30-1.09) $p=0.091$			
Changes in EDSS from baseline to wk 52	-0.08 (0.52)	0.05 (0.61)	0.09 (0.71)	621	1 Class I

	p=0.01	*p*=0.49			
Mean number of new gadolinium-enhanced lesions at wk 52	0.3 (0.9) *p*<0.0001	0.2 (0.7) *p*<0.0001	1.4 (2.3)	621	1 Class I
Mean number of new or newly-enlarging T2 hyperintense lesions at wk 52	2.4 (2.0-3.0) *p*<0.0001	1.7 (1.4-2.2) *p*<0.0001	8.1 (6.7-9.9)	621	1 Class I
Multiple Sclerosis Impact Scale, Physical Impact Score, change from baseline to wk 52	-1.0 (11.8) *p*=0.00082	1.4 (13.5) *p*=0.13	3.0 (13.5)	621	1 Class I
Multiple Sclerosis Impact Scale, Psychological Impact Score, change from baseline to wk 52	-1.8 (15.8) *p*=0.068	-0.5 (15.3) *p*=0.43	0.6 (14.4)	621	1 Class I
EQ- visual analogue scale	2.9 (13.3) *p*<0.0001	1.0 (12.8) *p*=0.015	-1.8 (13.2)	621	1 Class I
EQ-5D summary health index	0.01 (0.18) *p*=0.0091	-0.02 (0.20) p=0.35	-0.04 (0.20)	621	1 Class I
SF-12 Physical component	1.2 (7.3) *p*=0.012	0.5 (7.3) *p*=0.10	-0.4 (7.0)	621	1 Class I
SF-12 Mental component	0.7 (9.6) *p*=0.012	-0.1 (8.6) *p*=0.23	-1.4 (9.2)	621	1 Class I
Any adverse effect	151/208	159/209	161/204	621	1 Class I
Any serious adverse effect	32/208	36/209	53/204	621	1 Class I
Death	1/208	0/209	0/204	621	1 Class I
Infections	104/208	112/209	89/204	621	1 Class I
Cutaneous events	38/208	45/209	27/204	621	1 Class I
ALT or AST abnormalities	70/208	76/209	71/204	621	1 Class I

Outcomes	**Daclizumab 150 mg or 300 mg**	**Placebo**	**Number of participants**	**Quality of evidence**
Annualized relapse rate at 52 wk	0.179 (0.123-0.261)	0.434 (0.347-0.544)	163	1 Class II
Rate ratio	0.466 (0.318-0.682)			
Confirmed disability progression at 52 wk	8/163	18/163	163	1 Class II
Hazard ratio	0.414 (0.182-0.944)			
Mean number of new gadolinium-enhanced lesions at wk 52	0.2 (0.8)	1.4 (2.40)	163	1 Class II
Ratio	0.120 (0.060-0.241)			
Mean number of new or newly enlarging T2 hyperintense lesions at wk 52	2.1 (3.7)	8.0 (9.5)	163	1 Class II
Ratio	0.271(0.215-0.340)			

Outcomes	**Low-dose daclizumab and interferon beta**	**High-dose daclizumab and interferon beta**	**Placebo and interferon beta**	**Number of participants**	**Quality of evidence**
Patients with relapse between 8 and 24 wk	19/78	16/75	19/77	230	1 Class II
Annualized relapse rate (adjusted for number of relapse in 2 y before study entry and baseline disease status	0.29 *p*=0.35	0.27 *p*=0.30	0.41	230	1 Class II
Median change in EDSS score between baseline and wk	0 (range -2 to 4)	0 (range -2 to 2)	0 (range -2 to 3)	230	1 Class II

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Mean number of new or enlarged gadolinium-enhanced lesions between 8 and 24 wk	3.58	1.32	4.75	230	1 Class II
Difference	25% (-76-68%); *p*=0.51	72% (34-88%); *p*=0.004			
Mean number of new or enlarged T2 lesions at wk 24	2.2 (4.0) *p*=0.60	1.1 (2.3) *p*=0.007)	3.4 (6.4)	230	1 Class II
Any adverse effect	78/78	71/75	75/77	230	1 Class II
Infections	54/78	51/75	52/77	230	1 Class II
Skin and subcutaneous tissue disorders	14/78	6/75	6/77	230	1 Class II

Table e-17. Dimethyl fumarate, key outcomes of interest

Outcomes	**Study**	**Placebo**	**Dimethyl fumarate 240 mg orally twice daily**	**Relative effect**	**Number of participants**	**Number of studies and class**
Proportion of patients with at least one relapse at 2 y	**Meta-analysis**	337/771	215/769	**Risk ratio 0.64 (0.54-0.77)**	1540	
	Fox 2012	149/363	104/359	0.71 (0.58, 0.87)	722	Class I
	Gold 2012	188/408	111/410	0.59 (0.49, 0.71)	818	Class II
Proportion of patients with disability worsening at 2 y	**Meta-analysis**	172/771	112/768	**Risk ratio 0.65 (0.53-0.81)**	1539	
	Fox 2012	62/363	47/359	0.77 (0.54, 1.09)	722	Class I
	Gold 2012	110/408	65/409	0.59(0.45, 0.78)	817	Class II
Annualized relapse rate at 2 y	**Meta-analysis**	771	769	**Rate ratio 0.51 (0.44, 0.59)**	1540	
	Fox 2012	363	359	0.55 (0.45, 0.67)	722	Class I
	Gold 2012	408	410	0.47 (0.39, 0.58)	818	Class II
New or enlarging T2 weighted hyperintense lesions at 2 y	**Meta-analysis**			**SMD 0.493 (0.291, 0.694)**		
	Fox 2012	n=139 Adjusted mean number of lesions 17.4 (13.5,22.4), SD 26.8	n=140 Adjusted mean number of new lesions 5.1 (3.9, 6.6) SD 8.1	SMD 0.622 (0.382, 0.863)	279	Class I
	Gold 2012	n=408 Adjusted mean number of lesions 17.0 (12.9, 22.4) SD 49.0	n=410 Adjusted mean number of lesions 2.6 (2.0, 3.5) SD 7.7	SMD 0.411 (0.273, 0.550)	818	Class II
Gadolinium-enhanced lesions at 2 y	**Meta-analysis**			**SMD 0.488 (0.293, 0.682)**		
	Fox 2012	n=144 Number of lesions 2.0±5.6	n=147 Number of lesions 0.5±1.7	SMD 0.364 (0.132, 0.596)	291	Class I
	Gold 2012	n=408 Number of lesions 1.8±4.2	n=410 Number of lesions 0.1±0.6	SMD 0.567 (0.428, 0.707)	818	Class II
New T1 weight hypointense	Fox 2012	n=139	n=140	SMD 0.444 (0.206, 0.681)	279	Class I

lesions at 2 y		Adjusted mean number of lesions 7.0 (5.3, 9.2) SD 11.7	Adjusted mean number of lesions 3.0 (2.3, 4.0) SD 5.1			
Number of patients who discontinued study drug because of adverse events excluding relapses at 2 y	**Meta-analysis**	45/771	98/769	**Risk difference 6.8% (2.8, 10.7)**	1540	
	Fox 2012	21/363	38/359	Risk difference 4.8% (0.79, 8.9)	722	Class I
	Gold 2012	24/408	60/410	Risk difference 8.8% (4.6, 13.0)	818	Class II
Number of patients with serious infections at 2 y	**Meta-analysis**	11/771	17/769	**Risk difference 0.8% (-0.7, 2.2)**	1540	
	Fox 2012	4/363	7/359	Risk difference 0.8% (-1.1, 3.0)	722	Class I
	Gold 2012	7/408	10/410	Risk difference 0.7% (-1.4, 2.9)	818	Class II

Other outcomes from trials

Mean change in SF-36 Physical Component summary scores from baseline to 2 y	**Meta-analysis**			**Mean difference 1.54 (0.79, 2.30)**	1474	
	Fox 2012			1.20 (0.06, 2.34)	685	Class I
	Gold 2012			1.81 (0.81, 2.81)	789	Class II
Mean change in SF-36 Mental Component summary scores from baseline to 2 y	**Meta-analysis**			**Mean difference 0.93 (-0.06, 1.93)**	1474	
	Fox 2012			0.52 (-0.98, 2.02)	685	Class I
	Gold 2012			1.26 (-0.07, 2.59)	789	Class II
Number of patients with adverse effect excluding relapses at 2 y	**Meta-analysis**	376/771	512/769	**Risk ratio 1.37 (1.25, 1.49)**	1540	
	Fox 2012	178/363	228/359	1.30 (1.14, 1.48)	722	Class I
	Gold 2012	198/408	284/410	1.43 (1.27, 1.61)	818	Class II
Number of patients with flushing at 2 y	**Meta-analysis**	33/771	264/769	**Risk ratio 8.01 (5.66, 11.34)**	1540	
	Fox 2012	13/363	110/359	8.56 (4.91, 14.92)	722	Class I
	Gold 2012	20/408	154/410	7.66 (4.91, 11.96)	818	Class II
Number of patients with upper-abdominal pain at 2 y	**Meta-analysis**	45/771	76/769	**Risk ratio 1.69 (1.19, 2.41)**	1540	
	Fox 2012	17/363	36/359	2.14 (1.23, 3.74	722	Class I
	Gold 2012	28/408	40/410	1.42 (0.89, 2.26)	818	Class II
Number of patients with nausea at 2 y	**Meta-analysis**	67/771	93/769	**Risk ratio 1.39 (1.03, 1.87)**	1540	
	Fox 2012	29/363	40/359	1.39 (0.88, 2.20)	722	Class I
	Gold 2012	38/408	53/410	1.39 (0.94, 2.06)	818	Class II
Number of patients with diarrhea at 2 y	**Meta-analysis**	83/771	107/769	**Risk ratio 1.31 (0.91, 1.87)**	1540	
	Fox 2012	28/363	45/359	1.63 (1.04, 2.55)	722	Class I
	Gold 2012	55/408	62/410	1.12 (0.80, 1.57)	818	Class II
Number of patients with proteinuria at 2 y	**Meta-analysis**	59/771	67/769	**Risk ratio 1.14 (0.81, 1.59)**	1540	
	Fox 2012	25/363	29/359	1.17 (0.70, 1.96)	722	Class I
	Gold 2012	34/408	38/410	1.11 (0.71, 1.73)	818	Class II
Number of patients with	**Meta-analysis**	6/771	34/769	**Risk ratio 5.69 (2.40, 13.46)**	1540	

decreased lymphocyte count of less than 0.5 x 10^9 per liter at 2 y						
	Fox 2012	3/363	18/359	6.07 (1.8, 20.42)	722	Class I
	Gold 2012	3/408	16/410	5.31 (1.56, 18.08)	818	Class II
Number of patients with a decreased white blood cell count of less than 3.0 x 10^9 per liter at 2 y	**Meta-analysis**	8/771	52/769	**Risk ratio 6.53 (3.13, 13.64)**	1540	
	Fox 2012	4/363	36/359	9.10 (3.27, 25.30)	722	Class I
	Gold 2012	4/408	16/410	3.98 (1.34, 11.80)	818	Class II
Number of patients with an increased ALT level at least 3 times the upper limit of the normal range at 2 y	**Meta-analysis**	35/771	45/769	**Risk ratio 1.33 (0.57, 3.07)**	1540	
	Fox 2012	23/363	20/359	0.88 (0.49, 1.57)	722	Class I
	Gold 2012	12/408	25/410	2.07 (1.06, 4.07)	818	Class II
Number of patients with gastrointestinal events at 2 y	**Meta-analysis**	195/771	276/769	**Risk ratio 1.43 (1.11, 1.85)**	1540	
	Fox 2012	74/363	121/359	1.65 (1.29, 2.12)	722	Class I
	Gold 2012	121/408	155/410	1.27 (1.05, 1.55)	818	Class II
Number of patients with infections at 2 y	**Meta-analysis**	447/771	463/769	**Risk ratio 1.04 (0.92, 1.18)**	1540	
	Fox 2012	182/363	201/359	1.12 (0.97, 1.28)	722	Class I
Number of patients with serious adverse (as defined in trial) events excluding relapses at 2 y	**Meta-analysis**	54/771	57/769	**Risk difference 0.3% (-3.4, 4)**	1540	
	Fox 2012	28/363	22/359	Risk difference -1.6% (-5.4, 2.2)	722	Class I
	Gold 2012	26/408	35/410	Risk difference 2.2% (-1.5, 6.2)	818	Class II

Table e-18. Dimethyl fumarate

Patients: Relapsing-remitting multiple sclerosis **Intervention: Dimethyl fumarate** **Comparison: Placebo or other disease-modifying therapy**							
Outcomes	**Study**	**Placebo**	**Dimethyl fumarate 240 mg orally twice daily**	**Relative effect**	**Number of participants**	**Number of studies and class**	**Comments (large magnitude of effect, dose response effect, inconsistency, indirectness, imprecision, publication bias)**
Proportion of patients with at		337/771	215/769	Risk ratio 0.64	1540		

least one relapse at 2 y				(0.54-0.77)			
	Fox 2012	149/363	104/359	0.71 (0.58, 0.87)	722	Class I	
	Gold 2012	188/408	111/410	0.59 (0.49, 0.71)	818	Class II	
Proportion of patients with disability worsening at 2 y		172/771	112/768	Risk ratio 0.65 (0.53-0.81)	1539		Indirectness; disability worsening was confirmed at 3 mo of follow-up
	Fox 2012	62/363	47/359	0.77 (0.54, 1.09)	722	Class I	
	Gold 2012	110/408	65/409	0.59(0.45, 0.78)	817	Class II	
Annualized relapse rate at 2 y		771	769	Rate ratio 0.51 (0.44, 0.59)	1540		
	Fox 2012	363	359	0.55 (0.45, 0.67)	722	Class I	
	Gold 2012	408	410	0.47 (0.39, 0.58)	818	Class II	
Mean change in SF-36 Physical Component summary scores from baseline to 2 y				Mean difference 1.54 (0.79, 2.30)	1474		
	Fox 2012			1.20 (0.06, 2.34)	685	Class I	
	Gold 2012			1.81 (0.81, 2.81)	789	Class II	
Mean change in SF-36 Mental Component summary scores from baseline to 2 y				Mean difference 0.93 (-0.06, 1.93)	1474		
	Fox 2012			0.52 (-0.98, 2.02)	685	Class I	
	Gold 2012			1.26 (-0.07, 2.59)	789	Class II	
Number of patients with adverse events excluding relapses at two y		376/771	512/769	Risk ratio 1.37 (1.25, 1.49)	1540		
	Fox 2012	178/363	228/359	1.30 (1.14, 1.48)	722	Class I	
	Gold 2012	198/408	284/410	1.43 (1.27, 1.61)	818	Class II	
Number of patients with serious adverse events excluding relapses at two y		54/771	57/769	Risk ratio 1.05 (0.63, 1.74)	1540		
	Fox 2012	28/363	22/359	0.79 (0.46, 1.36)	722	Class I	
	Gold 2012	26/408	35/410	1.34 (0.82, 2.18)	818	Class II	
Number of patients who discontinued study drug because of adverse events excluding relapses at two y		45/771	98/769	Risk ratio 2.18 (1.56, 3.06)	1540		
	Fox 2012	21/363	38/359	1.83 (1.10, 3.05)	722	Class I	
	Gold 2012	24/408	60/410	2.49 (1.58, 3.91)	818	Class II	
Number of patients with flushing at 2 y		33/771	264/769	Risk ratio 8.01 (5.66, 11.34)	1540		
	Fox 2012	13/363	110/359	8.56 (4.91, 14.92)	722	Class I	
	Gold 2012	20/408	154/410	7.66 (4.91, 11.96)	818	Class II	
Number of patients with upper-abdominal pain at 2 y		45/771	76/769	Risk ratio 1.69 (1.19, 2.41)	1540		
	Fox 2012	17/363	36/359	2.14 (1.23, 3.74	722	Class I	
	Gold 2012	28/408	40/410	1.42 (0.89, 2.26)	818	Class II	
Number of patients with nausea at 2 y		67/771	93/769	Risk ratio 1.39 (1.03, 1.87)	1540		
	Fox 2012	29/363	40/359	1.39 (0.88, 2.20)	722	Class I	
	Gold 2012	38/408	53/410	1.39 (0.94, 2.06)	818	Class II	
Number of patients with diarrhea at 2 y		83/771	107/769	Risk ratio 1.31 (0.91, 1.87)	1540		
	Fox 2012	28/363	45/359	1.63 (1.04, 2.55)	722	Class I	

	Gold 2012	55/408	62/410	1.12 (0.80, 1.57)	818	Class II	
Number of patients with proteinuria at 2 y		59/771	67/769	1.14 (0.81, 1.59)	1540		
	Fox 2012	25/363	29/359	1.17 (0.70, 1.96)	722	Class I	
	Gold 2012	34/408	38/410	1.11 (0.71, 1.73)	818	Class II	
Number of patients with decreased lymphocyte count of less than 0.5 x 10^9 per liter at 2 y		6/771	34/769	Risk ratio 5.69 (2.40, 13.46)	1540		
	Fox 2012	3/363	18/359	6.07 (1.8, 20.42)	722	Class I	
	Gold 2012	3/408	16/410	5.31 (1.56, 18.08)	818	Class II	
Number of patients with a decreased white blood cell count of less than 3.0 x 10^9 per lite4 at 2 y		8/771	52/769	6.53 (3.13, 13.64)	1540		
	Fox 2012	4/363	36/359	9.10 (3.27, 25.30)	722	Class I	
	Gold 2012	4/408	16/410	3.98 (1.34, 11.80)	818	Class II	
Number of patients with an increased ALT level at least 3 times the upper limit of the normal range at 2 y		35/771	45/769	1.33 (0.57, 3.07)	1540		
	Fox 2012	23/363	20/359	0.88 (0.49, 1.57)	722	Class I	
	Gold 2012	12/408	25/410	2.07 (1.06, 4.07)	818	Class II	
Number of patients with gastrointestinal events at 2 y		195/771	276/769	1.43 (1.11, 1.85)	1540		
	Fox 2012	74/363	121/359	1.65 (1.29, 2.12)	722	Class I	
	Gold 2012	121/408	155/410	1.27 (1.05, 1.55)	818	Class II	
Number of patients with infections at 2 y		447/771	463/769	1.04 (0.92, 1.18)	1540		
	Fox 2012	182/363	201/359	1.12 (0.97, 1.28)	722	Class I	
	Gold 2012	265/408	262/410	0.98 (0.89, 1.09)	818	Class II	
Number of patients with serious infections at 2 y		11/771	17/769	1.55 (0.73, 3.28)	1540		
	Fox 2012	4/363	7/359	1.77 (0.52, 5.99)	722	Class I	
	Gold 2012	7/408	10/410	1.42 (0.55, 3.70)	818	Class II	
New or enlarging T2 weighted hyperintense lesions at 2 y	Fox 2012	n=139 Adjusted mean number of lesions 17.4 (13.5,22.4)	n=140 Adjusted mean number of new lesions 5.1 (3.9, 6.6)	Ratio 0.29 (0.21, 0.41)	279	Class I	Indirectness; patients in the MRI cohort (only patients from those sites whose MRI capability was validated) with post-baseline MRI data. Time to MRI follow-up not stated.
	Gold 2012	n=408 Adjusted mean number of lesions 17.0 (12.9, 22.4)	n=410 Adjusted mean number of lesions 2.6 (2.0, 3.5)	Ratio 0.15 (0.10, 0.23)	818	Class II	
New T1 weight hypointense lesions at 2 y	Fox 2012	n=139 Adjusted mean number of lesions 7.0 (5.3,	n=140 Adjusted mean number of lessions3.0 (2.3,	Ratio 0.43(0.30, 0.61)	279	Class I	Indirectness

		9.2)	4.0)				
Gadolinium-enhanced lesions at 2 y	Fox 2012	n=144 Number of lesions 2.0±5.6	n=147 Number of lesions 0.5±1.7	Odds ratio 0.26 (0.15, 0.46)	291	Class I	Indirectness
	Gold 2012	n=408 Number of lesions 1.8±4.2	n=410 Number of lesions 0.1±0.6	Odds ratio 0.10 (0.05-0.22)	818	Class II	
Outcomes		**Placebo**	**Dimethyl Fumarate 240 mg orally 3 times daily**	**Relative effect**	**Number of participants**	**Number of studies and class**	
Proportion of patients with at least one relapse at 2 y		337/771	191/761	Risk ratio 0.57 (0.50-0.66)	1532		
	Fox 2012	149/363	83/345	0.59 (0.47, 0.73)	708	Class I	
	Gold 2012	188/408	108/416	0.56 (0.46, 0.68)	824	Class II	
Proportion of patients with disability worsening at 2 y		172/771	120/761	Risk ratio 0.70 (0.57-0.87)	1532		Indirectness; disability worsening was confirmed at three mo of follow-up
	Fox 2012	62/363	45/345	0.76 (0.54, 1.09	708	Class I	
	Gold 2012	110/408	75/416	0.67 (0.52, 0.87)	824	Class II	
Annualized relapse rate at 2 y		771	761	Rate ratio 0.51 (0.45-0.59)	1532		
	Fox 2012	363	345	0.50 (0.41, 0.61)		Class I	
	Gold 2012	408	416	0.53 (0.43, 0.64)		Class II	
Mean change in SF-36 Physical Component Summary scores from baseline to 2 y				Mean difference 1.51 (0.76, 2.26)	1461		
	Fox 2012			1.04 (-0.09, 2.17)	672	Class I	
	Gold 2012			1.87 (0.87, 2.87)	789	Class II	
Mean change in SF-36 Mental Component Summary scores from baseline to 2 y				Mean difference 1.19 (-0.70, 3.08)	1461		
	Fox 2012			0.18 (-1.32, 1.68)	672	Class I	
	Gold 2012			2.11 (0.84, 3.38)	789	Class II	
Number of patients with adverse events excluding relapses at 2 y		376/771	513/760	Risk ratio 1.38 (1.27, 1.51)	1531		
	Fox 2012	178/363	231/344	1.37 (1.2, 1.56)	707	Class I	
	Gold 2012	198/408	282/416	1.40 (1.24, 1.57)	824	Class II	
Number of patients with serious adverse effects excluding relapses at 2 y		54/771	57/760	Risk ratio 1.07 (0.75, 1.53)	1531		
	Fox 2012	28/363	24/344	0.90 (0.54, 1.53)	707	Class I	
	Gold 2012	26/408	33/416	1.24 (0.76, 2.04)	824	Class II	
Number of patients who discontinued study drug		45/771	96/760	Risk ratio 2.16 (1.54, 3.03)	1531		

because of adverse events excluding relapses at 2 y	Fox 2012	21/363	38/344	1.91 (1.14, 3.19)	707	Class I	
	Gold 2012	24/408	58/416	2.37 (1.5, 3.74)	824	Class II	
Number of patients with flushing at 2 y		33/771	215/760	Risk ratio 6.57 (4.62, 9.35)	1531		
	Fox 2012	13/363	83/344	6.74 (3.83, 11.86)	707	Class I	
	Gold 2012	20/408	132/416	6.47 (4.13, 10.15)	824	Class II	
Number of patients with upper abdominal pain at 2 y		45/771	85/760	Risk ratio 1.91 (1.35, 2.69)	1531		
	Fox 2012	17/363	33/344	2.05 (1.16, 3.61)	707	Class I	
	Gold 2012	28/408	52/416	1.82 (1.17, 2.82)	824	Class II	
Number of patients with nausea at 2 y		67/771	105/760	Risk ratio 1.59 (1.19, 2.12)	1531		
	Fox 2012	29/363	51/344	1.86 (1.21, 2.86)	707	Class I	
	Gold 2012	38/408	54/416	1.39 (0.94, 2.06)	824	Class II	
Number of patients with diarrhea at 2 y		83/771	128/760	Risk ratio 1.55 (1.20, 2.01)	1531		
	Fox 2012	28/363	50/344	1.88 (1.22, 2.92)	707	Class I	
	Gold 2012	55/408	78/416	1.39 (1.01, 1.91)	824	Class II	
Number of patients with proteinuria at 2 y		59/771	85/760	Risk ratio 1.46 (1.06, 2.00)	1531		
	Fox 2012	25/363	35/344	1.48 (0.90, 2.42)	707	Class I	
	Gold 2012	34/408	50/416	1.44 (0.95, 2.18)	824	Class II	
Number of patients with decreased lymphocyte count of less than 0.5 x 10^9 per liter at 2 y		6/771	31/760	Risk ratio 5.25 (2.20, 12.51)	1531		
	Fox 2012	3/363	14/344	4.92 (1.43, 16.99)	707	Class I	
	Gold 2012	3/408	17/416	5.56 (1.64, 18.82)	824	Class II	
Number of patients with a decreased white blood cell count of less than 3.0 x 10^9 per liter at 2 y		8/771	41/760	Risk ratio 5.23 (2.47, 11.07)	1531		
	Fox 2012	4/363	24/344	6.33 (2.22, 18.06)	707	Class I	
	Gold 2012	4/408	17/416	4.17 (1.41, 12.28)	824	Class II	
Number of patients with an increased ALT level at least 3 times the upper limit of the normal range at 2 y		35/771	45/760	Risk ratio 1.34 (0.61, 2.94)	1531		
	Fox 2012	23/363	20/344	0.92 (0.51, 1.64)	707	Class I	
	Gold 2012	12/408	25/416	2.04 (1.04, 4.01)	824	Class II	
Number of patients with gastrointestinal events at 2 y		195/771	318/760	Risk ratio 1.67 (1.31, 2.12)	1531		
	Fox 2012	74/363	134/344	1.91 (1.50, 2.44)	707	Class I	
	Gold 2012	121/408	184/416	1.49 (1.24, 1.79)	824	Class II	
Number of patients with infections at 2 y		447/771	476/760	Risk ratio 1.08 (0.99, 1.17)	1531		
	Fox 2012	182/363	193/344	1.12 (0.97, 1.29)	707	Class I	
	Gold 2012	265/408	283/416	1.05 (0.95, 1.15)	824	Class II	
Number of patients with serious infections at 2 y		11/771	15/760	Risk ratio 1.38 (0.64, 2.98)	1531		
	Fox 2012	4/363	7/344	1.85 (0.55, 6.25)	707	Class I	

	Gold 2012	7/408	8/416	1.12 (0.41, 3.06)	824	Class II	
New or enlarging T2 weighted hyperintense lesions at 2 y	Fox 2012	n=139 Adjusted mean number of lesions 17.4 (13.5,22.4)	n=140 Adjusted mean number of new lesions 4.7 (3.6, 6.2)	Ratio 0.27 (0.20, 0.38)	279	Class I	Indirectness; patients in the MRI cohort (only patients from those sites whose MRI capability was validated) with post-baseline MRI data. Time to MRI follow-up not stated.
	Gold 2012	n=408 Adjusted mean number of lesions 17.0 (12.9, 22.4)	n=416 Adjusted mean number of lesions 4.4 (3.2, 5.9)	Ratio 0.26 (0.17, 0.38)	824	Class II	
New T1 weight hypointense lesions at 2 y	Fox 2012	n=139 Adjusted mean number of lesions 7.0 (5.3, 9.2)	n=140 Adjusted mean number of lesions 2.4 (1.8, 3.2)	Ratio 0.35(0.24, 0.49)	279	Class I	Indirectness
Gadolinium-enhanced lesions at 2 y	Fox 2012	n=144 Number of lesions 2.0±5.6	n=144 Number of lesions 0.4±1.2	Odds ratio 0.35 (0.20, 0.5)	288	Class I	Indirectness
	Gold 2012	n=408 Number of lesions 1.8±4.2	n=416 Number of lesions 0.5±1.7	Odds ratio 0.27 (0.15, 0.46)	824	Class II	

Table e-19. Fingolimod 0.5 mg vs placebo, RRMS

Outcomes	Study	Placebo	Fingolimod 0.5 mg	Relative effect	Number of participants	Study class
Proportion of patients with at least one relapse at 6 mo	Saida 2012	20/57	12/57	Risk ratio 0.60 (0.327, 1.09)	114	Class I
Proportion of patients with at least one relapse at 2 y	Meta-analysis			Risk ratio 0.569 (0.501, 0.648)		
	FREEDOMS 2010	227/418	126/425	Risk ratio 0.546 (0.460, 0.647)	843	Class I
	FREEDOMS II 2014	168/355	102/358	Risk ratio 0.602 (0.494, 0.732)	713	Class II
Annualized relapse rate	Meta-analysis			SMD 0.447 (0.350, 0.544)		
	FREEDOMS 2010	0.40 SD 0.678	0.18 SD 0.368	SMD 0.404 (0.268, 0.541)	843	Class I
	FREEDOMS	0.40 SD 0.673	0.21 SD 0.386	SMD 0.351 (0.203, 0.499)	713	Class II

	II 2014					
	Saida 2012	0.99 SD 1.5	0.50 SD 1.1	SMD 0.373 (0.002, 0.743)	114	
Proportion of patients with disability progression over 2 y	Meta-analysis			Risk ratio 0.807 (0.676, 0.964)		
	FREEDOMS 2010	101/418	75/425	Risk ratio 0.73 (0.560,0.952)	843	Class I
	FREEDOMS II 2014	103/355	91/358	Risk ratio 0.876 (0.689, 1.113)	713	Class II
Proportion of patients with gadolinium enhancing lesions at 6 mo	Saida 2012	21/50	6/45	Risk ratio 0.318 (0.143, 0.686)	95	Class I
Proportion of patients with gadolinium-enhanced lesions at 24 mo	Meta-analysis			Risk ratio 0.33 (0.26, 0.42)		
	FREEDOMS 2010	116/332	38/369	Risk ratio 0.295 (0.211, 0.411)	701	Class I
	FREEDOMS II 2014	89/256	35/269	Risk ratio 0.374 (0.264, 0.53)	525	Class II
Proportion of patients with new or enlarging T2 lesions at 6 mo	Saida 2012	32/50	17/48	Risk ratio 0.553 (0.355, 0.840)	98	Class I
Proportion of patients with new or enlarging T2 lesions at 24 mo	Meta-analysis			Risk ratio 0.645 (0.589, 0.706)		
	FREEDOMS 2010	267/339	183/370	Risk ratio 0.628 (0.558, 0.705)	709	Class I
	FREEDOMS II 2014	186/251	131/264	Risk ratio 0.670 (0.58, 0.77)	515	Class II
Proportion of patients with adverse event−related discontinuation at 6 mo	Saida 2012	3/57	6/57	Risk difference 5.26% (-5.43, 16.41)	114	Class I
Proportion of patients with adverse event−related discontinuation at 2 y	Meta-analysis			Risk difference 3.6% (-4.4, 11.5)		
	FREEDOMS 2010	32/418	32/425	Risk difference -0.13% (-3.78, 3.51)	843	Class I
	FREEDOMS II 2014	37/355	66/358	Risk difference 8.01% (2.86, 13.16)	713	Class II
Death	FREEDOMS 2010	2/418	0/425	Risk difference -0.4% (-1.73, 0.48)	843	Class I
Lower respiratory tract or lung infection				Risk difference		
	FREEDOMS 2010	25/418	41/425	Risk difference 3.67% (0.02, 7.37)	843	Class I
	FREEDOMS II 2014	30/355	38/358	Risk difference 2.16% (-2.2, 6.54)	713	Class II
ALT 5 times normal	FREEDOMS II 2014	4/355	8/358	Risk difference 1.11% (0.94, 3.33)	713	Class II
Neoplasms	FREEDOMS	8/355	13/358	Risk difference 1.23% (-1.23, 4.1)	713	Class II

	II 2014					

Abbreviations: SMD =standardized mean difference; SD = standard deviation.

Table e-20. Fingolimod 0.5 mg vs interferon beta-1a, RRMS						
Outcomes	**Study**	**Fingolimod 0.5 mg**	**Interferon beta-1a**	**Relative effect**	**Number of participants**	**Study class**
Annualized relapse rate	TRANSFORMS 2010	0.16 SD 0.476	0.33 SD 0.845	SMD 0.248 (0.114, 0.382)	860	Class I
Proportion of patients with at least one relapse at 12 mo	TRANSFORMS 2010	75/429	129/431	Risk ratio 0.584 (0.455, 0.750)	860	Class I
Proportion of patients with new or enlarged T2 lesions at 12 mo	TRANSFORMS 2010	168/372	196/361	Risk ratio 0.832 (0.718, 0.963)	733	Class I
Proportion of patients with gadolinium-enhanced lesions at 12 mo	TRANSFORMS 2010	37/374	68/354	Risk ratio 0.515 (0.356, 0.747)	728	Class I
Proportion of patients with confirmed disability progression	TRANSFORMS 2010	25/429	34/431	Risk ratio 0.739 (0.451, 1.213)	860	Class I
Change from baseline in EDSS score	TRANSFORMS 2010	-0.08 SD 0.79	0.01 SD 0.78	SMD 0.115 (-0.019, 0.248)	860	Class I
Proportion of patients with adverse event−related discontinuation at 1 y	TRANSFORMS 2010	24/429	16/431	Risk difference 1.88% (-0.99, 4.84)	860	Class I
Proportion of patients with neoplasms	TRANSFORMS 2010	8/429	1/431	Risk difference 1.63% (0.22, 3.41)	860	Class I

Abbreviations: SD = standard deviation; SMD = standardized mean difference; EDSS = Expanded Disability Status Scale.

Table e-21. Subcutaneous glatiramer acetate (any dose) vs placebo for RRMS						
Outcomes	**Study**	**Placebo**	**Glatiramer (any dose subcutaneously)**	**Relative effect**	**Number of participants**	**Study class**
Proportion of patients with at least one relapse at 1 y	Meta-analysis			Relative risk 0.758 (0.571, 1.007)		
	Comi 2001	61/120	54/119	Relative risk 0.893 (0.685, 1.16)	239	Class II
	GALA 2013	159/461	301/943	Relative risk 0.667 (0.563, 0.793)	1404	Class I
Proportion of patients with at least one relapse at 2 y	Meta-analysis			Relative risk 0.817 (0.688, 0.970)		
	Bornstein 1987	17/23	11/25	Relative risk 0.595 (0.352, 0.965)	48	Class II
	CONFIRM 2012	149/363	112/350	Relative risk 0.780 (0.641, 0.947)	713	Class I
	Johnson 1995	92/126	83/125	Relative risk 0.909 (0.770, 1.071)	251	Class II
Annualized relapse rate	Meta-analysis			SMD 1.00 (0.048, 1.951)		
	CONFIRM 2012	0.40 SD 0.778	0.29 SD 0.573	SMD 0.161 (0.013, 0.308)	713	Class I
	GALA 2013	0.505 SD 1.046	0.331 SD 0.877	SMD 0.186 (0.074, 0.298)	1404	Class I
	Johnson 1995	0.84 SD 0.092	0.59 SD 0.092	SMD 2.717 (2.366, 3.069)		Class II
Proportion of patients with disability progression over 2 y	Meta-analysis			Relative risk 0.761 (0.534, 1.083)	1024	
	Bornstein 1987	11/23	5/25	Relative risk 0.418 (0.175, 0.967)	48	Class II

	CONFIRM 2012	62/363	56/350	Relative risk 0.937 (0.674, 1.301)	713	Class I
	Johnson 1995	36/126	26/125	Relative risk 0.728 (0.471, 1.124)	251	Class II
Cumulative gadolinium enhancing lesions at 6 and 12 mo	GALA 2013	1.639 SD 4.104	0.905 SD 2.602	SMD 0.231 (0.116, 0.345)	1325	Class I
Total number of new enhancing lesions at 9 mo	Comi 2001	26.0 SD 33.96	17.4 SD 24.0	SMD 0.292 (0.037, 0.547)	239	Class II
Cumulative new or newly enlarging T2 lesions at 6 and 12 mo	GALA 2013	5.592 SD 10.339	3.650 SD 7.721	SMD 0.224 (0.109, 0.338)	1325	Class I
Total number of new T2 lesions at 9 mo	Comi 2001	13.7 SD 12.05	9.4 SD 12.0	SMD 0.358 (0.102, 0.613)	239	Class II
Percentage change in brain parenchymal volume from baseline to mo 12	GALA 2013	-0.645 SD 0.965	-0.706 SD 1.087	SMD 0.058 (-0.059, 0.175)	1263	Class I
New or enlarging T2 lesions at 2 y	CONFIRM 2012	17.4 SD 26.8	8.0 SD 12.4	SMD 0.457 (0.225, 0.690)	292	Class I
New T1 lesions at 2 y	CONFIRM 2012	7.0 SD 11.7	4.1 SD 6.6	SMD 0.309 (0.079, 0.540)	293	Class I
Gadolinium-enhanced lesions at 2 y	CONFIRM 2012	2.0 SD 5.6	0.7 SD 1.8	SMD 0.320 (0.094, 0.546)	305	Class I
Proportion of patients with adverse event−related discontinuation at 1 y	Meta-analysis			Risk difference 1.7% (0.1, 3.2)		
	Comi 2001	2/120	3/119	Risk difference 0.8% (-3.67, 5.64)	239	Class II
	GALA 2013	6/461	29/943	Risk difference 1.77% (0, 3.26)	1404	Class I
Proportion of patients with adverse event−related discontinuation at 2 y `	Meta-analysis			Risk difference 2.2% (-1.4, 5.8)	1024	
	Bornstein 1987	0/25	2/25	Risk difference 8% (-6.52, 24.97)	50	Class II
	CONFIRM 2012	38/363	35/351	Risk difference -0.5% (-4.98, 7.26)	714	Class I
	Johnson 1995	1/126	5/125	Risk difference 3.21% (-1.03, 8.27)	251	Class II

Abbreviations: SMD = standardized mean difference; SD = standard deviation.

Table e-22. Subcutaneous glatiramer acetate 20 mg vs 40 mg for RRMS						
Outcomes	**Study**	**20 mg**	**40 mg**	**Relative effect**	**Number of participants**	**Study class**
Annualized relapse rate	Comi 2011	0.33 SD 0.81	0.35 SD 0.99	SMD 0.022 (-0.093, 0.138)	1155	Class II
Proportion of patients with at least one relapse at 1 y	Comi 2011	131/586	131/569	Risk ratio 1.03 (0.833, 1.274)	1155	Class II
Number of gadolinium-enhanced lesions at mo 12	Comi 2011	0.68 SD 2.3	0.54 SD 1.77	SMD 0.068 (-0.047, 0.183)	1155	Class II
Number of new T2 lesions at mo 12	Comi 2011	2.87 SD 6.57	2.72 SD 8.36	SMD 0.02 (-0.095, 0.135)	1155	Class II
Adverse event−related discontinuation over 1 y	Comi 2011	28/586	51/569	Risk difference 4.18% (1.27, 7.19)	1155	Class II

Abbreviations: SD = standard deviation; SMD = standardized mean difference.

Table e-23. Subcutaneous glatiramer acetate vs placebo for chronic progressive MS						
Outcomes	**Study**	**Placebo**	**Glatiramer**	**Relative effect**	**Number of participants**	**Number of studies and class**
Proportion of patients with confirmed disability progression over 2 y	Bornstein 1991	14/55	9/51	Risk ratio 0.693 (0.329, 1.461)	106	Class II

Table e-24. Subcutaneous glatiramer acetate vs placebo for primary progressive MS						
Outcomes	**Study**	**Placebo**	**Glatiramer**	**Relative effect**	**Number of participants**	**Number and class of studies**
Proportion of patients with confirmed disability progression over 2 y	Wolinsky 2007	148/316	290/627	Risk ratio 0.988 (0.855, 1.141)	943	Class II

Table e-25. Subcutaneous glatiramer acetate vs interferon beta-1a (Rebif) for RRMS						
Outcomes	**Study**	**Interferon beta-1a (Rebif)**	**Glatiramer acetate 20 mg**	**Relative effect**	**Number of participants**	**Study class**
Proportion of patients with at least one relapse at 2 y	Mikol 2008	126/386	132/378	Risk ratio 0.93 (0.7667, 1.1396)	764	Class II
Proportion of patients with 6-mo confirmed EDSS progression	Mikol 2008	45/386	33/378	Risk ratio 1.3354 (0.8741, 2.0391)	764	Class II
Proportion of patients with no T2 active lesions at 2 y	Mikol 2008	93/230	86/230	Risk ratio 1.0814 (0.8607, 1.3594)	460	Class II
Proportion of patients with no gadolinium-enhanced lesions at 2 y	Mikol 2008	186/230	154/230	Risk ratio 1.2078 (1.0829, 1.3524)	460	Class II
Proportion of patients with adverse event−related discontinuation	Mikol 2008	23/381	19/375	Risk difference 0.97% (-2.39, 4.35)	756	Class II

Abbreviation: EDSS = Expanded Disability Status Scale.

Table e-26. Subcutaneous glatiramer acetate vs interferon beta-1b (Betaseron) for RRMS							
Outcomes	**Study**	**Interferon beta-1b 500 micrograms**	**Interferon beta-1b 250 micrograms**	**Glatiramer acetate 20 mg**	**Relative effect**	**Number of participants**	**Study class**
Proportion of patients with at least one relapse at 2 y	O'Connor 2009	360/899	377/897	186/448	Interferon beta 500 vs 250 Risk ratio 0.9528 (0.8528, 1.0644) Interferon beta 500 vs glatiramer acetate Risk ratio 0.9645 (0.8438, 1.107) Interferon beta 250 vs glatiramer acetate Risk ratio 1.0123 (0.8873, 1.1598)	2244	Class II
	Cadavid		17/36	11/39	Risk ratio 1.6742 (0.9293, 3.056)	75	

	2009						
Proportion of patients with confirmed EDSS progression at 2 y	O'Connor 2009	200/899	244/897	92/448	Interferon beta 500 vs 250 Risk ratio 0.8178 (0.6953, 0.9618) Interferon beta 500 vs glatiramer acetate Risk ratio 1.0833 (0.8721, 1.3508) Interferon beta 250 vs glatiramer acetate Risk ratio 1.3246 (1.0751, 1.6387)	2244	Class II
Proportion of patients with combined active lesions on MRI at 1 y	Cadavid 2009		29/36	29/39	Risk ratio 1.0833 (0.8393, 1.4024)	75	
Proportion of patients with new lesions on MRI at 2 y	Cadavid 2009		30/36	32/39	Risk ratio 1.0156 (0.81, 1.2669)	75	
Any injection site reaction	O'Connor 2009	485/887	427/888	259/445	Interferon beta 500 vs 250 Risk difference 6.59% (1.94, 11.20) Interferon beta 500 vs glatiramer **acetate** Risk difference -3.52% (-9.09, 2.14) Interferon beta 250 vs glatiramer acetate Risk difference -10.12% (-15.67, -4.44)	2220	Class II
Influenza-like illness	O'Connor 2009	401/887	359/888	25/445	Interferon beta 500 vs 250 Risk difference 4.78% (0.18, 9.36) Interferon beta 500 vs glatiramer acetate Risk difference 39.59% (35.47, 43.33) Interferon beta 250 vs glatiramer acetate Risk difference 34.81% (30.74, 38.53)	2220	Class II

EDSS = Expanded Disability Status Scale.

Table e-27. Subcutaneous glatiramer acetate vs interferon beta-1a (Rebif or Avonex) for RRMS

Outcomes	Study	Interferon beta-1a subcutaneous Rebif	Interferon beta-1a intramuscular Avonex	Glatiramer acetate 20 mg	Relative effect	Number of participants	Study class
New T2 lesions at 2 y	Calabrese 2012	1.2 SD 1.0	1.3 SD 1.1	1.2 SD 1.0	Rebif vs Avonex SMD -0.095 (-0.502, 0.312) Rebif vs glatiramer acetate SMD 0 (-0.404, 0.404) Avonex vs glatiramer acetate SMD 0.095 (-0.307, 0.498)	141	Class II
New gadolinium-enhanced lesions at 2 y	Calabrese 2012	1.0 SD 1.0	0.9 SD 0.9	1.1 SD 1.0	Rebif vs Avonex SMD 0.105 (-0.302, 0.512) Rebif vs glatiramer acetate SMD -0.10 (-0.505, 0.305) Avonex vs glatiramer acetate SMD -0.210 (-0.613, 0.193)	141	Class II

Abbreviations: SD = standard deviation; SMD = standardized mean difference.

Table e-28. Combined glatiramer acetate and interferon beta-1a (Avonex) vs interferon beta-1a (Avonex) vs glatiramer acetate for RRMS							
Outcomes	**Study**	**Combined glatiramer acetate and interferon beta-1a**	**Interferon beta-1a**	**Glatiramer acetate**	**Relative effect**	**Number of participants**	**Study class**
Proportion of patients with at least one relapse at 3 ye	Lublin 2013	115/499	65/250	53/259	Combined vs interferon Risk ratio 0.8864 (0.684, 1.156) Combined vs glatiramer acetate Risk ratio 1.126 (0.848, 1.506) Interferon vs glatiramer acetate Risk ratio 1.271 (0.926, 1.744)	1008	Class I
Proportion of patients with EDSS progression over 3 y	Lublin 2013	113/472	52/241	61/246	Combined vs interferon Risk ratio 1.1096 (0.835, 1.485) Combined vs glatiramer acetate Risk ratio 0.966 (0.740, 1.268) Interferon vs glatiramer acetate Risk ratio 0.8701 (0.6299, 1.201)	959	Class I
T2 lesion volume at mo 36	Lublin 2013	8.99 SD 10.92	9.42 SD 10.16	10.93 SD 12.39	Combined vs interferon SMD -0.40 (-0.215, 0.134) Combined vs glatiramer acetate SMD -0.169 (-0.336, -0.002) Interferon vs glatiramer acetate SMD -0.132 (-0.329, 0.064)	790	Class I

Abbreviation: SMD = standardized mean difference.

Table e-29. Immunoglobulins vs placebo in relapsing−remitting multiple sclerosis

Outcomes	Study	Placebo	Immunoglobulins	Relative effect	Number of participants	Number and class of studies
Proportion of patients with at least one relapse at 1 y	Meta-analysis			Risk ratio 0.771 (0.50, 1.19)	219	
	Fazekas 2008	13/41	36/86	Risk ratio 1.32 (0.81, 2.24)	128	Class I
	Achiron 1998	19/20	12/20	Risk ratio 0.63 (0.44, 0.92)	40	Class II
	Lewanska 2002	16/18	18/33	Risk ratio 0.61 (0.43, 0.87)	51	Class II
Proportion of patients with at least one relapse at 2 y	Meta-analysis			Risk ratio 0.743 (0.609, 0.905)	190	
	Achiron 1998	20/20	15/20	Risk ratio 0.76 (0.58,0.98)	40	Class II
	Fazekas 1997	47/73	35/75	Risk ratio 0.72 (0.53, 0.97)	150	Class I
Annualized relapse rate				SMD 1.20 (0.113, 2.29)		
	Fazekas 1997	0.83 SD 0.97	0.42 SD 0.74	SMD 0.476 (0.149, 0.803)		Class I
	Fazekas 2008	0.50 SD 1.02	0.94 SD 1.99	SMD -0.253 (-0.626, 0.120)		Class I
	Lewanska 2002	1.24 SD 0.75	0.88 SD 1.13	SMD 0.384 (-0.079, 0.846)		Class II
	Achiron 1998	1.42 SD 0.23	0.42 SD 0.14	SMD 5.25 (3.95, 6.56)		Class I
Proportion of patients with disability progression over 2 y	Meta-analysis			Risk ratio 0.70 (0.39, 1.24)	190	
	Achiron 1998	4/20	4/20	Risk ratio 1.00 (0.29, 3.45)	40	Class II
	Fazekas 1997	19/75	12/75	Risk ratio 0.63 (0.33, 1.21)	150	Class I

Change in EDSS score over 1 y	Lewanska 2002	0.29 SD 0.37	-0.469 SD 0.37	SMD 2.051 (1.353, 2.750)		Class I
Change in EDSS score over 2 y	Fazekas 1997	0.12 SD 1.1	-0.23 SD 0.88	SMD 0.352 (0.027, 0.677)		Class II
Proportion of patients with adverse event−related discontinuation at 1 y	Meta-analysis			Risk difference 4.7% (0.6, 8.8)		
	Fazekas 2008	0/41	1/87	Risk difference 1.15% (-7.47, 6.23)	128	Class I
	Lewanska 2002	0/18	2/33	Risk difference 6.06% (-12.07, 19.61)	51	Class II
Proportion of patients with adverse event−related discontinuation at 2 y	Fazekas 1997	1/75	3/75	Risk difference 2.67% (-3.74, 9.86)	150	Class I

Abbreviation: SMD = standardized mean difference; SD = standard deviation; EDSS = Expanded Disability Status Scale.

Table e-30. Immunoglobulins vs placebo in progressive multiple sclerosis

Outcomes	Study	Placebo	Immunoglobulins	Relative effect	Number of participants	Number and class of studies
Proportion of patients with at least one relapse at 1 y	Hommes 2004	53/159	55/159	Relative risk 1.038 (0.764, 1.410)		Class II
Proportion of patients with at least one relapse at 2 y	Meta-analysis			Relative risk 0.958 (0.793, 1.156)		
	Hommes 2004	83/159	77/159	Relative risk 0.928 (0.745, 1.155)		Class II
	Pohlau 2007	35/98	37/99	Relative risk 1.046 (0.724, 1.512)		Class II
Proportion of patients with disability progression over 2 y	Meta-analysis			Relative risk 0.963 (0.739, 1.254)		
	Hommes 2004	70/159	77/159	Relative risk 1.10 (0.867, 1.395)		Class II
	Pohlau 2007	60/98	51/99	Relative risk 0.84 (0.66, 1.08)		Class II

Table e-31. Methotrexate vs placebo in chronic progressive multiple sclerosis

Outcomes	Study	Placebo	Methotrexate	Relative effect	Number of participants	Number and class of studies
Proportion of patients who relapsed over 18 mo	Currier 1993	2/11	6/13	Risk ratio 2.539 (0.766, 9.462)	24	Class III
Proportion of patients who relapsed over 2 y	Goodkin 1995	5/29	6/31	Risk ratio 1.123 (0.406, 3.13)	60	Class II
Proportion of patients with worsening of EDSS by at least 1 point over 18 mo	Currier 1993	0/11	2/13	Risk ratio 3.38 (0.31, 37.249)	24	Class III
Proportion of patients with disability progression over 2 y	Goodkin 1995	15/29	13/31	Risk ratio 0.811 (0.473, 1.381)	60	Class II
Proportion of patients with gadolinium-enhanced lesions at 1 y	Goodkin 1996	1/17	4/20	Risk ratio 3.40 (0.556, 21.266)	60	Class II
Proportion of patients with	Goodkin	4/15	1/10	Risk ratio 0.375 (0.062, 2.032)	60	Class II

gadolinium-enhanced lesions at 2 y	1996					

Table e-32. Methotrexate vs placebo in relapsing−remitting multiple sclerosis

Outcomes	Study	Placebo	Methotrexate	Relative effect	Number of participants	Number and class of studies
Proportion of patients who relapsed over 18 mo	Currier 1993	7/11	2/9	Risk ratio 0.349 (0.097, 1.037)	20	Class III
Proportion of patients with worsening of EDSS by at least 1 point over 18 mo	Currier 1993	5/11	3/9	Risk ratio 0.733 (0.244, 2.00)	20	Class III

Table e-33. Methotrexate vs interferon beta-1a in relapsing−remitting multiple sclerosis

Outcomes	Study	Interferon beta 1a	Methotrexate	Relative effect	Number of participants	Number and class of studies
Relapses at 12 mo	Ashtari 2011	1.98±0.83	2.37±0.99	SMD 0.427 (-0.016, 0.870)	40	Class III
EDSS at 12 mo	Ashtari 2011	0.57±0.78	0.97±0.83	SMD 0.497 (0.052, 0.942)	40	Class III

Abbreviations: standardized mean difference; EDSS = Expanded Disability Status Scale.

Table e-34. Mitoxantrone vs placebo in relapsing−remitting multiple sclerosis

Outcomes	Study	Mitoxantrone	Placebo	Relative effect	Number of participants	Study class
Patients with relapse over 12 mo	Millefiorini 1997	8/27	18/24	Risk ratio 0.395 (0.208, 0.709)	51	Class I
Patients with relapse over 24 mo	Millefiorini 1997	10/27	19/24	Risk ratio 0.468 (0.268, 0.772)	51	Class I
Patients with disability progression over 24 mo	Millefiorini 1997	2/27	9/24	Risk ratio 0.198 (0.052, 0.729)	51	Class I
New lesions on T2 MRI from baseline to 24 mo	Millefiorini 1997	3.5 SD 3.4, n=23	7.3 SD 8.0 n=19	SMD 0.641 (0.018, 1.264)	42	Class I
Enlarging lesions on T2 MRI from baseline to 24 mo	Millefiorini 1997	4.3 SD 4.7 n=23	4.3 SD 4.7 n=19	SMD 0 (-0.608, 0.608)	42	Class I

Abbreviation: standardized mean difference.

Table e-35. Mitoxantrone vs placebo in relapsing−progressive multiple sclerosis

Outcomes	Study	Mitoxantrone 12 mg/m^2	Placebo	Relative effect	Number of participants	Study class
Change in EDSS at 24 mo	Hartung 2002	-0.13 (SD 0.90) n=60	0.23 (SD 1.01) n=64	SMD 0.37 (0.02, 0.73)	124	Class II
Patients with disability progression over 24 mo (less than 1 EDSS from baseline)	Hartung 2002	5/60	16/64	Risk ratio 0.333 (0.134, 0.822)	124	Class II
Patients with relapses over 24 mo	Hartung 2002	26/60	41/64	Risk ratio 0.676 (0.477, 0.943)	124	Class II

Patients with hospital admissions	Hartung 2002	24/60	43/64	Risk difference -27.19 (-42.54, -9,63)	124	Class II
Patients with active lesions	Hartung 2002	0/31	5/37	Risk ratio 0.239 (0.038, 1.526)	68	Class II
Amenorrhea	Hartung 2002	7/25	0/31	Risk difference 28.0% (10.4, 47.58)	56	Class II
Nausea/vomiting	Hartung 2002	47/62	13/64	Risk difference 55.49% (38.97, 67.52)	126	Class II
Alopecia	Hartung 2002	38/62	20/64	Risk difference 30.04% (12.65, 45.01)	126	Class II
Urinary tract infections	Hartung 2002	20/62	8/64	Risk difference 19.76% (5.21, 33.52)	126	Class II
Leukopenia	Hartung 2002	12/62	0/64	Risk difference 19.35% (9.62, 30.85)	126	Class II

Abbreviations: EDSS = Expanded Disability Status Scale; SD = standard deviation; SMD = standardized mean difference.

Table e-36. Mycophenolate mofetil plus interferon beta-1a vs interferon beta-1a plus placebo for RRMS

Outcomes	Study	Interferon beta-1a plus MMF 1,000 mg twice daily	Interferon beta-1a plus placebo	Relative effect	Number of participants	Number and class of studies
Proportion of patients with at least one relapse at 1 y	Meta-analysis			RR 0.63 (0.177, 2.234)	50	
	Etemadifar 2011	0/13	1/13	RR 0.50 (0.03, 7.27)	26	Class II
	Remington 2010	2/12	3/12	RR 0.67 (0.16, 2.78)	24	Class II
EDSS at 1 y	Meta-analysis			SMD 0.02 (-0.53, 0.57)	50	
	Etemadifar 2011	1.80±0.99	1.76±1.07	SMD 0.04 (-0.73, 0.81)	26	Class II
	Remington 2010	1.7±1.32	1.7±1.05	SMD 0.00 (-0.80, 0.80)	24	Class II
Change in EDSS at 1 y	Etemadifar 2011	0.80±0.52	0.96±0.87	SMD 0.22 (-0.56, 0.99)	26	Class II
New T2 lesions at 1 y	Etemadifar 2011	0.54±0.77	1.85±3.2	SMD 0.55 (-0.24, 1.33)	26	Class II
New gadolinium-enhanced lesions at 1 y	Etemadifar 2011	0/13	2/13	RR 0.50 (0.07, 3.54)	26	Class II
T2 lesion volume change (%) at 1 y	Remington 2010	16±43	70±134	SMD 0.52 (-0.29, 1.34)	24	Class II
Black hole volume change (%) at 1 y	Remington 2010	32±455	119±320	SMD 0.21 (-0.59, 1.02)	24	Class II
Brain volume change (%) at 1 y	Remington 2010	-0.34±0.69	-0.95±0.93	SMD 0.72 (-0.11, 1.55)	24	
Gadolinium-enhanced lesion volume change (%) at 1 y	Remington 2010	-128±275	124±457	SMD 0.65 (-0.18, 1.47)	24	Class II
Hauser ambulation index at 1 y	Remington 2010	0.45±0.7	0.42±0.5	SMD 0.05 (-0.75, 0.85)	24	Class II

MSQOL Physical	Remington 2010	70±24	73±17	SMD 0.14 (-0.66, 0.94)	24	Class II
MSQOL Emotional	Remington 2010	76±16	79±21	SMD 0.16 (-0.65, 0.96)	24	Class II

Table e-37. Mycophenolate mofetil vs interferon beta-1a in RRMS

Outcomes	Study	MMF 1,000 mg twice daily	Interferon beta-1a	Relative effect	Number of participants	Number and class of studies
Proportion of patients with at least one relapse at 6 mo	Frohman 2010	2/16	2/19	RR 1.18 (0.22, 6.16)	35	Class III
Mean number of new T2 lesions at 6 mo	Frohman 2010	2.6±1.4	9.7±25	SMD 0.384 (-0.287, 1.055)	35	Class III
Mean number of new gadolinium-enhanced lesions at 6 mo	Frohman 2010	1.1±1.8	7.2±17.4	SMD 0.473 (-0.202, 1.147)	35	Class III

Table e-38. Pegylated interferon vs placebo for relapsing-remitting multiple sclerosis

Outcomes	Study	Placebo	Pegylated interferon	Relative effect	Number of participants	Study class
Proportion of patients with at least one relapse at 1 y	ADVANCE 2014	142/500	195/1012	Risk ratio 0.6785 (0.5633, 0.8196)	1512	Class I
Annualized relapse rate at 1 y	ADVANCE 2014 125 micrograms every 2 wk	0.397 SD 0.873	0.256 SD 0.646	SMD 0.184 (0.06, 0.307)	1012	Class I
	ADVANCE 2014 125 micrograms every 4 wk	0.397 SD 0.873	0.288 SD 0.69	SMD 0.139 (0.014, 0.263)	1000	Class I
Proportion of patients with disability progression over 1 y	ADVANCE 2014	50/500	62/1012	Risk ratio 0.6126 (0.43, 0.8751)	1512	Class I
New or newly enlarging T2 weighted lesions at 1 y	ADVANCE 2014 125 micrograms every 2 wk	10.9 SD 16.14	3.6 SD 6.00	SMD 0.602 (0.476, 0.728)	1012	Class I
	ADVANCE 2014 125 micrograms every 4 wk	10.9 SD 16.14	7.9 SD 11.52	SMD 0.214 (0.09, 0.338)	1000	Class I
Proportion of patients with adverse event−related discontinuation at 1 y	ADVANCE 2014	7/500	49/1012	Risk difference 3.44% (1.58, 5.11)	1512	Class I
Severe adverse effects, defined as symptoms that cause severe discomfort, incapacitation, or significant	ADVANCE 2014	53/500	172/1012	Risk difference 6.4% (2.68, 9.82)	1512	Class I

effect on patients' daily life						

Abbreviations: SD = standard deviation; SMD = standardized mean difference

Table e-39. Rebif vs placebo in relapsing−remitting multiple sclerosis

Outcomes	Study	Placebo	Rebif	Relative effect	Number of participants	Study class
Proportion of patients with at least one relapse at 1 y	OWIMS 1999 22 or 44 micrograms once a wk **(dose not used clinically)**	64/100	123/193	Relative risk 0.9958 (95%CI 0.8377, 1.2056)	293	Class I
	PRISMS 1998 22 or 44 micrograms 3 times a wk	146/187	220/373	Relative risk 0.7554 (0.675, 0.8495)	560	Class I
Proportion of patients with at least one relapse at 2 y	PRISMS 1998 22 or 44 micrograms 3 times a wk	157/187	263/373	Relative risk 0.8398 (0.7688, 0.9235)	560	Class I
Relapse rate over 16 wk	IMPROVE 2012 44 micrograms 3 times a wk	0.33 SD 0.593	0.14 SD 0.391	SMD 0.406 (0.093, 0.719)	180	Class II
Proportion of patients with disability progression over 2 y	PRISMS 1998 22 or 44 micrograms 3 times a wk	77/187	118/373	Relative risk 0.77 (0.61, 0.96)	560	Class I
Change in EDSS over 2 y	PRISMS 1998 44 micrograms 3 times a wk	0.48 SD 1.3	0.24 SD 1.1	SMD 0.199 (-0.005, 0.403)	371	Class I
Patients with new T2 lesions over 4 mo	IMPROVE 2012 44 micrograms 3 times a wk	30/60	27/120	Relative risk 0.45 (0.2998, 0.6857)	180	Class II
Patients with new T2 activity over 2 y	PRISMS 1998 44 micrograms 3 times a wk	169/184	126/182	Relative risk 0.7538 (0.6736, 0.8349)	366	Class I
Proportion of patients with adverse event−related discontinuation at 1 y	OWIMS 1999 22 or 44 micrograms once a wk **(dose not used clinically)**	0/100	5/193	Risk difference 2.59% (-1.39, 5.92)	293	Class I
Proportion of patients with adverse event−related discontinuation at 2 y	PRISMS 1998	2/187	15/373	Risk difference 2.95% (-0.21, 5.58)	560	Class I

Abbreviations: SMD = standardized mean difference; EDSS = Expanded Disability Status Scale.

Table e-40. Rebif vs Avonex in relapsing−remitting multiple sclerosis

Population: RRMS **Intervention: Rebif 44 micrograms subcutaneous 3 times a wk** **Comparator: Avonex 30 micrograms intramuscular once a wk**						
Outcomes	**Study**	**Rebif 44 micrograms intramuscular 3 times a wk**	**Avonex 30 micrograms** once **a wk**	**Relative effect**	**Number of participants**	**Study class**
Proportion of patients with at least one relapse at 1 y	EVIDENCE 2007	148/339	175/338	Relative risk 0.8432 (0.7192, 0.9876)	677	Class II
Proportion of patients with new or enlarging T2 lesions	EVIDENCE 2007	92/339	149/338	Relative risk 0.6156 (0.4979, 0.7596)	677	Class II
Adverse event−related discontinuation at 1 y	EVIDENCE 2007	19/339	18/338	Risk difference 0.28% (-3.27, 3.83)	677	Class II
Injection site reactions	EVIDENCE 2007	85/339	33/337	Risk difference 15.31% (9.67, 20.9)	676	Class II

Table e-41. Rebif vs Betaseron in relapsing−remitting multiple sclerosis

Population: RRMS **Intervention: Rebif 22 micrograms subcutaneous once a wk (dose not used clinically)** **Comparator: Betaseron 250 micrograms subcutaneous every other d**						
Outcomes	**Study**	**Rebif 22 micrograms subcutaneous once a wk**	**Betaseron 250 mc micrograms subcutaneous every other d**	**Relative effect**	**Number of participants**	**Study class**
Annualized relapse rate	Koch-Henriksen 2006	0.70 SD 0.641 n=143	0.71 SD 0.673 n=158	SMD 0.015 (-0.211, 0.241)	301	Class III
Proportion of patients with a 1.0-point progression on the EDSS relative to baseline	Koch-Henriksen 2006	36/143	33/158	Relative risk 1.2053 (0.7987, 1.8169)	301	Class III

Table e-42. Rebif vs placebo in secondary progressive multiple sclerosis

Outcomes	**Study**	**Placebo**	**Rebif**	**Relative effect**	**Number of participants**	**Number and class of studies**
Proportion of patients with at least one relapse over 3 y	Andersen 2004 Rebif 22 micrograms once per wk **(dose not used clinically)**	68/178	72/186	Relative risk 1.01 (0.783, 1.313)	364	Class III
Mean exacerbations per person y	SPECTRIMS 2001 22 micrograms 3	0.71 SD 0.219 n=205	0.50 SD 0.443 n=209	SMD 0.599 (0.402, 0.796)	414	Class I

	times a wk					
	SPECTRIMS 2001 44 micrograms 3 times a wk	0.71 SD 0.219 n=205	0.50 SD 0.401 n=204	SMD 0.650 (0.452, 0.849)	409	Class I
Proportion of patients with disability progression over 2 y	SPECTRIMS 2001 Rebif 22 micrograms or 44 micrograms 3 times per wk	109/205	205/413	Relative risk 0.93 (0.79, 1.10)	618	Class I
Proportion of patients with disability progression over 3 y	Andersen 2004 Rebif 22 micrograms once per wk **(dose not used clinically)**	68/178	77/186	Relative risk 1.084 (0.843, 1.396)	364	Class III
	SPECTRIMS 2001 Rebif 22 micrograms or 44 micrograms 3 times per wk	133/205	245/413	Relative risk 0.91 (0.80, 1.04)	618	Class I
Adverse event−related discontinuation	SPECTRIMS 2001 Rebif 22 micrograms or 44 micrograms 3 times per wk	5/205	33/413	Risk difference 5.55% (1.69, 8.88)	618	Class I

Abbreviations: SD = standard deviation; SMD = standardized mean difference.

Table e-43 Rituximab vs placebo in relapsing−remitting multiple sclerosis

Outcomes	Study	Rituximab	Placebo	Relative effect	Number of participants	Study class
Relapses at 24 wk	Hauser 2008	10/69	12/35	Risk ratio 0.4227 (0.2097, 0.8771)	104	Class II
Relapses at 48 wk	Hauser 2008	14/69	14/35	Risk ratio 0.5072 (0.2807, 0.9444)	104	Class II
Annualized adjusted relapse rate from wk 0−24	Hauser 2008	0.4 (0.23-0.60) SD 0.784	0.8 (0.53-1.31) SD 1.177	SMD 0.428 (0.018, 0.839)	104	Class II
Annualized adjusted relapse rate from wk 0−48	Hauser 2008	0.4 (0.24-0.57) SD 0.699	0.7 (0.46-1.12) SD 0.996	SMD 0.370 (-0.040, 0.780)	104	Class II
Mean number of gadolinium-enhanced lesions at wk 12, 16, 20, 24	Hauser 2008	0.5±2.0	5.5±15.0	SMD 0.56 (0.15, 0.98)	104	Class II
Mean change in volume of lesions detected on T2 MRI from baseline to wk 24	Hauser 2008	-163.1±1187.6	436.3±1358.4	SMD 0.502 (0.09, 0.915)	104	Class II
Mean change in volume of lesions detected on T2 MRI from baseline to wk 36	Hauser 2008	-175.4±1188.1	417.8±1305.1	SMD 0.483 (0.071, 0.895)	104	Class II

Any adverse effect	Hauser 2008	68/69	35/35	Risk difference -1.45% (-7.76, 8.51)	104	Class II
"Serious" adverse effect	Hauser 2008	9/69	5/35	Risk difference -1.24% (-17.49, 11.52)	104	Class II
Adverse event leading to withdrawal from study	Hauser 2008	3/69	2/35	Risk difference -1.37% (-14.57, 7.35)	104	Class II
Infection-associated effect	Hauser 2008	48/69	25/35	Risk difference -1.86% (-18.76, 17.20)	104	Class II
Infection-associated serious adverse effect	Hauser 2008	2/69	2/35	Risk difference 2.82% (-15.88, 5.37)	104	Class II

Abbreviations: SD = standard deviation; SMD = standardized mean difference.

Table e-44. Rituximab vs placebo in primary progressive multiple sclerosis

Outcomes	Study	Rituximab	Placebo	Relative effect	Participants	Study class
Proportion of patients with confirmed disease progression at wk 48	Hawker 2009	20.2% (59/292)	19.3% (28/147)	Risk ratio 1.0608 (0.7147, 1.5915)	439	Class II
Proportion of patients with confirmed disease progression at wk 96	Hawker 2009	30.2% (88/292)	38.5% (57/147)	Risk ratio 0.7772 (0.5984, 1.02)	439	Class II
Mean T2 volume change from baseline to wk 96	Hawker 2009	1507±3739	2205±4306	SMD 0.177 (-0.021, 0.376)	439	Class II
Mean brain volume change from baseline to wk 96	Hawker 2009	-10.8±40.3	-9.9±37.0	SMD 0.023 (-0.175, 0.221)	439	Class II
EDSS change from baseline to wk 96	Hawker 2009	0.33±1.0	0.45±1.0	SMD 0.12 (-0.078, 0.318)	439	Class II
Total adverse effects	Hawker 2009	289/292	147/147	Risk difference -1.03% (-2.98, 1.61)	439	Class II
Adverse effects leading to discontinuation of study drug	Hawker 2009	9/292	1/147	Risk difference 2.4% (-1.0, 5.13)	439	Class II
Serious adverse effects	Hawker 2009	48/292	20/147	Risk difference 2.83% (-4.68, 9.41)	439	Class II
Infection-associated events	Hawker 2009	199/292	96/147	Risk difference 2.84% (-6.26, 12.32)	439	Class II
Infection-associated serious adverse effects	Hawker 2009	13/292	1/147	Risk difference 3.7% (0.19, 6.84)	439	Class II

Abbreviations: SMD = standardized mean difference; EDSS = Expanded Disability Status Scale.

Table e-45. Teriflunomide vs placebo in RRMS: Main outcomes of interest

Outcomes	Study	Placebo	Teriflunomide	Relative effect	Number of participants	Number and class of studies
Proportion of patients with at least one relapse at 1 y				**Risk ratio 0.86 (0.78, 0.95)**		
	TEMSO 2011	169/363	295/725	Risk ratio 0.87 (0.76, 1.01)	1088	Class II

	TOWER 2014	183/389	309/780	Risk ratio 0.84 (0.73, 0.97)	1169	Class II
Proportion of patients with at least one relapse at 2 y	TEMSO 2011	220/363	387/725	Risk ratio 0.88 (0.79, 0.98)	1088	Class II
Annualized relapse rate, teriflunomide 14-mg dose				**SMD 0.259 (0.160, 0.357)**	1597	
	TOWER 2014	0.50±0.75	0.32±0.54	SMD 0.274 (0.131, 0.417)	758	Class II
	TEMSO 2011	0.54±0.73	0.37±0.63	SMD 0.249 (0.103, 0.396)	721	Class II
	O'Connor 2006	0.81±1.22	0.55±1.12	SMD 0.222 (-0.14, 0.584)	118	Class II
Annualized relapse rate, teriflunomide 7-mg dose				**SMD 0.208 (0.111, 0.305)**		
	TOWER 2014	0.50±0.75	0.39±0.67	SMD 0.155 (0.016, 0.294)	795	Class II
	TEMSO 2011	0.54±0.73	0.37±0.54	SMD 0.265 (0.119, 0.411)	728	Class II
	O'Connor 2006	0.81±1.22	0.58±0.85	SMD 0.219 (-0.137, 0.575)	122	Class II
Proportion of patients with disability progression over 2 y, teriflunomide 14-mg dose				**Risk ratio 0.763 (0.624, 0.933)**		
	TEMSO 2011	99/363	72/358	Risk ratio 0.737 (0.565, 0.961)	721	Class II
	TOWER 2014	76/388	58/370	Risk ratio 0.800 (0.587, 1.09)	758	Class II
Proportion of patients with disability progression over 2 y, teriflunomide 7-mg dose				**Risk ratio 0.922 (0.683, 1.245)**		
	TEMSO 2011	99/363	79/365	Risk ratio 0.794 (0.614, 1.026)	721	Class II
	TOWER 2014	76/388	86/407	Risk ratio 1.079 (0.820, 1.4197)	758	Class II
Change in EDSS score from baseline to wk 48						
Teriflunomide 14-mg dose	TOWER 2014	0.09±0.99	-0.05±0.96	SMD 0.144 (0.001, 0.286)	758	Class II
Teriflunomide 7-mg dose	TOWER 2014	0.09±0.99	0.04±1.01	SMD 0.05 (-0.089, 0.189)	795	Class II
MRI total lesion volume, change from baseline to 2 y						
Teriflunomide 14-mg dose	TEMSO 2011	2.21±7.00	0.72±7.59	SMD 0.204 (0.058, 0.351)	721	Class II
Teriflunomide 7-mg dose	TEMSO 2011	2.21±7.00	1.31±6.80	SMD 0.130 (0.015, 0.276)	728	Class II
Volume of T1 hypointense lesions from baseline to 2 y						
Teriflunomide 14-mg dose	TEMSO 2011	0.53±1.06	0.33±1.01	SMD 0.193 (0.047, 0.339)	721	Class II
Teriflunomide 7-mg dose	TEMSO 2011	0.53±1.06	0.55±1.15	SMD 0.018 (-0.127, 0.163)	728	Class II
Volume of T2 hyperintense lesions from baseline to 2 y						
Teriflunomide 14-mg dose	TEMSO 2011	1.67±6.47	0.39±6.90	SMD 0.191 (0.045, 0.338)	721	Class II
Teriflunomide 7-mg dose	TEMSO 2011	1.67±6.47	0.81±6.18	SMD 0.136 (0.01, 0.281)	728	Class II
Proportion of patients with T1 contrast-enhanced lesions over 36 wk						
Teriflunomide 14-mg dose	O'Connor 2006	45/61	35/57	Risk ratio 0.832 (0.645, 1.074)	118	Class II
Teriflunomide 7-mg dose	O'Connor 2006	45/61	37/61	Risk ratio 0.822 (0.639, 1.057)	122	Class II
Proportion of patients with new or enlarging T2 lesions over 36 wk						
Teriflunomide 14-mg dose	O'Connor 2006	46/61	34/57	Risk ratio 0.791 (0.612, 1.023)	118	Class II
Teriflunomide 7-mg dose	O'Connor 2006	46/61	32/61	Risk ratio 0.696 (0.527, 0.919)	122	Class II
Proportion of patients with	TOWER 2014	25/389	114/780	Risk difference 8.19% (4.49, 11.53)	1169	Class II

adverse event−related discontinuation at 1 y						
Proportion of patients with adverse event−related discontinuation at 2 y	TEMSO 2011	29/363	75/725	Risk difference 2.36% (-1.47, 5.75)	1088	Class II
Death				Risk difference 0% (-0.8, 0.8)		
	TOWER 2014	1/385	3/780	Risk difference 0.12% (-1.1, 0.9)	1165	Class II
	TEMSO 2011	0/360	0/726	Risk difference 0% (-1.06, 0.53)	1086	Class II
Serious infections	TOWER 2014	11/385	25/780	Risk difference 0.35% (-2.07, 2.29)	1165	Class II

Teriflunomide vs placebo in RRMS: Other outcomes of interest

Change in SF-36 physical health summary score from baseline to wk 48						
Teriflunomide 14-mg dose	TOWER 2014	-1.08±8.08	-0.11±8.08	SMD 0.120 (-0.022, 0.263)	758	Class II
Teriflunomide 7-mg dose	TOWER 2014	-1.08±8.08	-0.40±8.07	SMD 0.084 (-0.055, 0.223)	795	Class II
Change in SF-36 mental health summary score from baseline to wk 48						
Teriflunomide 14-mg dose	TOWER 2014	-2.91±11.62	-1.43±11.74	SMD 0.127 (-0.016, 0.269)	758	Class II
Teriflunomide 7-mg dose	TOWER 2014	-2.91±11.62	-2.03±11.50	SMD 0.076 (-0.063, 0.215)	795	Class II
ALT increased				**Risk ratio 1.672 (1.275, 2.192)**	2430	
	TOWER 2014	32/385	98/780	Risk ratio 1.512 (1.034, 2.210)	1165	Class II
	TEMSO 2011	24/360	95/726	Risk ratio 1.963 (1.277, 3.016)	1086	Class II
	O'Connor 2006	6/61	17/118	Risk ratio 1.465 (0.609, 3.524)	179	Class II
Hair thinning				**Risk ratio 2.733 (1.927, 3.878)**	2430	
	TOWER 2014	17/385	92/780	Risk ratio 2.671 (1.616, 4.416)	1165	Class II
	TEMSO 2011	12/360	85/726	Risk ratio 3.512 (1.945, 6.343)	1086	Class II
	O'Connor 2006	6/61	20/118	Risk ratio 1.723 (0.730, 4.066)	179	Class II
Neutropenia	TOWER 2014	11/385	64/780	Risk ratio 2.872 (1.533, 5.381)	1165	Class II
Any infection	TOWER 2014	197/385	363/780	Risk ratio 0.910 (0.804, 1.029)	1165	Class II

Abbreviation: SMD = standardized mean difference.