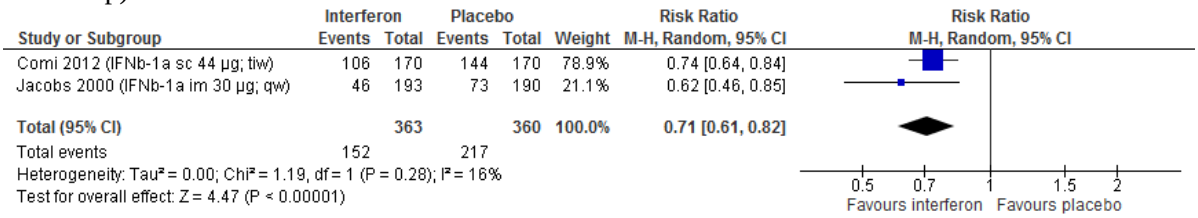
Appendix 6_ Forest plots

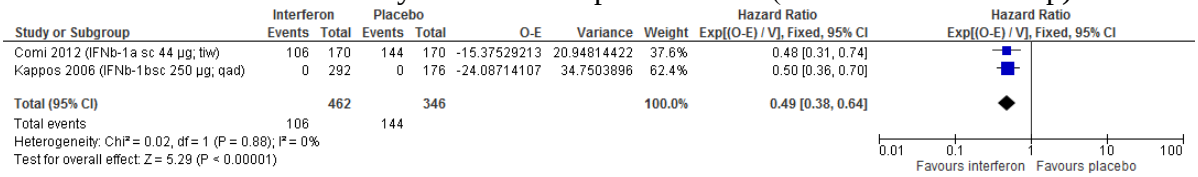
Review question 1

1. Interferon compared with placebo

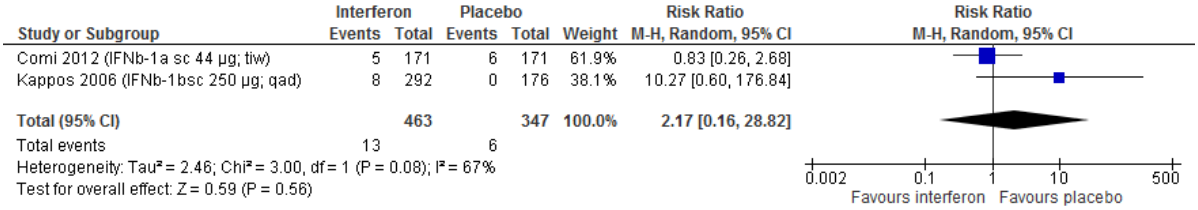
Conversion to clinically definite multiple sclerosis [1] – number of participants (104 weeks' follow-up)



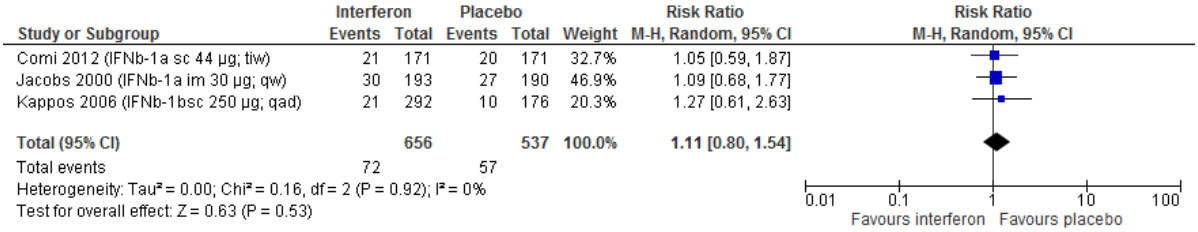
Time to conversion to clinically definite multiple sclerosis[2] (104 weeks' follow-up)



Tolerability/side effects - discontinuation due to side effects (104 weeks' follow-up)



Tolerability/side effects - discontinuation due to any reason (104 weeks' follow-up)



Tolerability/side effects - discontinuation of study drug due to side effects (104 weeks' follow-up)

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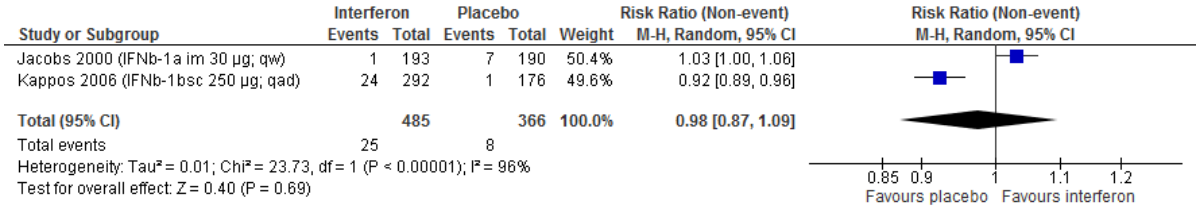
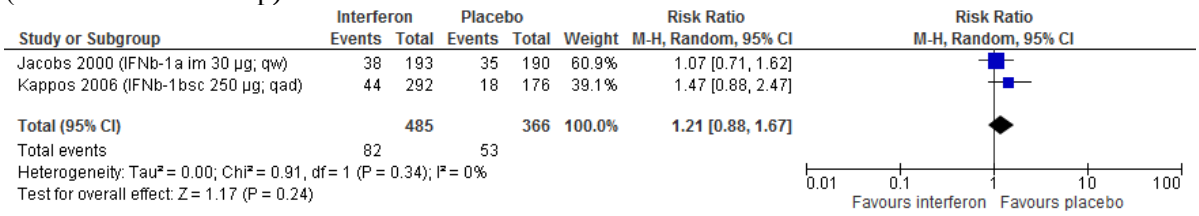
[1] Comi 2012: To meet the McDonald criteria for diagnosis of MS, patients had to have evidence of spatial and temporal dissemination of MRI lesions or a second clinical attack. For patients without a second attack, MRI follow-up scans were assessed and lesions were classified qualitatively as persisting, new, or enlarging and the location recorded as infratentorial, juxtacortical, periventricular, or deep white matter. Dissemination in space on MRI was defined as three of the following: at least one gadolinium-enhancing lesion or at least nine T2 hyper-intense lesions; at least one infratentorial lesion; at least one juxtacortical lesion; or at least three periventricular lesions. Alternatively, dissemination in space could be defined as at least two MRI lesions consistent with MS plus positive CSF. Dissemination in time was defined as a new gadolinium enhancing lesion more than 3 months after onset of the first clinical demyelinating event (at a site different from the initial event) or a new T2 lesion at any time compared with a scan at least 30 days after the onset of the initial clinical event.

Jacobs 2000: Defined as (1) the occurrence of a new symptomatic neurological event attributable to a different part of the CNS than the initial episode (prior to CHAMPS study entry) and in the absence of fever or infection lasting more than 48 hours (2) symptomatic progressive neurologic deterioration, defined as an increase of 1.5 points in Expanded Disability Status Scale score. CDMS required confirmation by an independent blinded outcomes committee

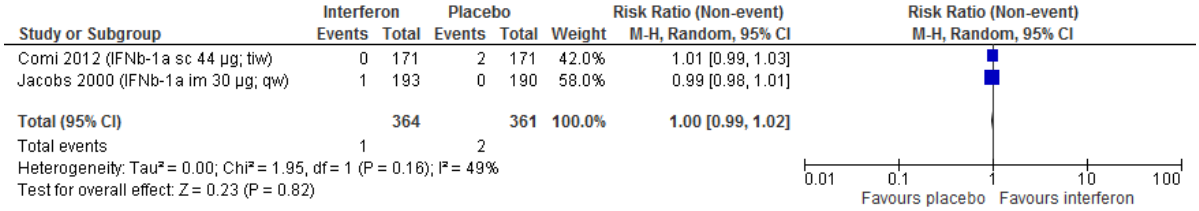
[2] Kappos 2006: CDMS was defined according to slightly modified Poser criteria by 1) a relapse with clinical evidence of at least one CNS lesion, and if the first presentation was monofocal distinct from the lesion responsible for the CIS presentation, or 2) sustained progression by 1.5 points on the EDSS reaching a total EDSS score of 2.5 and confirmed at a consecutive visit 3 months later.



Tolerability/side effects - discontinuation of study drug due to any reason (risk of non-event) (104 weeks' follow-up)



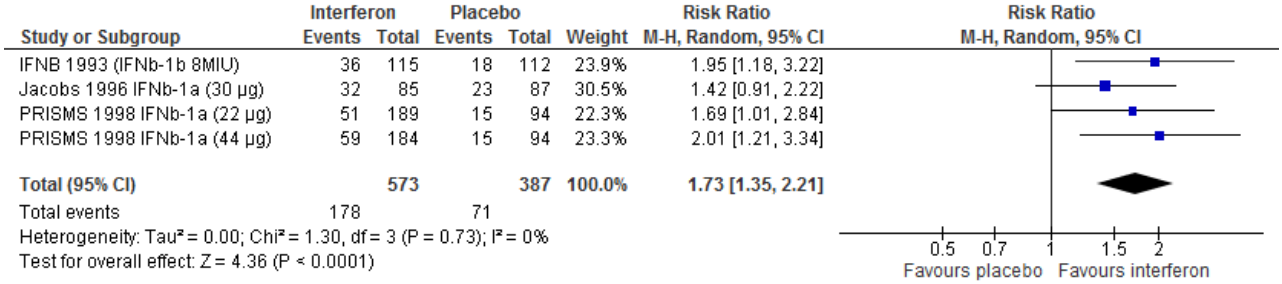
Mortality (risk of non-event) (104 weeks' follow-up)



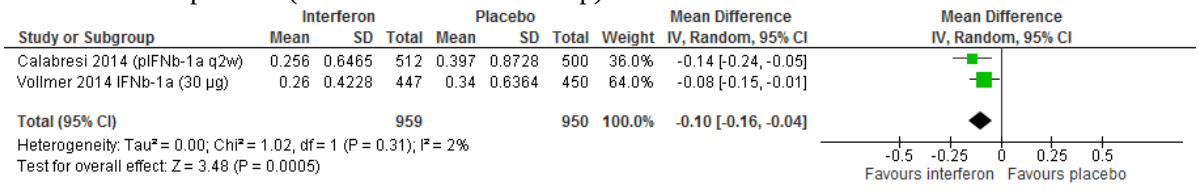
Review question 2

1. Interferon compared with placebo

Relapse - number of participants relapse free (104 weeks' follow-up)

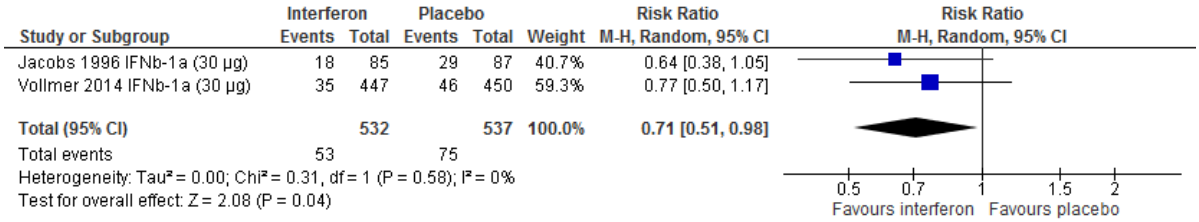


Annualised relapse rate (48-104 weeks' follow-up)

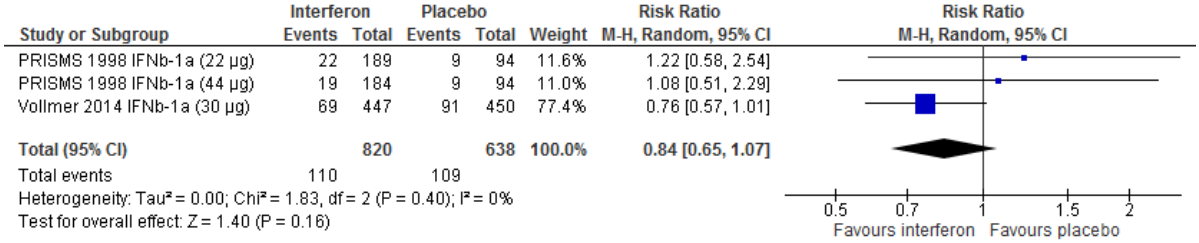


Disability progression[3] – number of participants worsened (104 weeks' follow-up)

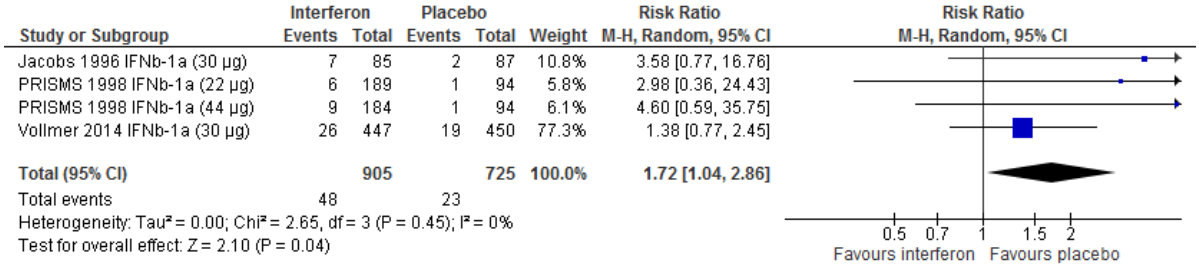
[3] Jacobs 1996: Deterioration from baseline by at least 1.0 point on the EDSS persisting for at least 6 months
Vollmer 2014: defined as a 1.0 point increase in EDSS score if baseline score was between 0 and 5.0, or a 0.5 point increase if baseline score was 5.5, sustained for 6 months



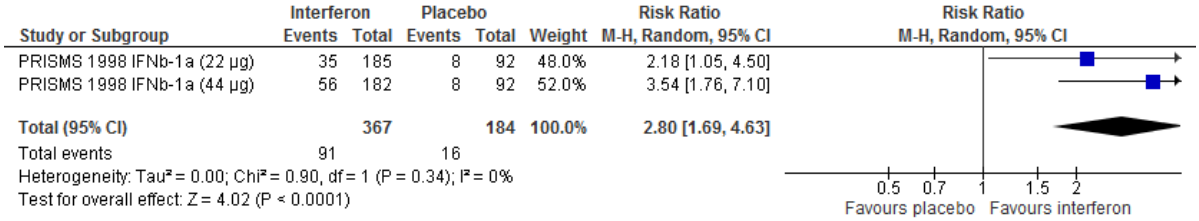
Discontinuation due to any reason (104 weeks' follow-up)



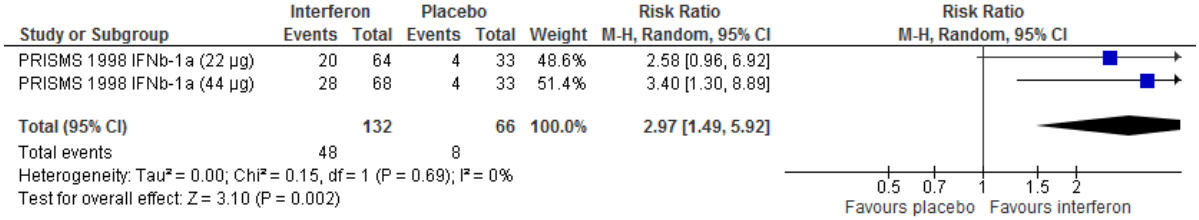
Discontinuation due to side effects (104 weeks' follow-up)



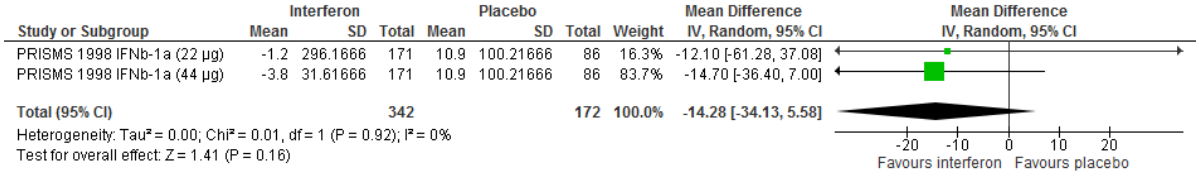
T2 active lesions – number of participants with no activity (104 weeks' follow-up)



Combined unique active lesions - number of participants with no activity (104 weeks' follow-up)

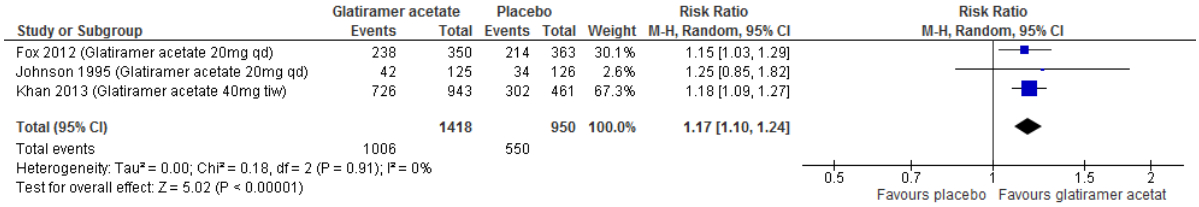


Burden of disease (percent change from baseline of total areas of all MS lesions; mm2) - 104 weeks follow-up

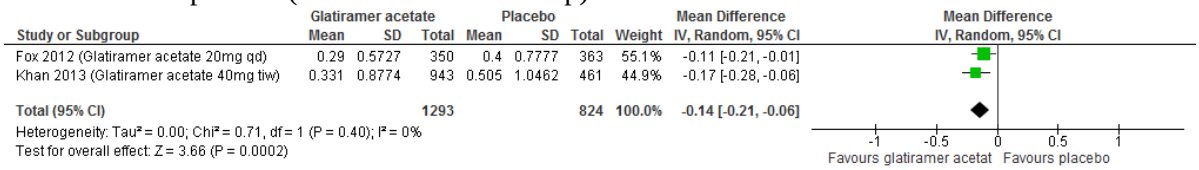


2. Glatiramer acetate compared with placebo

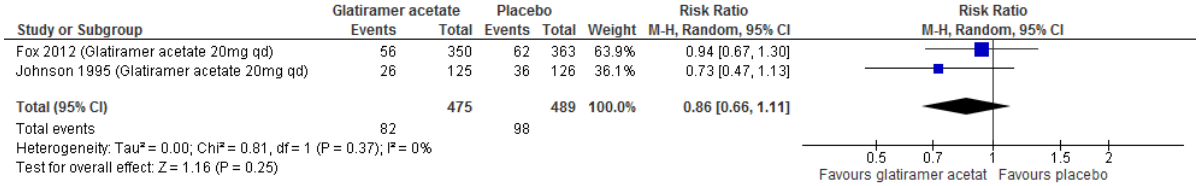
Relapse - number of participants relapse free (52-104 weeks' follow-up)



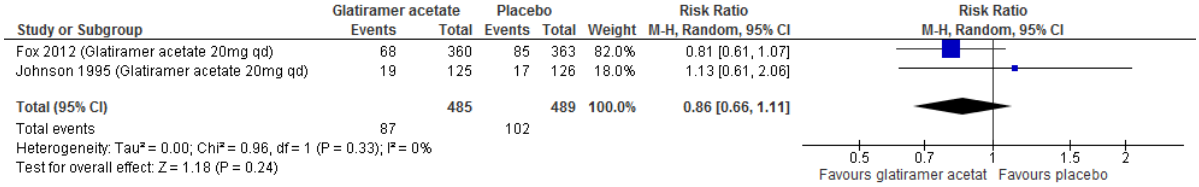
Annualised relapse rate (52-96 weeks' follow-up)



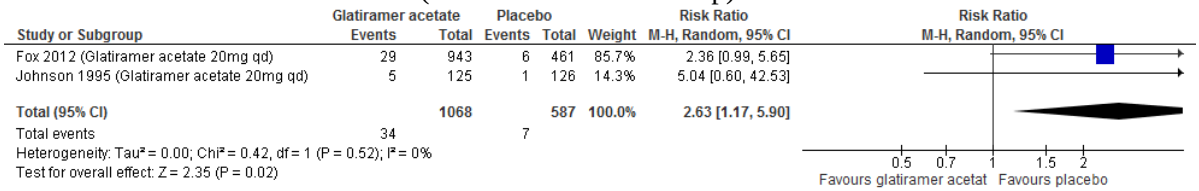
Disability progression[4] – number of participants worsened (96-104 weeks' follow-up)



Discontinuation due to any reason (96-104 weeks' follow-up)

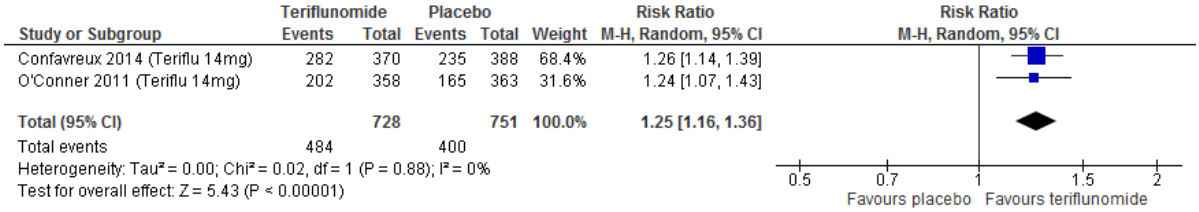


Discontinuation due to side effects (96-104 weeks' follow-up)



3. Teriflunomide compared with placebo

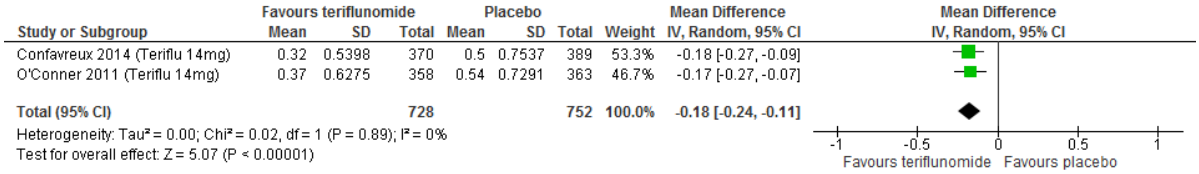
Relapse - number of participants relapse free (48-108 weeks' follow-up)



Annualised relapse rate (48-108 weeks' follow-up)

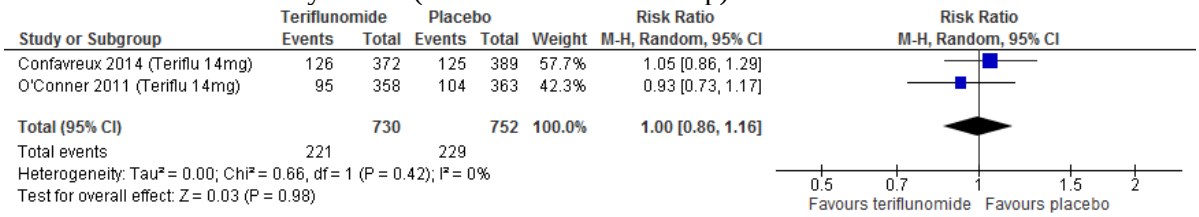
[4] Fox 2012: defined as an increase in the EDSS score of at least 1.0 point in patients with a baseline score of 1.0 or more or an increase of at least 1.5 points in patients with a baseline score of 0, confirmed at least 12 weeks later

Johnson 1995: EDSS increase of at least 1 point sustained at 3 months

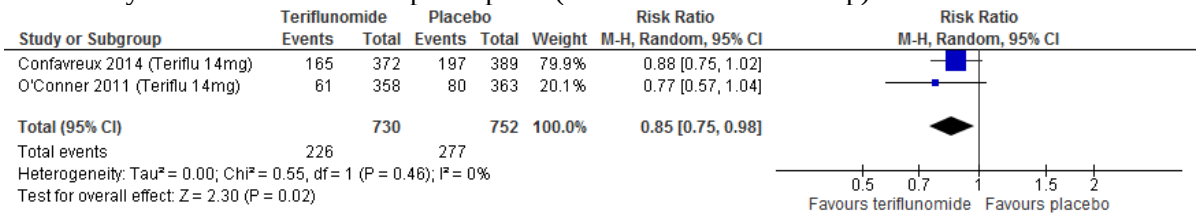


Disability progression[5] – number of participants worsened (48-108 weeks' follow-up)

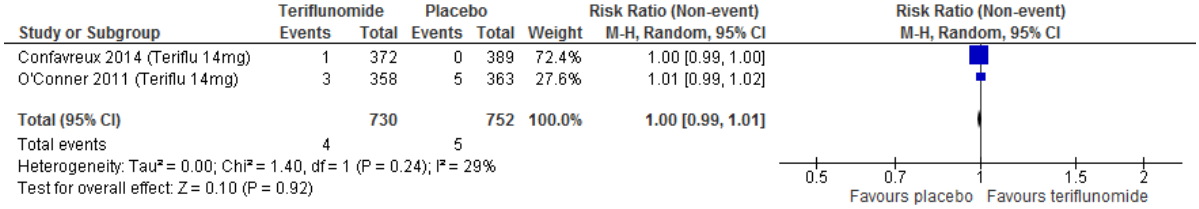
Discontinuation due to any reason (48-108 weeks' follow-up)



Risk of any infection – number of participants (48-108 weeks' follow-up)

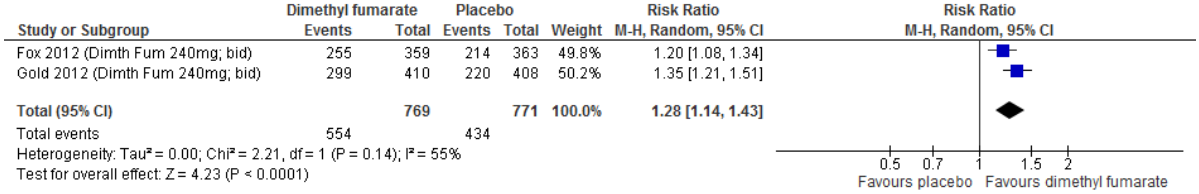


Risk of cancer – number of participants with any neoplasm (risk of non-event) (48-108 weeks' follow-up)

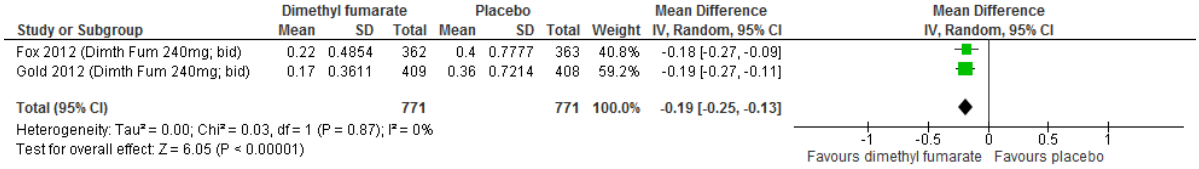


4. Dimethyl fumarate compared with placebo

Relapse - number of participants relapse free (104 weeks' follow-up)

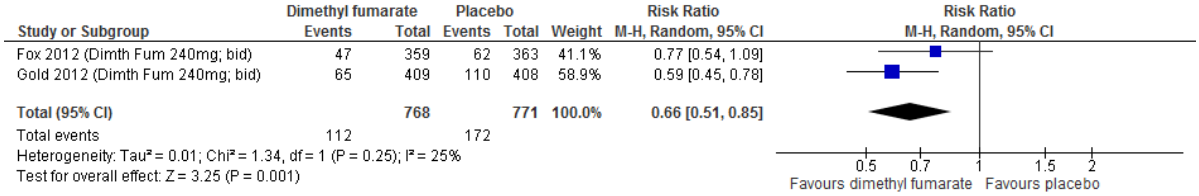


Annualised relapse rate (104 weeks' follow-up)

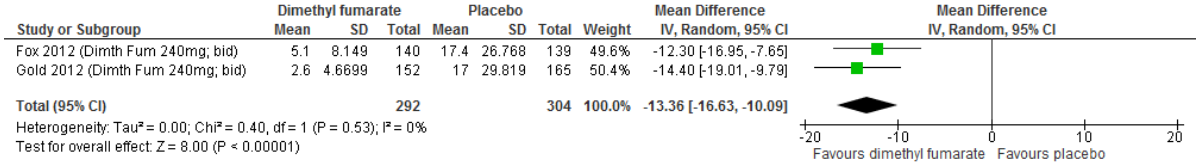


[5] Sustained disability progression was defined as an increase from baseline of at least 1.0 point in the EDSS score (or at least 0.5 points for patients with a baseline EDSS score greater than 5.5) that persisted for at least 12 weeks

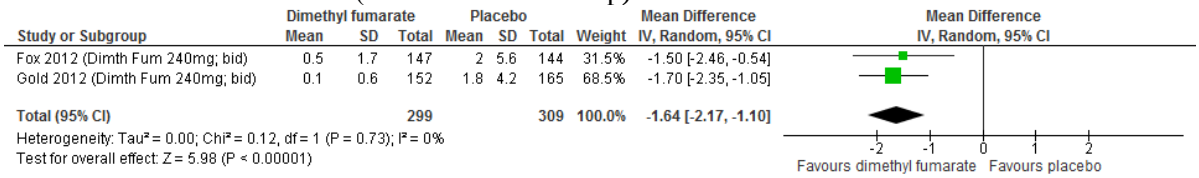
Disability progression[6] – number of participants worsened (104 weeks' follow-up)



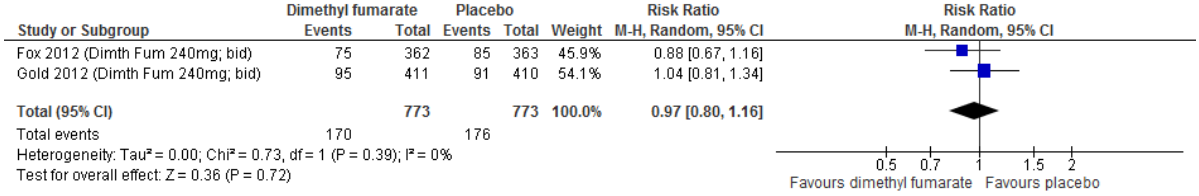
New or newly enlarging T2 lesions – mean number (104 weeks' follow-up)



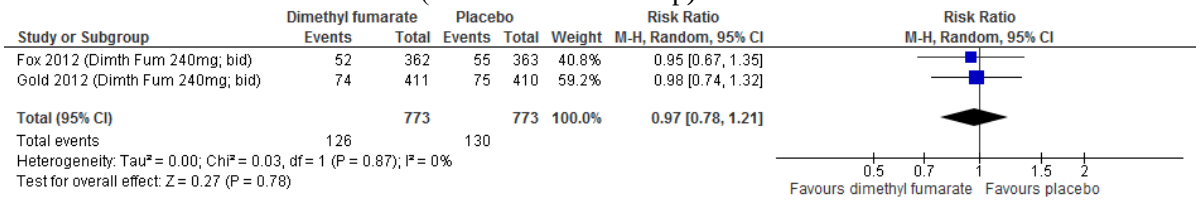
GAD lesions – mean number (104 weeks' follow-up)



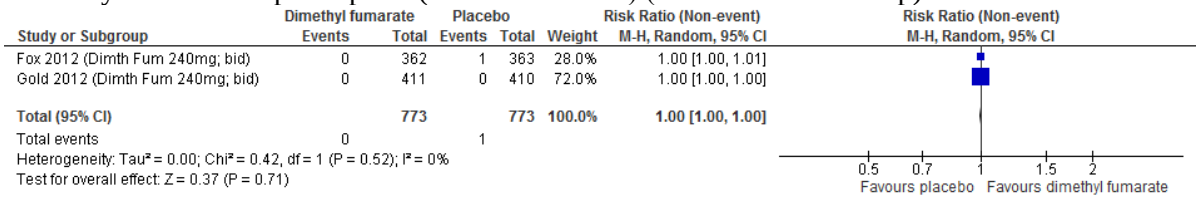
Discontinuation due to any reason (104 weeks' follow-up)



Discontinuation due to side effects (104 weeks' follow-up)



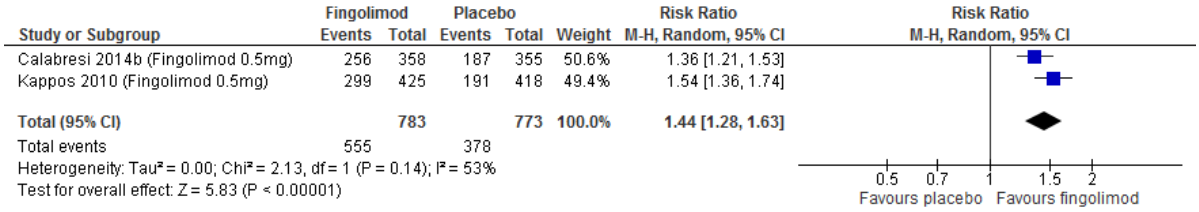
Mortality – number of participants (risk of non-event) (104 weeks' follow-up)



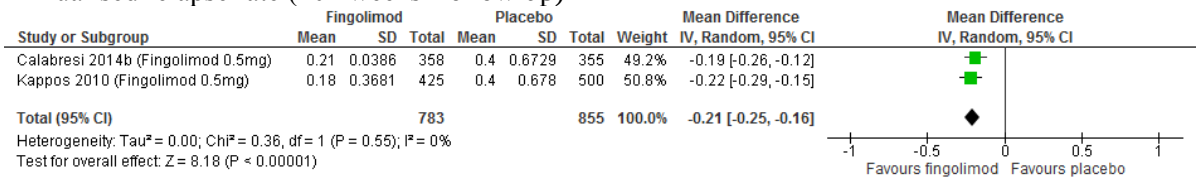
5. Fingolimod compared with placebo

Relapse - number of participants relapse free (104 weeks' follow-up)

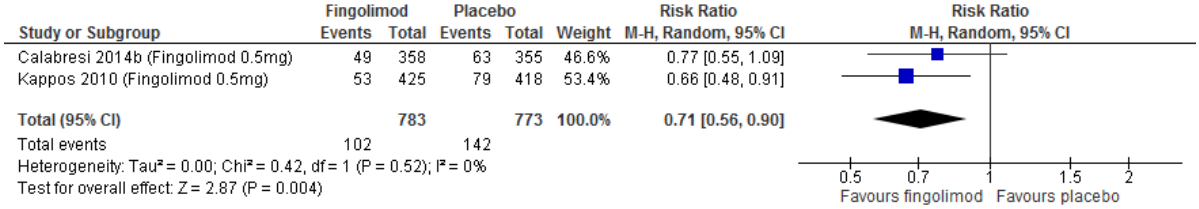
[6] Defined as an increase in the EDSS score of at least 1.0 point in patients with a baseline score of 1.0 or more or an increase of at least 1.5 points in patients with a baseline score of 0, confirmed at least 12 weeks later



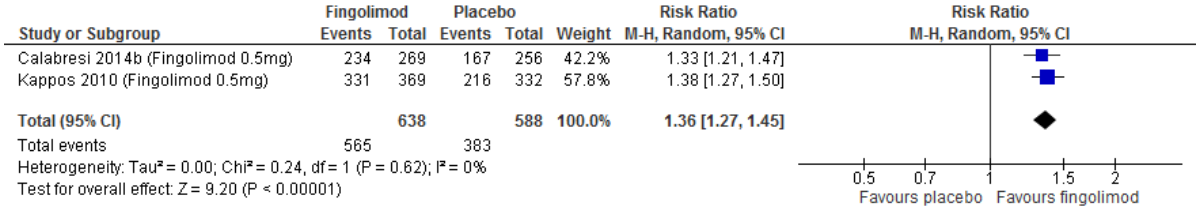
Annualised relapse rate (104 weeks' follow-up)



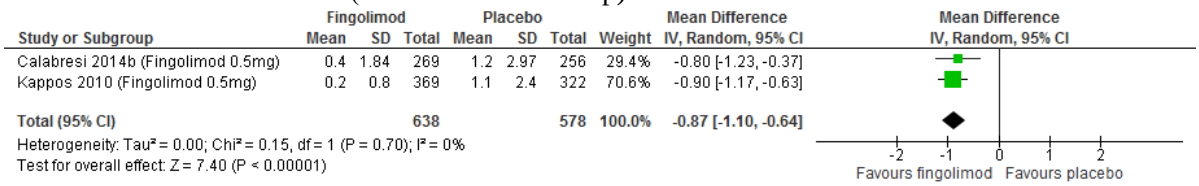
Disability progression[7] – number of participants worsened (104 weeks' follow-up)



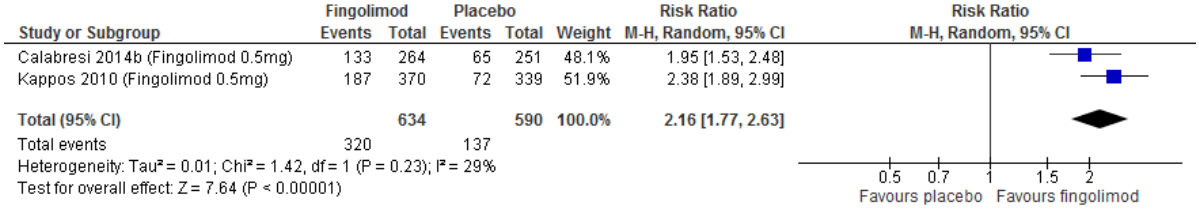
GAD lesions – number of participants with no lesions (104 weeks' follow-up)



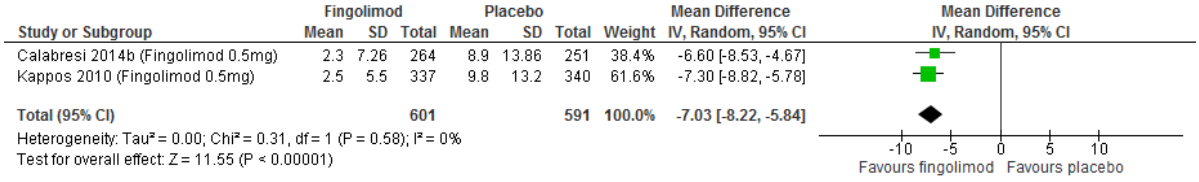
GAD lesions - mean number (104 weeks' follow-up)



New or newly enlarged T2 lesions (number of patients with no lesions)

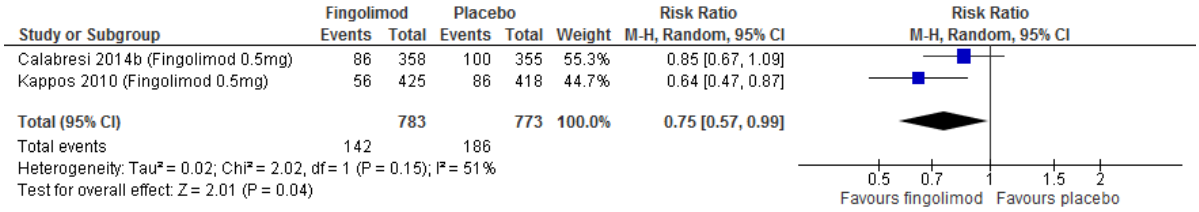


New or newly enlarging T2 lesions – mean number (104 weeks' follow-up)

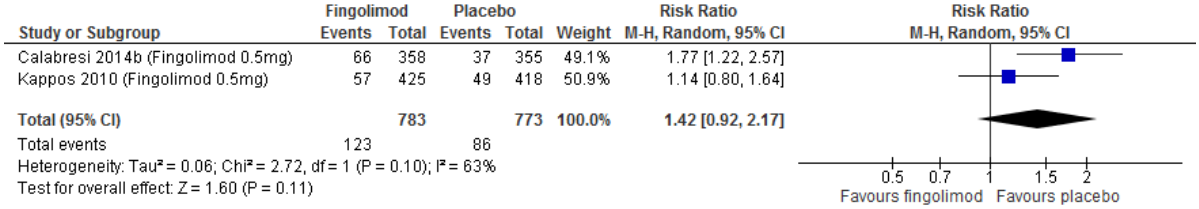


Discontinuation due to any reason (104 weeks' follow-up)

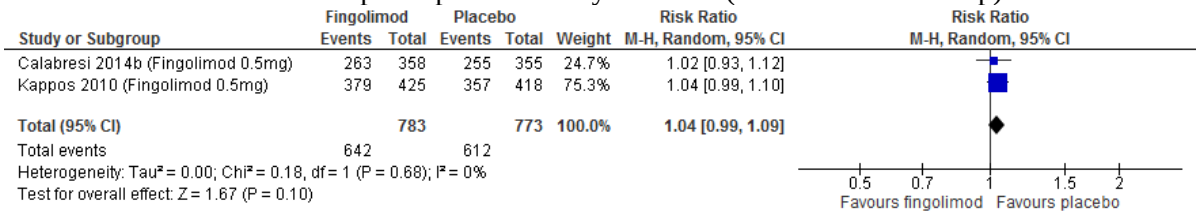
[7] Calabresi 2014b: defined as a 1 point EDSS change (0·5 point if baseline EDSS was >5·0)
Kappos 2010: Defined as an increase of one point in the EDSS score (or half a point if the baseline EDSS score was equal to 5.5), confirmed after 6 months, with an absence of relapse at the time of assessment and with all EDSS scores measured during that time meeting the criteria for disability progression.



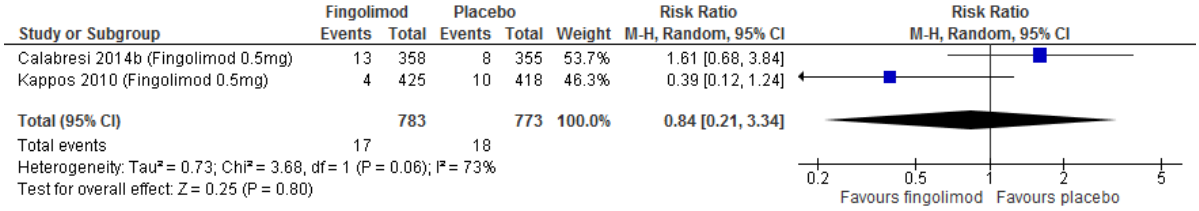
Discontinuation due to side effects (104 weeks' follow-up)



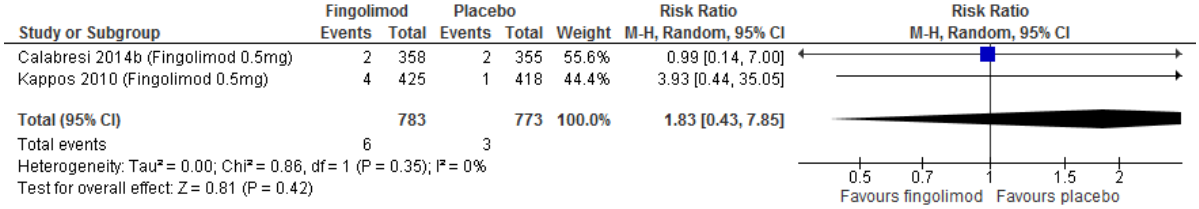
Risk of infection – number of participants with any infection (104 weeks' follow-up)



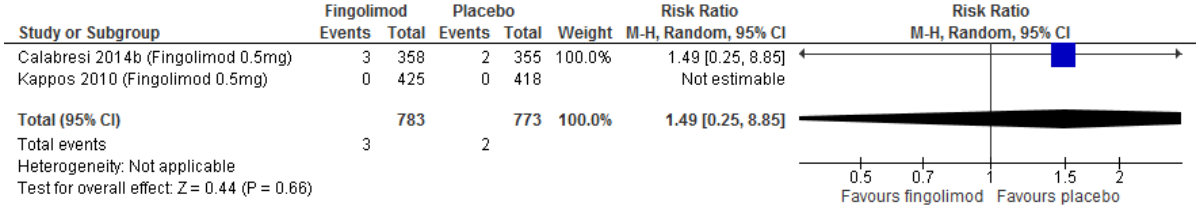
Risk of cancer – number of participants with any neoplasm (104 weeks' follow-up)



Risk of bradycardia – number of participants (104 weeks' follow-up)



Risk of macular edema – number of participants (104 weeks' follow-up)

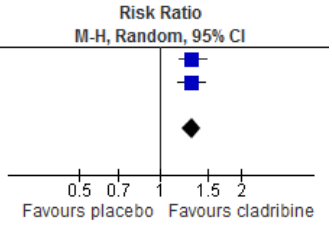


6. Cladribine compared with placebo

Relapse - number of participants relapse free (96 weeks' follow-up)

Study or Subgroup	Cladribine Events	Cladribine Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Giovannoni 2010 (Cladribine 3.5mg/kg)	345	433	133	219	50.0%	1.31 [1.17, 1.47]
Giovannoni 2010 (Cladribine 5.25mg/kg)	360	456	133	219	50.0%	1.30 [1.16, 1.46]
Total (95% CI)		**889**		**438**	**100.0%**	**1.31 [1.20, 1.42]**
Total events	705		266			

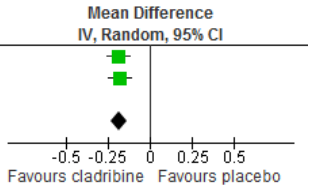
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.91); I² = 0%
Test for overall effect: Z = 6.35 (P < 0.00001)



Annualised relapse rate (96 weeks' follow-up)

Study or Subgroup	Cladribine Mean	Cladribine SD	Cladribine Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
Giovannoni 2010 (Cladribine 3.5mg/kg)	0.14	0.2653	433	0.33	0.48	219	50.0%	-0.19 [-0.26, -0.12]
Giovannoni 2010 (Cladribine 5.25mg/kg)	0.15	0.2723	456	0.33	0.48	219	50.0%	-0.18 [-0.25, -0.11]
Total (95% CI)			**889**			**438**	**100.0%**	**-0.19 [-0.23, -0.14]**

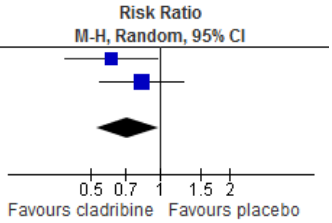
Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 1 (P = 0.84); I² = 0%
Test for overall effect: Z = 7.51 (P < 0.00001)



Discontinuation due to any reason (96 weeks' follow-up)

Study or Subgroup	Cladribine Events	Cladribine Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Giovannoni 2010 (Cladribine 3.5mg/kg)	35	433	29	219	45.9%	0.61 [0.38, 0.97]
Giovannoni 2010 (Cladribine 5.25mg/kg)	50	456	29	219	54.1%	0.83 [0.54, 1.27]
Total (95% CI)		**889**		**438**	**100.0%**	**0.72 [0.53, 0.99]**
Total events	85		58			

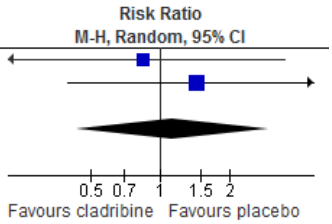
Heterogeneity: Tau² = 0.00; Chi² = 0.89, df = 1 (P = 0.34); I² = 0%
Test for overall effect: Z = 2.05 (P = 0.04)



Discontinuation due to side effects (96 weeks' follow-up)

Study or Subgroup	Cladribine Events	Cladribine Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Giovannoni 2010 (Cladribine 3.5mg/kg)	5	433	3	219	45.4%	0.84 [0.20, 3.49]
Giovannoni 2010 (Cladribine 5.25mg/kg)	9	456	3	219	54.6%	1.44 [0.39, 5.27]
Total (95% CI)		**889**		**438**	**100.0%**	**1.13 [0.43, 2.94]**
Total events	14		6			

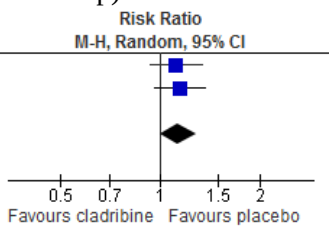
Heterogeneity: Tau² = 0.00; Chi² = 0.30, df = 1 (P = 0.58); I² = 0%
Test for overall effect: Z = 0.25 (P = 0.80)



Risk of infection – number of participants with any infection (96 weeks' follow-up)

Study or Subgroup	Cladribine Events	Cladribine Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Giovannoni 2010 (Cladribine 3.5mg/kg)	205	430	93	218	49.3%	1.12 [0.93, 1.34]
Giovannoni 2010 (Cladribine 5.25mg/kg)	222	454	93	218	50.7%	1.15 [0.96, 1.37]
Total (95% CI)		**884**		**436**	**100.0%**	**1.13 [1.00, 1.29]**
Total events	427		186			

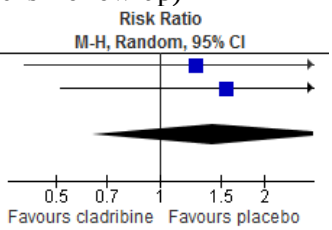
Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 1 (P = 0.85); I² = 0%
Test for overall effect: Z = 1.89 (P = 0.06)



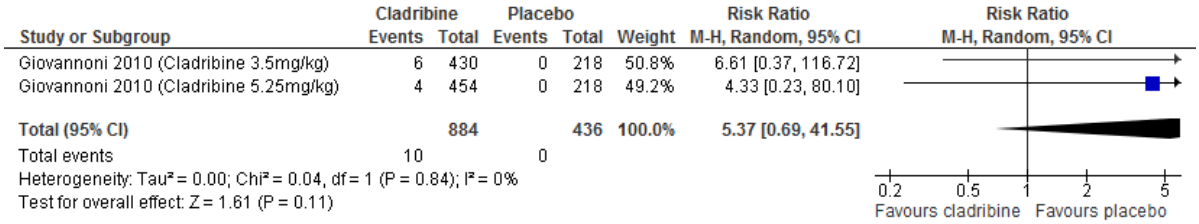
Risk of infection – number of participants with a serious infection (96 weeks' follow-up)

Study or Subgroup	Cladribine Events	Cladribine Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Giovannoni 2010 (Cladribine 3.5mg/kg)	10	430	4	218	48.3%	1.27 [0.40, 3.99]
Giovannoni 2010 (Cladribine 5.25mg/kg)	13	454	4	218	51.7%	1.56 [0.51, 4.73]
Total (95% CI)		**884**		**436**	**100.0%**	**1.41 [0.64, 3.13]**
Total events	23		8			

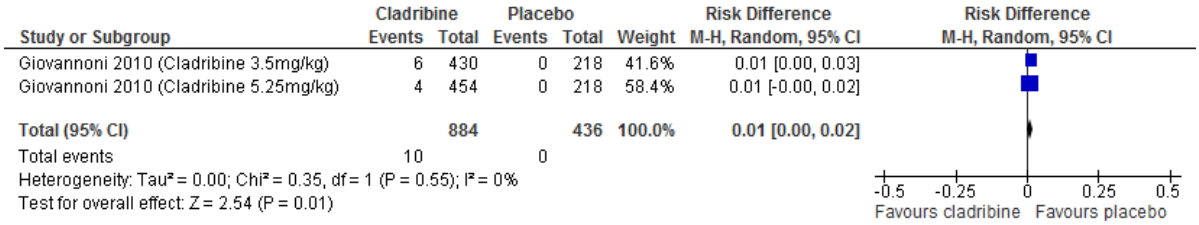
Heterogeneity: Tau² = 0.00; Chi² = 0.07, df = 1 (P = 0.80); I² = 0%
Test for overall effect: Z = 0.85 (P = 0.40)



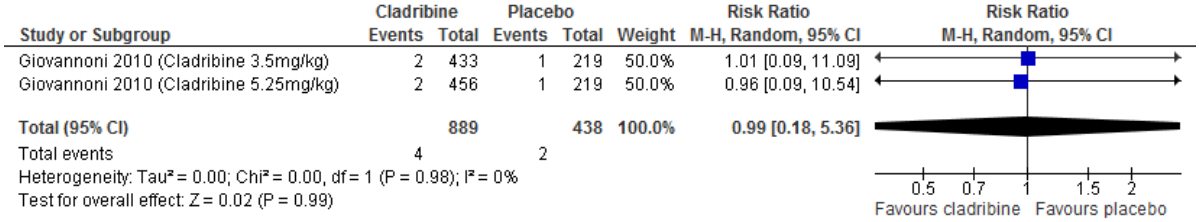
Risk of cancer – number of participants with any neoplasm (96 weeks' follow-up)



Risk difference of cancer – number of participants with any neoplasm (96 weeks' follow-up)

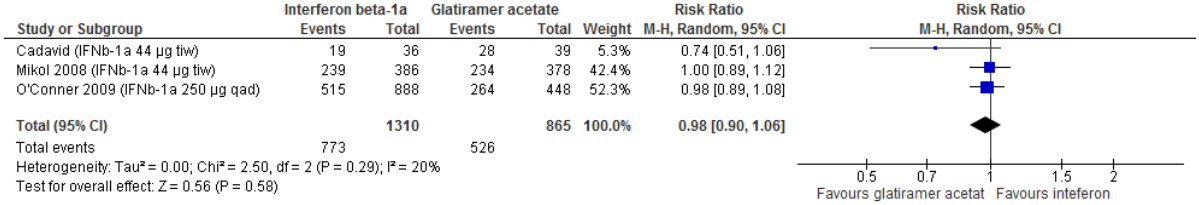


Mortality – number of participants who died (96 weeks' follow-up)

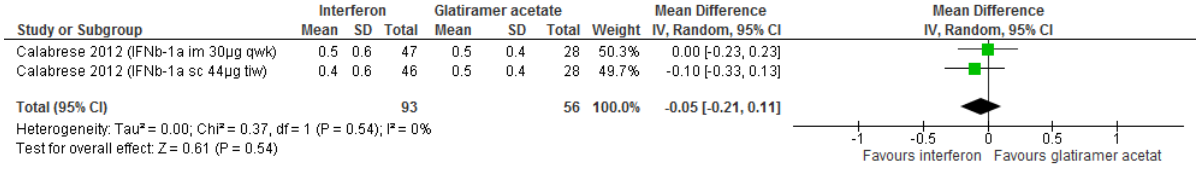


7. Interferon compared with glatiramer acetate

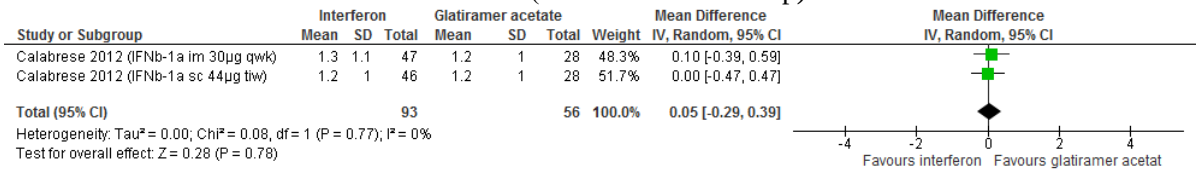
Relapse - number of participants relapse free (96-104 weeks' follow-up)



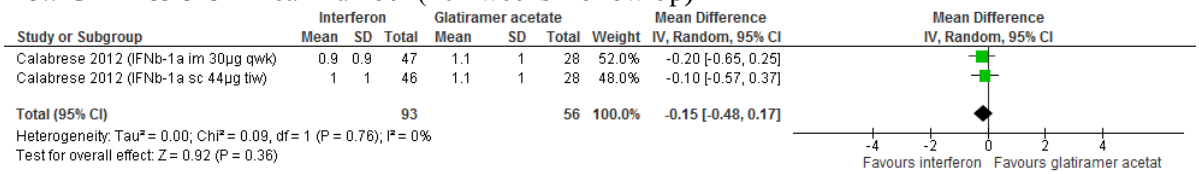
Annualised relapse rate (96-104 weeks' follow-up)



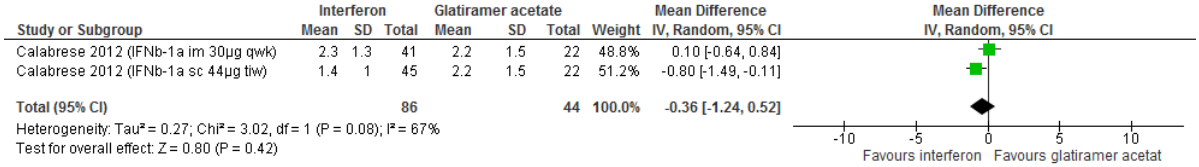
New T2 white matter lesion – mean number (104 weeks' follow-up)



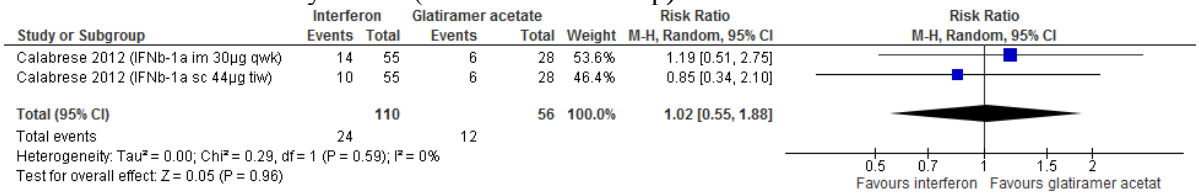
New GAD lesions – mean number (104 weeks' follow-up)



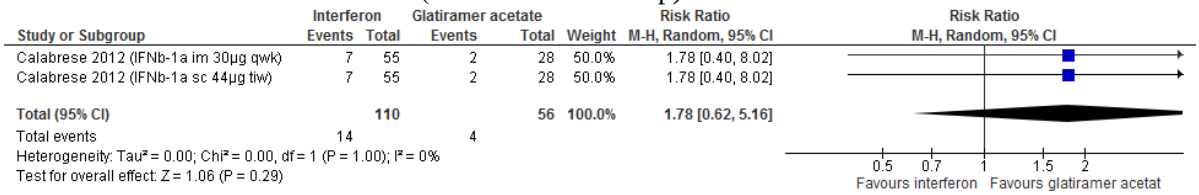
New cortical lesions - mean number (48 months follow-up)



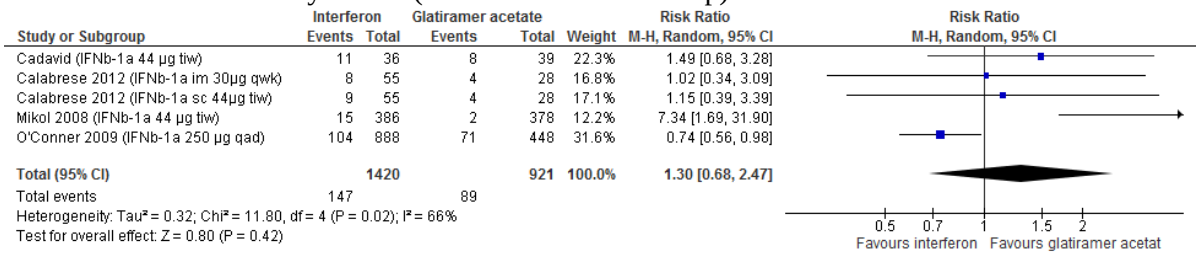
Discontinuation due to any reason (48 weeks' follow-up)



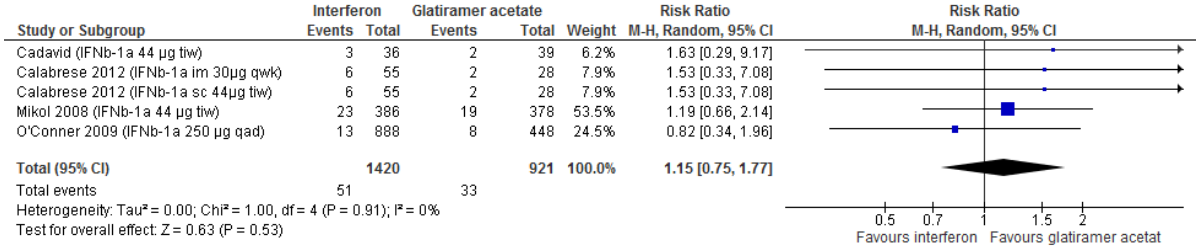
Discontinuation due to side effects (48 weeks' follow-up)



Discontinuation due to any reason (96-104 weeks' follow-up)

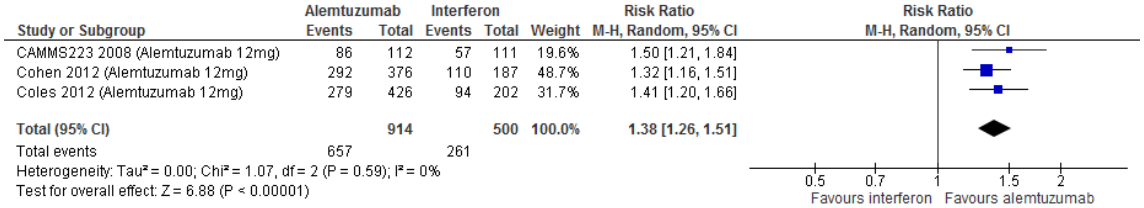


Discontinuation due to side effects (96-104 weeks' follow-up)

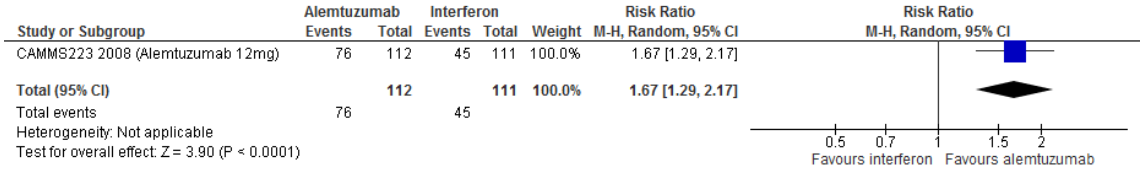


8. Alemtuzumab compared with interferon

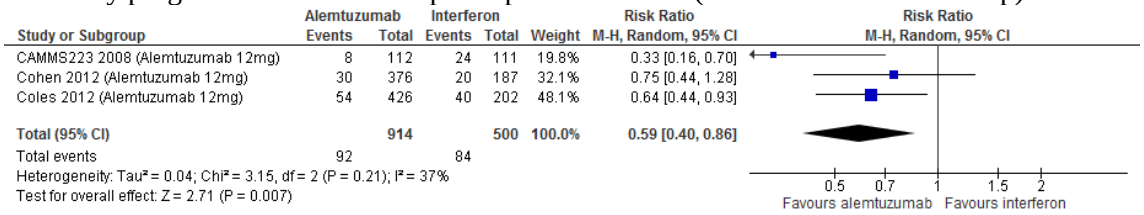
Relapse - number of participants relapse free (104-156 weeks' follow-up)



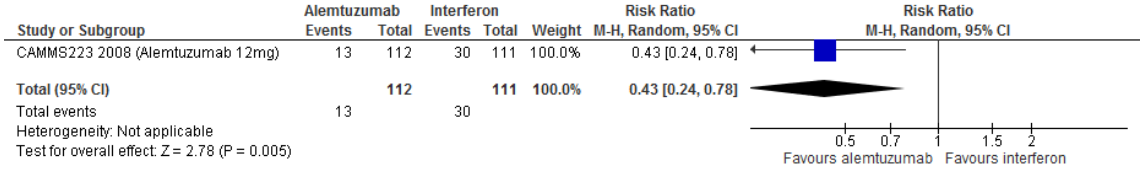
Relapse - number of participants relapse free (260 weeks' follow-up)



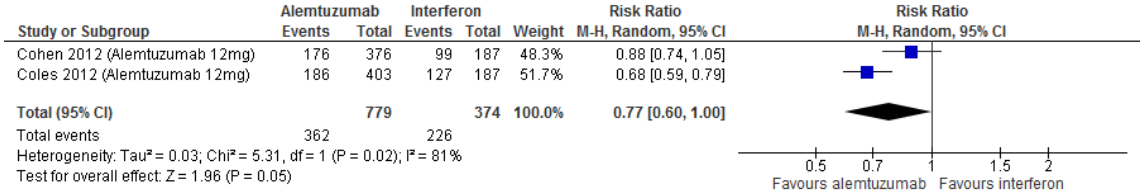
Disability progression[8] – number of participants worsened (104-156 weeks' follow-up)



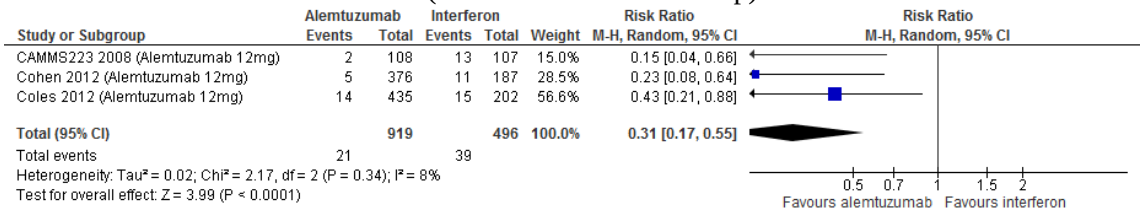
Disability progression - number of participants worsened (260 weeks' follow-up)



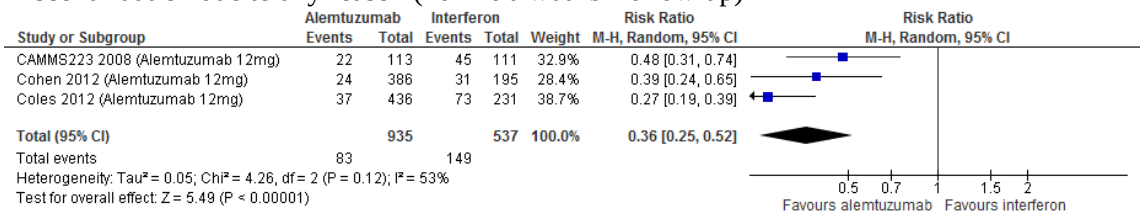
New or enlarging T2-hyperintense lesions – number of participants (104 weeks' follow-up)



Discontinuation due to side effects (104-156 weeks' follow-up)



Discontinuation due to any reason (104-156 weeks' follow-up)

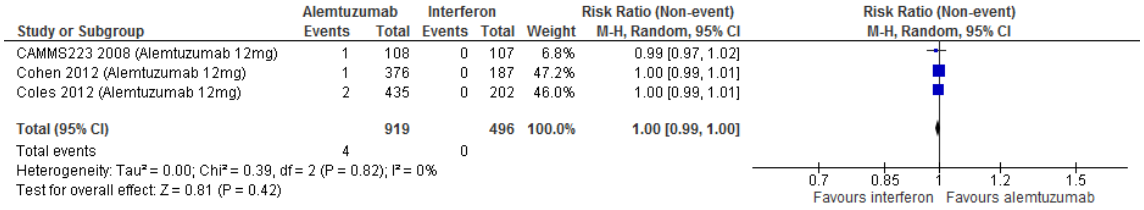


Mortality – number of participants (risk of non-event) (104-156 weeks' follow-up)

[8] Coles 2012: Defined as a decrease from baseline by at least one EDSS point confirmed over 6 months for patients with baseline EDSS scores of at least 2·0

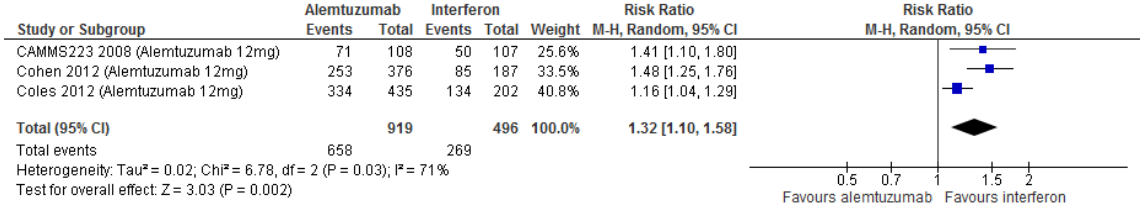
Cohen 2012: Defined as sustained accumulation of disability was defined as an increase from baseline of at least one EDSS point (or ≥1·5 points if baseline EDSS score was 0) confirmed over 6 months

CAMMS223 2011: A sustained accumulation of disability was defined as 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 at 6 months.

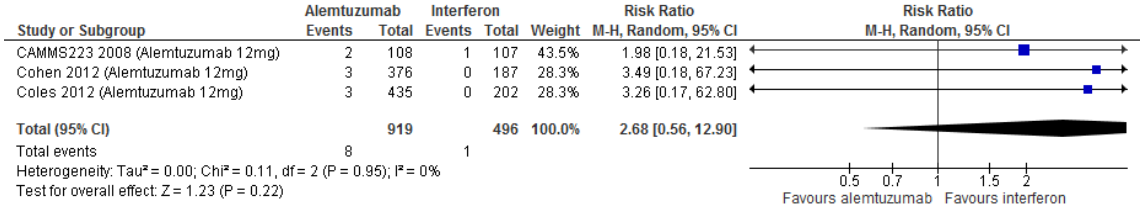


Risk of malignancy – number of participants (104-156 weeks' follow-up)

Risk of infection – number of participants with any infection (104-156 weeks' follow-up)

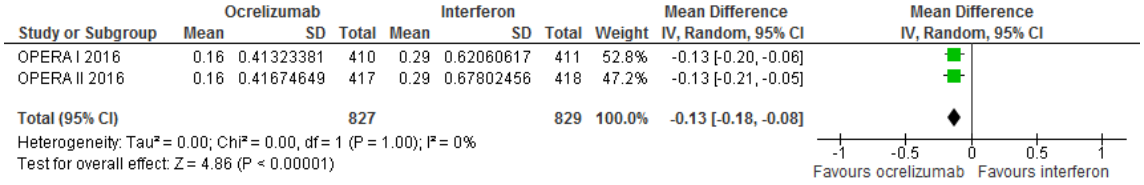


Risk of immune thrombocytopenia purpura – number of participants with any disorder (104-156 weeks' follow-up)

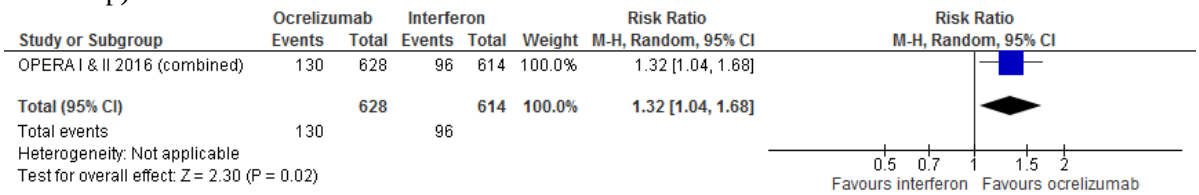


9. Ocrelizumab compared with interferon

Annualised relapse rate (96 weeks' follow-up)

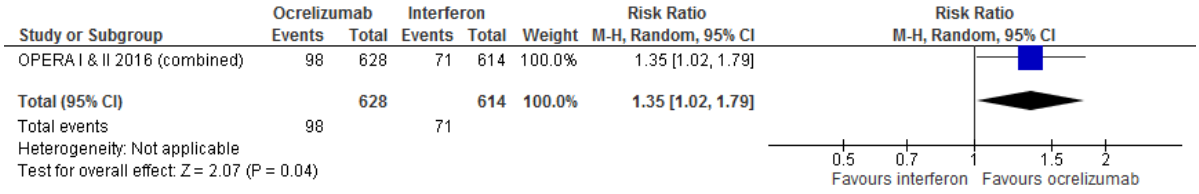


Disability improvement[9] confirmed at 12 weeks – number of participants improved (96 weeks' follow-up)

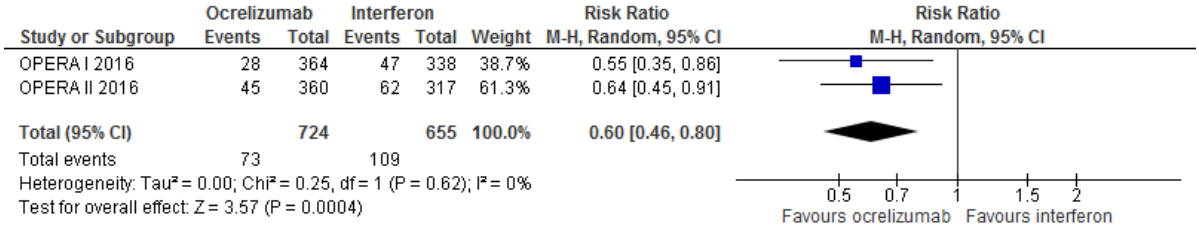


Disability improvement confirmed at 24 weeks – number of participants improved (96 weeks' follow-up)

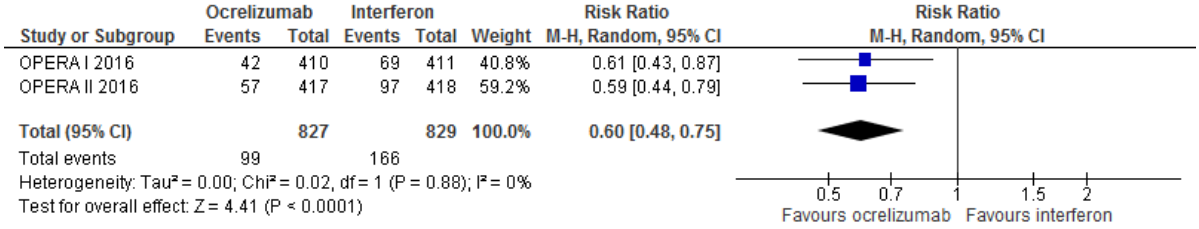
[9] For patients with a baseline EDSS score of ≥2.0 and ≤5.5, disability improvement was defined as a reduction in EDSS score ≥1.0 point compared with baseline EDSS score. For patients with a baseline EDSS score of >5.5, disability improvement was defined as a reduction in EDSS score of ≥0.5 point



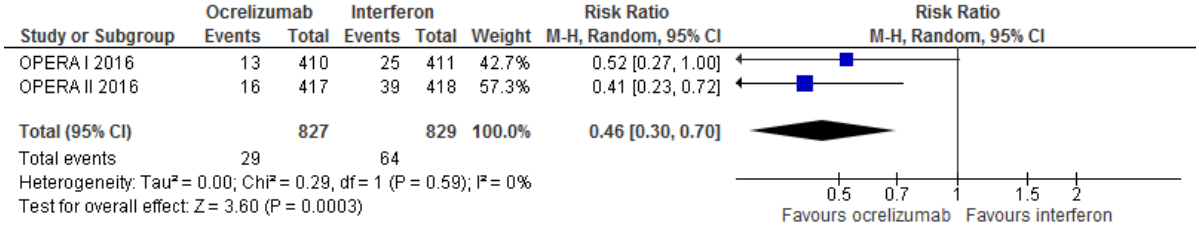
Disability progression[10] - number of participants worsened (96 weeks' follow-up)



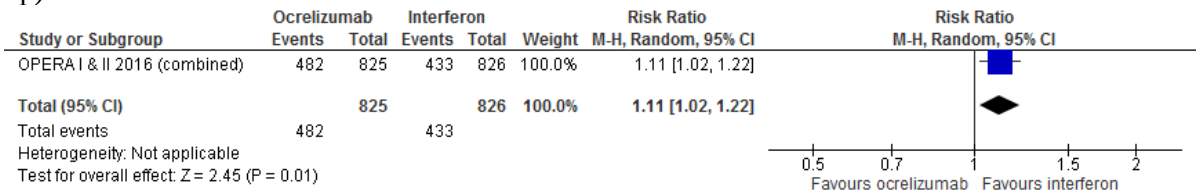
Discontinuation due to any reason (96 weeks' follow-up)



Discontinuation due to side effects (96 weeks' follow-up)

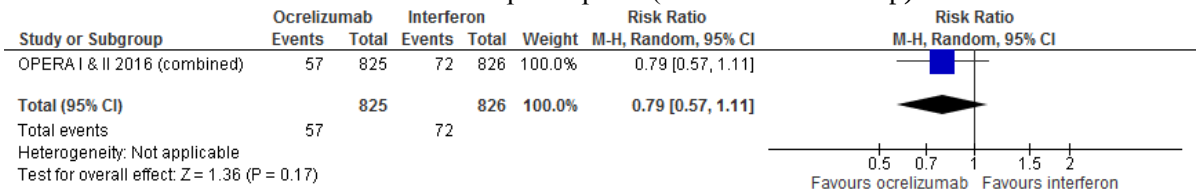


Risk of infection – number of participants with infections and infestations (96 weeks' follow-up)



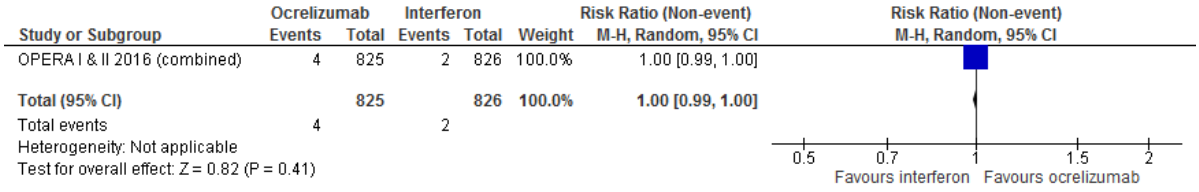
Risk of influenza-like illness

Risk of serious adverse event – number of participants (96 weeks' follow-up)

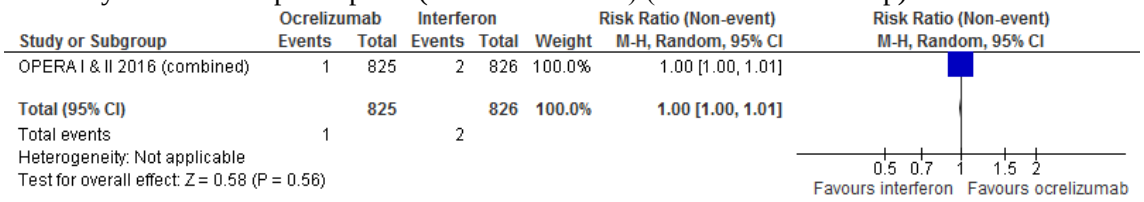


Risk of malignancy – number of participants (risk of non-event) (96 weeks' follow-up)

[10] Disability definitions (EDSS score at Week 96 compared with baseline): worsened, an increase of >0.5;



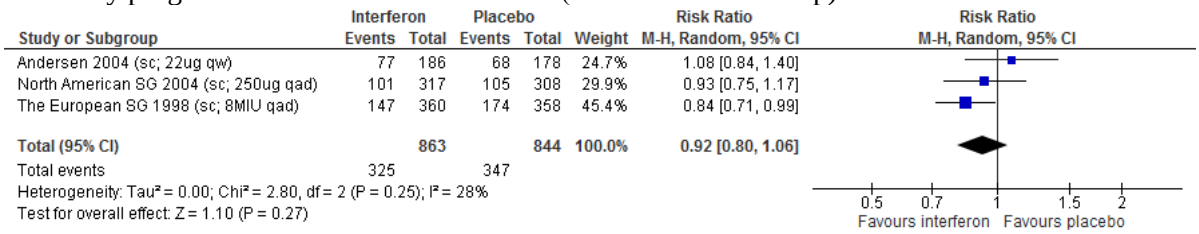
Mortality – number of participants (risk of non-event) (96 weeks' follow-up)



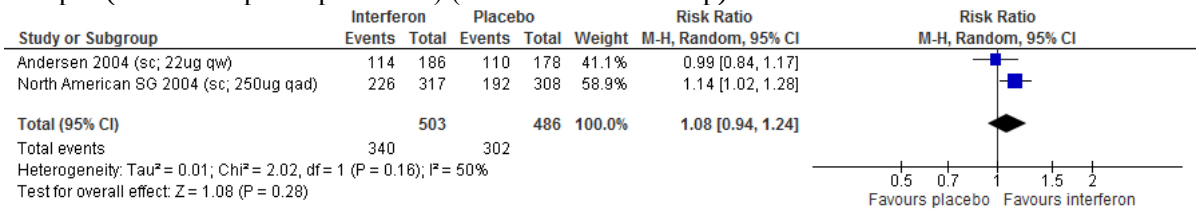
Review question 2_ Secondary progressive MS

1. Interferon compared with placebo

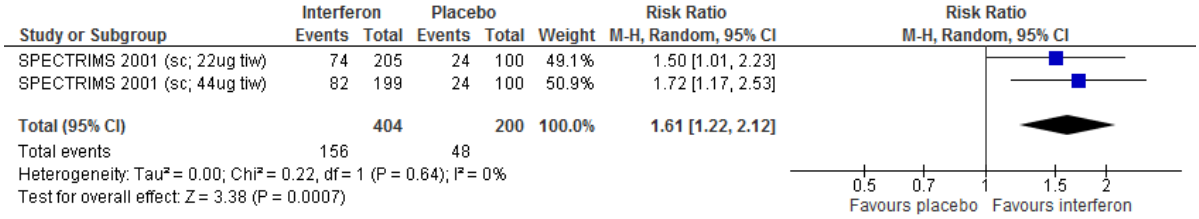
Disability progression[11] confirmed at 6 months (156 weeks' follow-up)



Relapse (number of participants free) (156 weeks' follow-up)



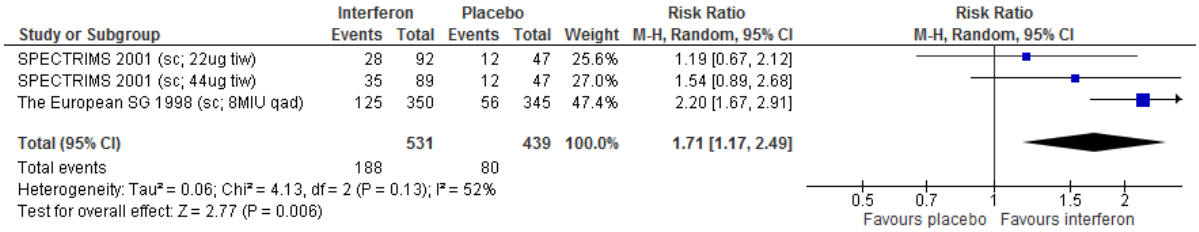
Participants free from new or newly enlarging T2 lesions (156 weeks' follow-up)



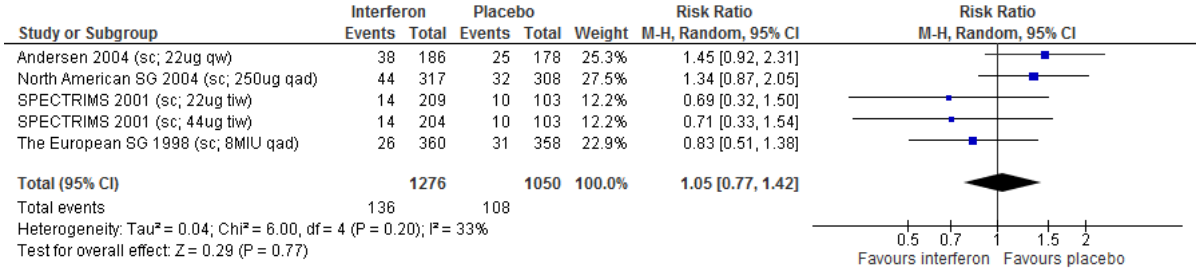
Participants free from combined unique activity (156 weeks' follow-up)

[11] Andersen 2004: defined as an increase from baseline by at least 1.0 point (or 0.5 points if the baseline EDSS score was 5.5 or higher) and confirmed at two consecutive scheduled visits separated by 6 months.

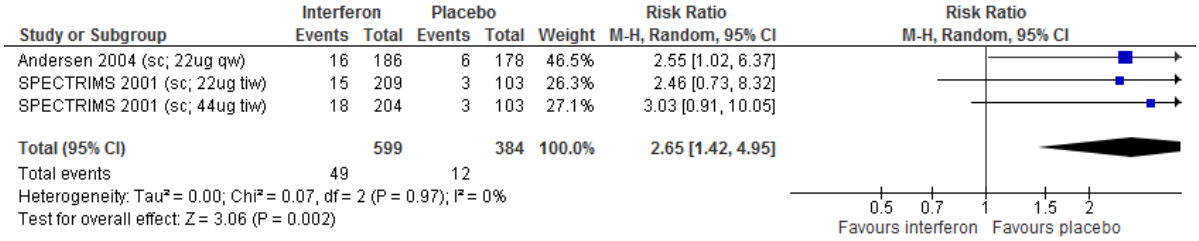
North American Study Group 2004 and The European Study Group: defined as a 1.0 point from the baseline EDSS score (0.5 points if the baseline EDSS score was 6.0 to 6.5) confirmed at two consecutive scheduled examinations spanning 6 months from the onset of progression.



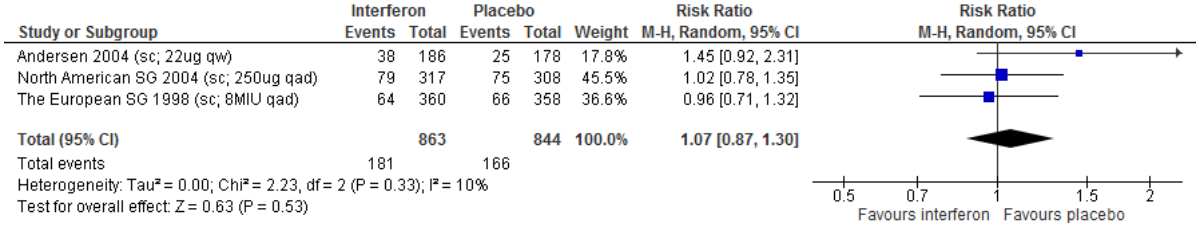
Discontinuation due to any reason (156 weeks' follow-up)



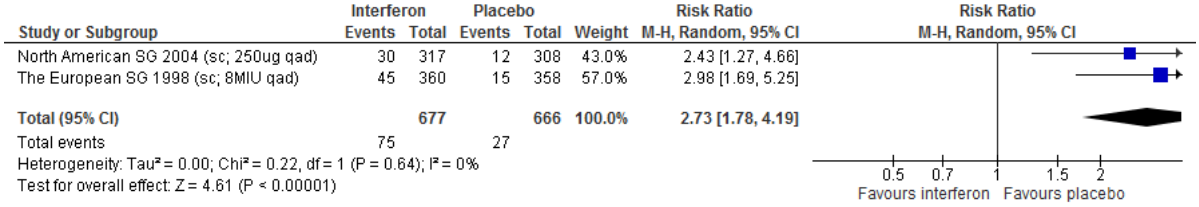
Discontinuation due to side effects (156 weeks' follow-up)



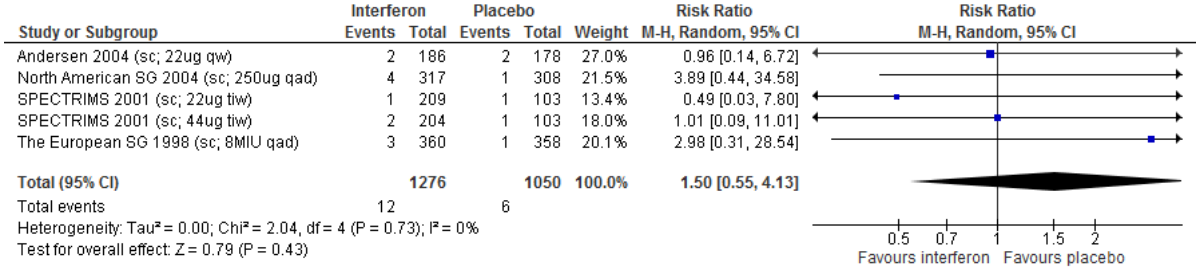
Discontinuation of study drug due to any reason (156 weeks' follow-up)



Discontinuation of study drug due to side effects (156 weeks' follow-up)



Mortality (risk of non-event) (156 weeks' follow-up)



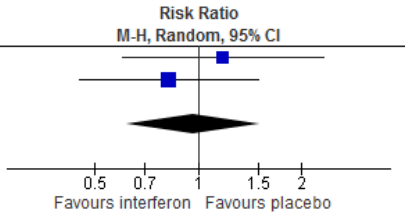
Review question 3

1. Interferon compared with placebo for primary progressive multiple sclerosis

Disability progression confirmed at three months[12] – number of participants worsened (104 weeks' follow-up)

Study or Subgroup	Interferon Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Leary 2003 (IFNb1a im; 30ug)	8	15	9	20	44.4%	1.19 [0.60, 2.33]
Montalban 2004 (IFNb1b sc; 8 MIU)	12	36	15	37	55.6%	0.82 [0.45, 1.51]
Total (95% CI)		**51**		**57**	**100.0%**	**0.97 [0.62, 1.52]**
Total events	20		24			

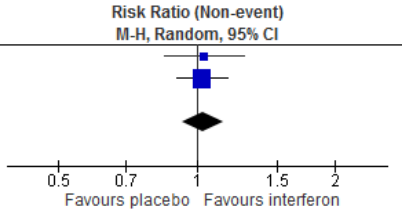
Heterogeneity: Tau² = 0.00; Chi² = 0.63, df = 1 (P = 0.43); I² = 0%
Test for overall effect: Z = 0.15 (P = 0.88)



Discontinuation of study drug due to any reason (104 weeks' follow-up)

Study or Subgroup	Interferon Events	Total	Placebo Events	Total	Weight	Risk Ratio (Non-event) M-H, Random, 95% CI
Leary 2003 (IFNb1a im; 30ug)	1	15	2	20	28.0%	1.04 [0.85, 1.27]
Montalban 2004 (IFNb1b sc; 8 MIU)	2	36	3	37	72.0%	1.03 [0.91, 1.16]
Total (95% CI)		**51**		**57**	**100.0%**	**1.03 [0.93, 1.14]**
Total events	3		5			

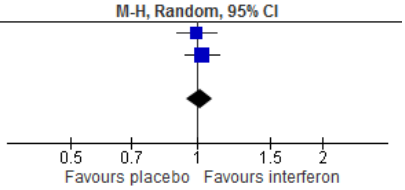
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.94); I² = 0%
Test for overall effect: Z = 0.56 (P = 0.58)



Discontinuation of study drug due to any reason (risk of non-event) (104 weeks' follow-up)

Study or Subgroup	Interferon Events	Total	Placebo Events	Total	Weight	Risk Ratio (Non-event) M-H, Random, 95% CI
Leary 2003 (IFNb1a im; 30ug)	0	15	0	20	42.4%	1.00 [0.90, 1.12]
Montalban 2004 (IFNb1b sc; 8 MIU)	1	36	2	37	57.6%	1.03 [0.93, 1.13]
Total (95% CI)		**51**		**57**	**100.0%**	**1.02 [0.95, 1.09]**
Total events	1		2			

Heterogeneity: Tau² = 0.00; Chi² = 0.14, df = 1 (P = 0.71); I² = 0%
Test for overall effect: Z = 0.43 (P = 0.67)



[12] Leary 2003: Disability progression defined as a 1.0 point increase in EDSS score for subjects with a baseline EDSS score 5.0, or a 0.5 point increase for subjects with a baseline 5.5. Progression was considered sustained if documented at two consecutive visits 3 months apart; the time of the first visit was recorded as the time to progression.

Montalban 2004: Disability progression defined as ≥1.0 and ≥0.5 point increases on the EDSS for three months in those with baseline scores of ≤5.0 and ≥5.5, respectively.