# Appendix 6\_ Forest plots

## **Review question 1**

#### 1. Interferon compared with placebo

Conversion to clinically definite multiple sclerosis <sup>1</sup> – number of participants (104 weeks' follow-up)

	Interfe	ron	Place	bo		Risk Ratio	Risk Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI			
Comi 2012 (IFNb-1a sc 44 µg; tiw)	106	170	144	170	78.9%	0.74 [0.64, 0.84]	-			
Jacobs 2000 (IFNb-1a im 30 μg; qw)	46	193	73	190	21.1%	0.62 [0.46, 0.85]	<del></del>			
Total (95% CI)		363		360	100.0%	0.71 [0.61, 0.82]	•			
Total events	152		217							
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 1.19	-	05 07 1 15 7								
Test for overall effect: Z = 4.47 (P < 0.0)	0.5 0.7 1 1.5 2 Favours interferon Favours placeho									

# Time to conversion to clinically definite multiple sclerosis<sup>2</sup> (104 weeks' follow-up)

	Interfe	ron	Place	bo				Hazard Ratio	Hazard Ratio		
Study or Subgroup	Events	Total	Events	Total	O-E	Variance	Weight	Exp[(O-E) / V], Fixed, 95% CI	Exp[(O-E) / V], Fixed, 95% CI		
Comi 2012 (IFNb-1a sc 44 µg; tiw)	106	170	144	170	-15.37529213	20.94814422	37.6%	0.48 [0.31, 0.74]			
Kappos 2006 (IFNb-1bsc 250 μg; qad)	0	292	0	176	-24.08714107	34.7503896	62.4%	0.50 [0.36, 0.70]	-		
Total (95% CI)		462		346			100.0%	0.49 [0.38, 0.64]	•		
Total events	106		144								
Heterogeneity: Chi <sup>2</sup> = 0.02, df = 1 (P = 0.8		6							0.01 0.1 10	100	
Test for overall effect: Z = 5.29 (P < 0.000	01)								Favours interferon Favours placebo	100	

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

,	Interfe	ron	Place	bo		Risk Ratio	Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI		
Comi 2012 (IFNb-1a sc 44 µg; tiw)	5	171	6	171	61.9%	0.83 [0.26, 2.68]	<b>—</b>		
Kappos 2006 (IFNb-1bsc 250 μg; qad)	8	292	0	176	38.1%	10.27 [0.60, 176.84]	<del></del>		
Total (95% CI)		463		347	100.0%	2.17 [0.16, 28.82]			
Total events	13		6						
Heterogeneity: Tau² = 2.46; Chi² = 3.00, d	lf=1 (P=	0.08);	l²= 67%				0.002 0.1 1 10 500		
Test for overall effect: $Z = 0.59$ (P = 0.56)							Favours interferon Favours placeho		

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

	Interferon		Placebo		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	<b>Events</b>	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Comi 2012 (IFNb-1a sc 44 µg; tiw)	21	171	20	171	32.7%	1.05 [0.59, 1.87]	
Jacobs 2000 (IFNb-1a im 30 μg; qw)	30	193	27	190	46.9%	1.09 [0.68, 1.77]	<del></del>
Kappos 2006 (IFNb-1bsc 250 µg; qad)	21	292	10	176	20.3%	1.27 [0.61, 2.63]	<del>- •</del>
Total (95% CI)		656		537	100.0%	1.11 [0.80, 1.54]	<b>*</b>
Total events	72		57				
Heterogeneity: Tau² = 0.00; Chi² = 0.16, d	f=2(P=	0.92);1	P= 0%				0.01 0.1 1 10 100
Test for overall effect: $Z = 0.63$ (P = 0.53)		Favours interferon Favours placebo					

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

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

<sup>&</sup>lt;sup>2</sup> 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.

	Interfe	ron	Placebo			Risk Ratio (Non-event)	Risk Ratio (Non-event)
Study or Subgroup	<b>Events</b>	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Jacobs 2000 (IFNb-1a im 30 μg; qw)	1	193	7	190	50.4%	1.03 [1.00, 1.06]	-
Kappos 2006 (IFNb-1bsc 250 µg; qad)	24	292	1	176	49.6%	0.92 [0.89, 0.96]	
Total (95% CI)		485		366	100.0%	0.98 [0.87, 1.09]	
Total events	25		8				
Heterogeneity: Tau <sup>2</sup> = 0.01; Chi <sup>2</sup> = 23.73, Test for overall effect: $Z = 0.40$ (P = 0.69)	-	0.85 0.9 1 1.1 1.2					
100110101010110100112 0:10 (1 0:00)					Favours placebo Favours interferon		

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

	Interferon Place			bo		Risk Ratio	Risk Ratio
Study or Subgroup	<b>Events</b>	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Jacobs 2000 (IFNb-1a im 30 μg; qw)	38	193	35	190	60.9%	1.07 [0.71, 1.62]	-
Kappos 2006 (IFNb-1bsc 250 μg; qad)	44	292	18	176	39.1%	1.47 [0.88, 2.47]	<del>  -</del>
Total (95% CI)		485		366	100.0%	1.21 [0.88, 1.67]	<b>*</b>
Total events	82		53				
Heterogeneity: Tau² = 0.00; Chi² = 0.91, d Test for overall effect: Z = 1.17 (P = 0.24)	f=1 (P=	0.34);	l² = 0%				0.01 0.1 1 10 100  Favours interferon Favours placebo

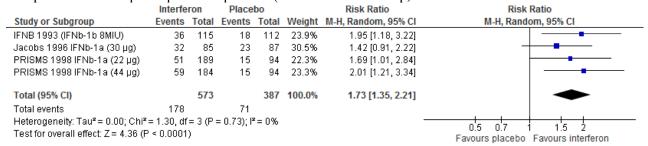
#### Mortality (risk of non-event) (104 weeks' follow-up)

						,				
	Interfe	ron	Place	bo		Risk Ratio (Non-event)		Risk Ratio (Non-event)		
Study or Subgroup	<b>Events</b>	Total	<b>Events</b>	Total	Weight	M-H, Random, 95% CI		M-H, Rando	om, 95% CI	
Comi 2012 (IFNb-1a sc 44 µg; tiw)	0	171	2	171	42.0%	1.01 [0.99, 1.03]				
Jacobs 2000 (IFNb-1a im 30 μg; qw)	1	193	0	190	58.0%	0.99 [0.98, 1.01]		•		
Total (95% CI)		364		361	100.0%	1.00 [0.99, 1.02]				
Total events	1		2							
Heterogeneity: Tau² = 0.00; Chi² = 1.95, Test for overall effect: Z = 0.23 (P = 0.82		= 0.16	); I² = 499	6			0.01	0.1 Favours placebo	1 10 Favours interferon	100

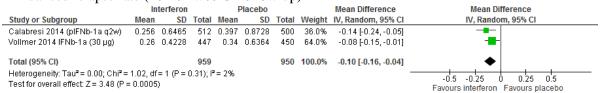
#### **Review question 2**

### 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<sup>3</sup> – number of participants worsened (104 weeks' follow-up)

<sup>&</sup>lt;sup>3</sup> 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

	Interfe	ron	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Jacobs 1996 IFNb-1a (30 μg)	18	85	29	87	40.7%	0.64 [0.38, 1.05]	
Vollmer 2014 IFNb-1a (30 µg)	35	447	46	450	59.3%	0.77 [0.50, 1.17]	
Total (95% CI)		532		537	100.0%	0.71 [0.51, 0.98]	
Total events	53		75				
Heterogeneity: Tau² = 0.00; Chi²	= 0.31, d	05 07 1 15 2					
Test for overall effect: Z = 2.08 (F	P = 0.04)	Favours interferon Favours placebo					

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

	Interfe	ron	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
PRISMS 1998 IFNb-1a (22 μg)	22	189	9	94	11.6%	1.22 [0.58, 2.54]	
PRISMS 1998 IFNb-1a (44 μg)	19	184	9	94	11.0%	1.08 [0.51, 2.29]	
Vollmer 2014 IFNb-1a (30 μg)	69	447	91	450	77.4%	0.76 [0.57, 1.01]	<del></del>
Total (95% CI)		820		638	100.0%	0.84 [0.65, 1.07]	
Total events	110		109				
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup>	= 1.83, df	= 2 (P	= 0.40); F	<sup>2</sup> =0%		-	
Test for overall effect: Z = 1.40 (F	9 = 0.16)						0.5 0.7 1 1.5 2 Favours interferon Favours placebo

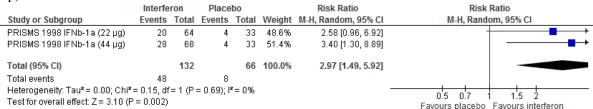
### Discontinuation due to side effects (104 weeks' follow-up)

	Interfe	ron	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Jacobs 1996 IFNb-1a (30 µg)	7	85	2	87	10.8%	3.58 [0.77, 16.76]	-
PRISMS 1998 IFNb-1a (22 μg)	6	189	1	94	5.8%	2.98 [0.36, 24.43]	<del></del>
PRISMS 1998 IFNb-1a (44 μg)	9	184	1	94	6.1%	4.60 [0.59, 35.75]	<del></del>
Vollmer 2014 IFNb-1a (30 μg)	26	447	19	450	77.3%	1.38 [0.77, 2.45]	<del></del>
Total (95% CI)		905		725	100.0%	1.72 [1.04, 2.86]	
Total events	48		23				
Heterogeneity: Tau² = 0.00; Chi²	= 2.65, df	= 3 (P	= 0.45); P	= 0%			05 07 1 15 2
Test for overall effect: Z = 2.10 (F	9 = 0.04)						Favours interferon Favours placebo

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

	Interferon Placebo Risk Ratio		Risk Ratio	Risk Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
PRISMS 1998 IFNb-1a (22 μg)	35	185	8	92	48.0%	2.18 [1.05, 4.50]	
PRISMS 1998 IFNb-1a (44 μg)	56	182	8	92	52.0%	3.54 [1.76, 7.10]	
Total (95% CI)		367		184	100.0%	2.80 [1.69, 4.63]	
Total events	91		16				
Heterogeneity: Tau² = 0.00; Chi²	= 0.90, df	= 1 (P	= 0.34); F	= 0%		-	0.5 0.7 1 1.5 2
Test for overall effect: Z = 4.02 (F	o < 0.0001	)					Favours placebo Favours interferon

# 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

		Placebo			Mean Difference	Mean Difference			
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
PRISMS 1998 IFNb-1a (22 μg)	-1.2	296.1666	171	10.9	100.21666	86	16.3%	-12.10 [-61.28, 37.08]	<del>-</del>
PRISMS 1998 IFNb-1a (44 μg)	-3.8	31.61666	171	10.9	100.21666	86	83.7%	-14.70 [-36.40, 7.00]	<del></del>
Total (95% CI)			342			172	100.0%	-14.28 [-34.13, 5.58]	
Heterogeneity: Tau $^2$ = 0.00; Chi $^2$ : Test for overall effect: Z = 1.41 (P			.92); l²:	= 0%					-20 -10 0 10 20 Favours interferon Favours placebo

# 2. Glatiramer acetate compared with placebo

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

	Glatiramer ac	Glatiramer acetate		Placebo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Fox 2012 (Glatiramer acetate 20mg qd)	238	350	214	363	30.1%	1.15 [1.03, 1.29]	
Johnson 1995 (Glatiramer acetate 20mg qd)	42	125	34	126	2.6%	1.25 [0.85, 1.82]	<del></del>
Khan 2013 (Glatiramer acetate 40mg tiw)	726	943	302	461	67.3%	1.18 [1.09, 1.27]	<del></del>
Total (95% CI)		1418		950	100.0%	1.17 [1.10, 1.24]	•
Total events	1006		550				
Heterogeneity: Tau2 = 0.00; Chi2 = 0.18, df = 2 (	P = 0.91); $P = 0$	χ,					0.5 0.7 1 1.5 2
Test for overall effect: Z = 5.02 (P < 0.00001)							Favours placebo Favours glatiramer acetat

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

	Glatiramer acetate		Placebo		Mean Difference		Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Fox 2012 (Glatiramer acetate 20mg qd)	0.29	0.5727	350	0.4	0.7777	363	55.1%	-0.11 [-0.21, -0.01]	-
Khan 2013 (Glatiramer acetate 40mg tiw)	0.331	0.8774	943	0.505	1.0462	461	44.9%	-0.17 [-0.28, -0.06]	-
Total (95% CI)			1293			824	100.0%	-0.14 [-0.21, -0.06]	<b>◆</b>
Heterogeneity: Tauz = 0.00; Chiz = 0.71, df =	1 (P = 0.	$40$ ); $I^2 = 0$	%						-1 -0.5 0 0.5 1
Test for overall effect: Z = 3.66 (P = 0.0002)									Favoure distinamen anetat Favoure placeho

# Disability progression<sup>4</sup> – number of participants worsened (96-104 weeks' follow-up)

	Glatiramer acetate		te Placebo		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Fox 2012 (Glatiramer acetate 20mg qd)	56	350	62	363	63.9%	0.94 [0.67, 1.30]	<del></del>
Johnson 1995 (Glatiramer acetate 20mg qd)	26	125	36	126	36.1%	0.73 [0.47, 1.13]	<del></del>
Total (95% CI)		475		489	100.0%	0.86 [0.66, 1.11]	
Total events	82		98				
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.81, df = 1 ( Test for overall effect: Z = 1.16 (P = 0.25)	P = 0.37); I <sup>2</sup> = 09	6					0.5 0.7 1 1.5 2
1031101 0401411 011001. Z= 1.10 (1 = 0.23)							Favours glatiramer acetat Favours placebo

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

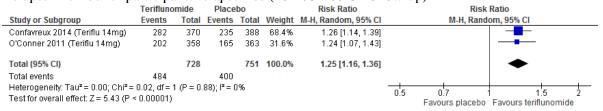
	Glatiramer acetate		amer acetate Placebo			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Fox 2012 (Glatiramer acetate 20mg qd)	68	360	85	363	82.0%	0.81 [0.61, 1.07]	<del></del>
Johnson 1995 (Glatiramer acetate 20mg qd)	19	125	17	126	18.0%	1.13 [0.61, 2.06]	
Total (95% CI)		485		489	100.0%	0.86 [0.66, 1.11]	
Total events	87		102				
Heterogeneity: Tau2 = 0.00; Chi2 = 0.96, df = 1 (	$P = 0.33$ ); $I^2 = 0\%$	6					0.5 0.7 1 1.5 2
Test for overall effect: Z = 1.18 (P = 0.24)							Favours glatiramer acetat Favours placebo

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

	Glatiramer ac	Glatiramer acetate		mer acetate Placebo				Risk Ratio	Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI				
Fox 2012 (Glatiramer acetate 20mg qd)	29	943	6	461	85.7%	2.36 [0.99, 5.65]					
Johnson 1995 (Glatiramer acetate 20mg qd)	5	125	1	126	14.3%	5.04 [0.60, 42.53]					
Total (95% CI)		1068		587	100.0%	2.63 [1.17, 5.90]					
Total events	34		7								
Heterogeneity: Tau² = 0.00; Chi² = 0.42, df = 1 (					05 07 1 15 2						
Test for overall effect: Z = 2.35 (P = 0.02)							Favours glatiramer acetat Favours placebo				

# 3. Teriflunomide compared with placebo

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



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

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

<sup>&</sup>lt;sup>4</sup> 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



# Disability progression<sup>5</sup> – number of participants worsened (48-108 weeks' follow-up)

	Terifluno	mide	Place	Placebo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Confavreux 2014 (Teriflu 14mg)	58	370	76	388	42.3%	0.80 [0.59, 1.09]	<del></del>
O'Conner 2011 (Teriflu 14mg)	72	358	99	363	57.7%	0.74 [0.57, 0.96]	<del></del>
Total (95% CI)		728		751	100.0%	0.76 [0.62, 0.93]	-
Total events	130		175				
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> =		-	0.5 0.7 1 1.5 2				
Test for overall effect: Z = 2.62 (P	= 0.009)					Favours teriflunomide Favours placebo	

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

	Terifluno	mide	Placebo			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Confavreux 2014 (Teriflu 14mg)	126	372	125	389	57.7%	1.05 [0.86, 1.29]	<del>-  </del>
O'Conner 2011 (Teriflu 14mg)	95	358	104	363	42.3%	0.93 [0.73, 1.17]	
Total (95% CI)		730		752	100.0%	1.00 [0.86, 1.16]	•
Total events	221		229				
Heterogeneity: Tau² = 0.00; Chi² =	0.66, df = 1	(P = 0.	.42); l² = 0	0%		-	05 07 1 15 2
Test for overall effect: Z = 0.03 (P =	0.98)						Favours teriflunomide Favours placebo

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

	Terifluno	mide	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	<b>Events</b>	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Confavreux 2014 (Teriflu 14mg)	165	372	197	389	79.9%	0.88 [0.75, 1.02]	
O'Conner 2011 (Teriflu 14mg)	61	358	80	363	20.1%	0.77 [0.57, 1.04]	<del></del>
Total (95% CI)		730		752	100.0%	0.85 [0.75, 0.98]	•
Total events	226		277				
Heterogeneity: Tau2 = 0.00; Chi2 =	0.55, df = 1	I(P = 0.	46); $I^2 = 0$	)%		-	05 07 1 15 2
Test for overall effect: Z = 2.30 (P =	= 0.02)						U.5 U.7 1 1.5 Z  Favours teriflunomide Favours placeho

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

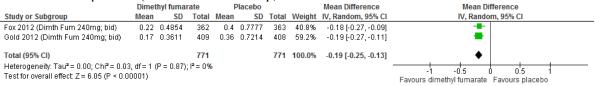
1,	Terifluno	mide	Place	Placebo Risk Ratio (Non-event)		Risk Ratio (Non-event)	Risk Ratio (Non-event)		
Study or Subgroup	Events	Total	<b>Events</b>	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI		
Confavreux 2014 (Teriflu 14mg)	1	372	0	389	72.4%	1.00 [0.99, 1.00]			
O'Conner 2011 (Teriflu 14mg)	3	358	5	363	27.6%	1.01 [0.99, 1.02]	†		
Total (95% CI)		730		752	100.0%	1.00 [0.99, 1.01]			
Total events	4		5						
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = Test for overall effect: $Z = 0.10$ (P		1 (P = 0.	.24); I² = 2	9%		0.5 0.7 1 1.5 2 Favours placebo Favours teriflunomide			

#### 4. Dimethyl fumarate compared with placebo

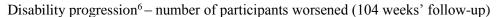
# Relapse - number of participants relapse free (104 weeks' follow-up)

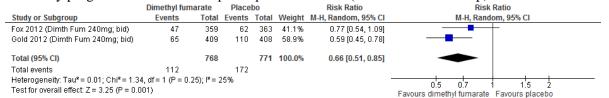
			1		`		1 /
	Dimethyl fur			bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	<b>Events</b>	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Fox 2012 (Dimth Fum 240mg; bid)	255	359	214	363	49.8%	1.20 [1.08, 1.34]	-
Gold 2012 (Dimth Fum 240mg; bid)	299	410	220	408	50.2%	1.35 [1.21, 1.51]	-
Total (95% CI)		769		771	100.0%	1.28 [1.14, 1.43]	•
Total events	554		434				
Heterogeneity: Tau² = 0.00; Chi² = 2.2	1, df = 1 (P = 0.	$14); I^2 = 6$	55%				05 07 1 15 2
Test for overall effect: Z = 4.23 (P < 0.0	0001)						Favours placeho Favours dimethyl fumarate

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



<sup>&</sup>lt;sup>5</sup> 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





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

	Dimet	ınyı tumai	rate		riacebo			Mean Difference	Mean Dr	пегепсе	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Rando	m, 95% CI	
Fox 2012 (Dimth Fum 240mg; bid)	5.1	8.149	140	17.4	26.768	139	49.6%	-12.30 [-16.95, -7.65]	<del></del>		
Gold 2012 (Dimth Fum 240mg; bid)	2.6	4.6699	152	17	29.819	165	50.4%	-14.40 [-19.01, -9.79]	<del></del>		
Total (95% CI)			292			304	100.0%	-13.36 [-16.63, -10.09]	•		
Heterogeneity: Tau² = 0.00; Chi² = 0.40 Test for overall effect: Z = 8.00 (P < 0.0		(P = 0.53)	I <sup>2</sup> = 0%	•					-20 -10 ( Favours dimethyl fumarate	) 10 Favours placebo	20

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

	Dimethy	/l fuma	rate	Placebo			Mean Difference		Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Fox 2012 (Dimth Fum 240mg; bid)	0.5	1.7	147	2	5.6	144	31.5%	-1.50 [-2.46, -0.54]	
Gold 2012 (Dimth Fum 240mg; bid)	0.1	0.6	152	1.8	4.2	165	68.5%	-1.70 [-2.35, -1.05]	
Total (95% CI)			299			309	100.0%	-1.64 [-2.17, -1.10]	•
Heterogeneity: Tau² = 0.00; Chi² = 0.12 Test for overall effect: Z = 5.98 (P < 0.0		= 0.73)	); I² = 09		Favours dimethyl fumarate Favours placebo				

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

	Dimethyl fum	arate	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	<b>Events</b>	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Fox 2012 (Dimth Fum 240mg; bid)	75	362	85	363	45.9%	0.88 [0.67, 1.16]	<del></del>
Gold 2012 (Dimth Fum 240mg; bid)	95	411	91	410	54.1%	1.04 [0.81, 1.34]	<del></del>
Total (95% CI)		773		773	100.0%	0.97 [0.80, 1.16]	•
Total events	170		176				
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.73	3, df = 1 (P = 0.3)	39); $I^2 = 0$	1%				05 07 1 15 2
Test for overall effect: Z = 0.36 (P = 0.7	2)						Favoure dimethyl fumarate Favoure placeho

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

	Dimethyl fum	arate	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Fox 2012 (Dimth Fum 240mg; bid)	52	362	55	363	40.8%	0.95 [0.67, 1.35]	<del></del>
Gold 2012 (Dimth Fum 240mg; bid)	74	411	75	410	59.2%	0.98 [0.74, 1.32]	<del></del> -
Total (95% CI)		773		773	100.0%	0.97 [0.78, 1.21]	•
Total events	126		130				
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.03	3, df = 1 (P = 0.8)	$(7); I^2 = 0$	1%				05 07 1 15 2
Test for overall effect: $Z = 0.27$ (P = 0.7	8)						Favours dimethyl fumarate Favours placebo

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

	Dimethyl fun	narate	Place	bo		Risk Ratio (Non-event)	Risk Ratio (Non-event)
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Fox 2012 (Dimth Fum 240mg; bid)	0	362	1	363	28.0%	1.00 [1.00, 1.01]	•
Gold 2012 (Dimth Fum 240mg; bid)	0	411	0	410	72.0%	1.00 [1.00, 1.00]	•
Total (95% CI)		773		773	100.0%	1.00 [1.00, 1.00]	
Total events	0		1				
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.4	12, df = 1 (P = 0.	$52); I^2 = 0$	0%				05 07 1 15 2
Test for overall effect: $Z = 0.37$ (P = 0.	71)						0.5 0.7 1 1.5 2  Favours placeho, Favours dimethyl fumarate

### 5. Fingolimod compared with placebo

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

<sup>&</sup>lt;sup>6</sup> 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)

	Fin	golimod		F	Placebo			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Calabresi 2014b (Fingolimod 0.5mg)	0.21	0.0386	358	0.4	0.6729	355	49.2%	-0.19 [-0.26, -0.12]	-
Kappos 2010 (Fingolimod 0.5mg)	0.18	0.3681	425	0.4	0.678	500	50.8%	-0.22 [-0.29, -0.15]	-
Total (95% CI)			783			855	100.0%	-0.21 [-0.25, -0.16]	<b>◆</b>
Heterogeneity: $Tau^2 = 0.00$ ; $Chi^2 = 0.36$ , Test for overall effect: $Z = 8.18$ (P < 0.00)		= 0.55);	I <sup>2</sup> = 0%	ı					-1 -0.5 0 0.5 1 Favours fingolimod Favours placebo

# Disability progression<sup>7</sup> – number of participants worsened (104 weeks' follow-up)

	Fingolii	mod	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	<b>Events</b>	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Calabresi 2014b (Fingolimod 0.5mg)	49	358	63	355	46.6%	0.77 [0.55, 1.09]	<del></del>
Kappos 2010 (Fingolimod 0.5mg)	53	425	79	418	53.4%	0.66 [0.48, 0.91]	
Total (95% CI)		783		773	100.0%	0.71 [0.56, 0.90]	-
Total events	102		142				
Heterogeneity: Tau² = 0.00; Chi² = 0.42,	df = 1 (P :	= 0.52);	$I^2 = 0\%$			-	0.5 0.7 1 1.5 2
Test for overall effect: Z = 2.87 (P = 0.00	4)						Favours fingolimod Favours placebo

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

	Fingolii	mod	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Calabresi 2014b (Fingolimod 0.5mg)	234	269	167	256	42.2%	1.33 [1.21, 1.47]	-
Kappos 2010 (Fingolimod 0.5mg)	331	369	216	332	57.8%	1.38 [1.27, 1.50]	-
Total (95% CI)		638		588	100.0%	1.36 [1.27, 1.45]	•
Total events	565		383				
Heterogeneity: Tau² = 0.00; Chi² = 0.24 Test for overall effect: Z = 9.20 (P < 0.00		= 0.62);	l² = 0%			_	0.5 0.7 1 1.5 2 Favours placebo Favours fingolimod

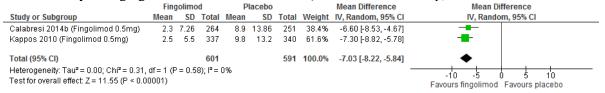
#### GAD lesions - mean number (104 weeks' follow-up)

	Fin	golimo	d	PI	acebo			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Calabresi 2014b (Fingolimod 0.5mg)	0.4	1.84	269	1.2	2.97	256	29.4%	-0.80 [-1.23, -0.37]	
Kappos 2010 (Fingolimod 0.5mg)	0.2	0.8	369	1.1	2.4	322	70.6%	-0.90 [-1.17, -0.63]	-
Total (95% CI)			638			578	100.0%	-0.87 [-1.10, -0.64]	•
Heterogeneity: Tau $^2$ = 0.00; Chi $^2$ = 0.15, Test for overall effect: Z = 7.40 (P < 0.00		P = 0.7	0); l² = I	0%				-	-2 -1 0 1 2 Favours fingolimod Favours placebo

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

	Fingolii	mod	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	<b>Events</b>	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Calabresi 2014b (Fingolimod 0.5mg)	133	264	65	251	48.1%	1.95 [1.53, 2.48]	_ <del></del>
Kappos 2010 (Fingolimod 0.5mg)	187	370	72	339	51.9%	2.38 [1.89, 2.99]	
Total (95% CI)		634		590	100.0%	2.16 [1.77, 2.63]	•
Total events	320		137				
Heterogeneity: Tau <sup>2</sup> = 0.01; Chi <sup>2</sup> = 1.42	df=1 (P:	= 0.23);	I²= 29%			_	05 07 1 15 2
Test for overall effect: Z = 7.64 (P < 0.00	0001)						Favours placebo Favours fingolimod

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



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

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.

<sup>&</sup>lt;sup>7</sup> Calabresi 2014b: defined as a 1 point EDSS change (0·5 point if baseline EDSS was >5·0)



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

	Fingolir	nod	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	<b>Events</b>	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Calabresi 2014b (Fingolimod 0.5mg)	66	358	37	355	49.1%	1.77 [1.22, 2.57]	
Kappos 2010 (Fingolimod 0.5mg)	57	425	49	418	50.9%	1.14 [0.80, 1.64]	<del>-   • -</del>
Total (95% CI)		783		773	100.0%	1.42 [0.92, 2.17]	
Total events	123		86				
Heterogeneity: Tau² = 0.06; Chi² = 2.72,	df = 1 (P =	= 0.10);	I <sup>2</sup> = 63%			-	0.5 0.7 1 1.5 2
Test for overall effect: $Z = 1.60$ (P = 0.11)	)						Favours fingolimod Favours placebo

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

	Fingolimo	d Pla	ebo		Risk Ratio	Risk Ratio
Study or Subgroup	Events To	otal Event	s Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Calabresi 2014b (Fingolimod 0.5mg)	263 3	358 25	5 355	24.7%	1.02 [0.93, 1.12]	<del></del>
Kappos 2010 (Fingolimod 0.5mg)	379 4	425 35	7 418	75.3%	1.04 [0.99, 1.10]	<b>=</b>
Total (95% CI)	7	783	773	100.0%	1.04 [0.99, 1.09]	•
Total events	642	61	2			
Heterogeneity: Tau² = 0.00; Chi² = 0.18 Test for overall effect: Z = 1.67 (P = 0.10		.68); I²= 09	·			0.5 0.7 1 1.5 2 Favours fingolimod Favours placebo

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

	Fingolii	nod	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	<b>Events</b>	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Calabresi 2014b (Fingolimod 0.5mg)	13	358	8	355	53.7%	1.61 [0.68, 3.84]	<del></del>
Kappos 2010 (Fingolimod 0.5mg)	4	425	10	418	46.3%	0.39 [0.12, 1.24]	<del></del>
Total (95% CI)		783		773	100.0%	0.84 [0.21, 3.34]	
Total events	17		18				
Heterogeneity: $Tau^2 = 0.73$ ; $Chi^2 = 3.68$ , Test for overall effect: $Z = 0.25$ (P = 0.80		= 0.06);	I² = 73%				0.2 0.5 1 2 5
1031101 0401411 011301. Z = 0.23 (1 = 0.00	,						Favours fingolimod Favours placebo

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

	Fingoni	noa	Place	DO		RISK RAUO	KISK KAUO
Study or Subgroup	Events	Total	<b>Events</b>	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Calabresi 2014b (Fingolimod 0.5mg)	2	358	2	355	55.6%	0.99 [0.14, 7.00]	•
Kappos 2010 (Fingolimod 0.5mg)	4	425	1	418	44.4%	3.93 [0.44, 35.05]	
Total (95% CI)		783		773	100.0%	1.83 [0.43, 7.85]	
Total events	6		3				
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.86,	df = 1 (P :	= 0.35);	$I^2 = 0\%$			-	05 07 1 15 3
Test for overall effect: $Z = 0.81$ (P = 0.42	)						Favours fingolimod Favours placebo

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

	Fingolir	nod	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	<b>Events</b>	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Calabresi 2014b (Fingolimod 0.5mg)	3	358	2	355	100.0%	1.49 [0.25, 8.85]	<b>←</b>
Kappos 2010 (Fingolimod 0.5mg)	0	425	0	418		Not estimable	_
Total (95% CI)		783		773	100.0%	1.49 [0.25, 8.85]	
Total events	3		2				
Heterogeneity: Not applicable Test for overall effect: Z = 0.44 (P = 0.66)							0.5 0.7 1.5 2 Favours fingolimod Favours placebo

# 6. Cladribine compared with placebo

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

	Cladril	oine	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	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=		05 07 1 15 2					
Test for overall effect: $Z = 6.35$ (P < 0.00001	)						Favours placebo Favours cladribine

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

	C	adribine		PI	acebo			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	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]	<b>•</b>
Heterogeneity: Tau $^z$ = 0.00; Chi $^z$ = 0.04, df: Test for overall effect: Z = 7.51 (P < 0.0000)		0.84); I²=			-0.5 -0.25 0 0.25 0.5 Favours cladribine Favours placebo				

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

	Cladril	oine	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	<b>Events</b>	Total	Weight	M-H, Random, 95% CI	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: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.89, df		05.07 1 15.2					
Test for overall effect: $Z = 2.05$ (P = 0.04)							Favours cladribine Favours placebo

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

	Cladril	oine	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	<b>Events</b>	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Giovannoni 2010 (Cladribine 3.5mg/kg)	5	433	3	219	45.4%	0.84 [0.20, 3.49]	+ <b>-</b>
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=	58); l² =	: 0%				05 07 1 15 2	
Test for overall effect: $Z = 0.25$ (P = 0.80)						Favours cladribine Favours placebo	

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

	Cladril	oine	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	<b>Events</b>	Total	Weight	M-H, Random, 95% CI	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: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.04, df:	= 1 (P = 0.	85); l² =	- 0%				05 07 1 15 7
Test for overall effect: Z = 1.89 (P = 0.06)							Favoure cladribing Favoure placeho

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

	Cladril	oine	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	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: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.07, df = Test for overall effect: $Z = 0.85$ (P = 0.40)	= 1 (P = 0.	80); l² =	= 0%				0.5 0.7 1 1.5 2
1651 101 0461 all 611601. Z = 0.00 (F = 0.40)							Favours cladribine Favours placebo

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

	Cladribine Placebo			bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	<b>Events</b>	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Giovannoni 2010 (Cladribine 3.5mg/kg)	6	430	0	218	50.8%	6.61 [0.37, 116.72]	
Giovannoni 2010 (Cladribine 5.25mg/kg)	4	454	0	218	49.2%	4.33 [0.23, 80.10]	
Total (95% CI)		884		436	100.0%	5.37 [0.69, 41.55]	
Total events	10		0				
Heterogeneity: $Tau^2 = 0.00$ ; $Chi^2 = 0.04$ , $df = 1$ (P = 0.84); $I^2 = 0\%$							0.2 0.5 1 2 5
Test for overall effect: $Z = 1.61$ (P = 0.11)							Favours cladribine Favours placebo

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



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

	Cladril	oine	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	<b>Events</b>	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Giovannoni 2010 (Cladribine 3.5mg/kg)	2	433	1	219	50.0%	1.01 [0.09, 11.09]	<del>+</del> + + + + + + + + + + + + + + + + + +
Giovannoni 2010 (Cladribine 5.25mg/kg)	2	456	1	219	50.0%	0.96 [0.09, 10.54]	<b>←</b>
Total (95% CI)		889		438	100.0%	0.99 [0.18, 5.36]	
Total events	4		2				
Heterogeneity: Tau $^2$ = 0.00; Chi $^2$ = 0.00, df= Test for overall effect: Z = 0.02 (P = 0.99)	98); l² =	= 0%				0.5 0.7 1 1.5 2 Favours cladribine Favours placebo	

### 7. Interferon compared with glatiramer acetate

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

	Interferon be	eta-1a	Glatiramer a	cetate		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Cadavid (IFNb-1a 44 µg tiw)	19	36	28	39	5.3%	0.74 [0.51, 1.06]	<del></del>
Mikol 2008 (IFNb-1a 44 µg tiw)	239	386	234	378	42.4%	1.00 [0.89, 1.12]	<del></del>
O'Conner 2009 (IFNb-1a 250 µg qad)	515	888	264	448	52.3%	0.98 [0.89, 1.08]	-
Total (95% CI)		1310		865	100.0%	0.98 [0.90, 1.06]	•
Total events	773		526				
Heterogeneity: Tau² = 0.00; Chi² = 2.50	df = 2 (P = 0.2)	9); l² = 20	0%				05 07 1 15 2
Test for overall effect: $Z = 0.56$ (P = 0.58	3)						Favours glatiramer acetat Favours inteferon

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

	Inte	rfero	n	Glatiran	ner ace	tate		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Calabrese 2012 (IFNb-1a im 30µg qwk)	0.5	0.6	47	0.5	0.4	28	50.3%	0.00 [-0.23, 0.23]	<del>-</del>
Calabrese 2012 (IFNb-1a sc 44µg tiw)	0.4	0.6	46	0.5	0.4	28	49.7%	-0.10 [-0.33, 0.13]	<del></del>
Total (95% CI)			93			56	100.0%	-0.05 [-0.21, 0.11]	•
Heterogeneity: Tau $^2$ = 0.00; Chi $^2$ = 0.37, df Test for overall effect: Z = 0.61 (P = 0.54)	= 1 (P =	0.54)	; I² = 09	6					-1 -0.5 0 0.5 1 Favours interferon Favours glatiramer acetat

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

	Inte	rfero	n	Glatirar	ner ace	tate		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Calabrese 2012 (IFNb-1a im 30µg qwk)	1.3	1.1	47	1.2	1	28	48.3%	0.10 [-0.39, 0.59]	<del>-</del>
Calabrese 2012 (IFNb-1a sc 44µg tiw)	1.2	1	46	1.2	1	28	51.7%	0.00 [-0.47, 0.47]	+
Total (95% CI)			93			56	100.0%	0.05 [-0.29, 0.39]	<b>+</b>
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.08, df Test for overall effect: Z = 0.28 (P = 0.78)	'= 1 (P =	0.77	); I² = 09	%					-4 -2 0 2 4

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

	Inte	rfero	n	Glatiran	ner ace	tate		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Calabrese 2012 (IFNb-1a im 30µg qwk)	0.9	0.9	47	1.1	1	28	52.0%	-0.20 [-0.65, 0.25]	-
Calabrese 2012 (IFNb-1a sc 44µg tiw)	1	1	46	1.1	1	28	48.0%	-0.10 [-0.57, 0.37]	+
Total (95% CI)			93			56	100.0%	-0.15 [-0.48, 0.17]	•
Heterogeneity: Tau² = 0.00; Chi² = 0.09, df Test for overall effect: Z = 0.92 (P = 0.36)	= 1 (P =	0.76)	); I² = 09	%				-	-4 -2 0 2 4 Favours interferon Favours glatiramer acetat

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

	Inte	rfero	on	Glatiran	ner ace	tate		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Calabrese 2012 (IFNb-1a im 30µg qwk)	2.3	1.3	41	2.2	1.5	22	48.8%	0.10 [-0.64, 0.84]	*
Calabrese 2012 (IFNb-1a sc 44µg tiw)	1.4	1	45	2.2	1.5	22	51.2%	-0.80 [-1.49, -0.11]	<b>-</b>
Total (95% CI)			86			44	100.0%	-0.36 [-1.24, 0.52]	•
Heterogeneity: $Tau^2 = 0.27$ ; $Chi^2 = 3.02$ , df Test for overall effect: $Z = 0.80$ (P = 0.42)	= 1 (P =	0.08)	); I² = 67	7%					-10 -5 0 5 10

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

	Interfer	on	Glatiramer ad	etate		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Calabrese 2012 (IFNb-1a im 30µg qwk)	14	55	6	28	53.6%	1.19 [0.51, 2.75]	<del></del>
Calabrese 2012 (IFNb-1a sc 44µg tiw)	10	55	6	28	46.4%	0.85 [0.34, 2.10]	-
Total (95% CI)		110		56	100.0%	1.02 [0.55, 1.88]	
Total events	24		12				
Heterogeneity: Tau $^2$ = 0.00; Chi $^2$ = 0.29, df Test for overall effect: Z = 0.05 (P = 0.96)	= 1 (P = 0.	.59); I²	= 0%			_	0.5 0.7 1 1.5 2 Favours interferon Favours glatiramer acetat

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

	Interfer	on	Glatiramer ac	etate		Risk Ratio	Risk Ratio
Study or Subgroup	Events 7	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Calabrese 2012 (IFNb-1a im 30µg qwk)	7	55	2	28	50.0%	1.78 [0.40, 8.02]	
Calabrese 2012 (IFNb-1a sc 44µg tiw)	7	55	2	28	50.0%	1.78 [0.40, 8.02]	
Total (95% CI)		110		56	100.0%	1.78 [0.62, 5.16]	
Total events	14		4				
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df	= 1 (P = 1.0	00); l² :	= 0%			-	05 07 1 15 2
Test for overall effect: Z = 1.06 (P = 0.29)							Favours interferon Favours glatiramer acetat

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

	Interfe	ron	Glatiramer ac	cetate		Risk Ratio	Risk Ratio
Study or Subgroup	<b>Events</b>	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Cadavid (IFNb-1a 44 µg tiw)	11	36	8	39	22.3%	1.49 [0.68, 3.28]	
Calabrese 2012 (IFNb-1a im 30µg qwk)	8	55	4	28	16.8%	1.02 [0.34, 3.09]	
Calabrese 2012 (IFNb-1a sc 44µg tiw)	9	55	4	28	17.1%	1.15 [0.39, 3.39]	-
Mikol 2008 (IFNb-1a 44 μg tiw)	15	386	2	378	12.2%	7.34 [1.69, 31.90]	
O'Conner 2009 (IFNb-1a 250 µg qad)	104	888	71	448	31.6%	0.74 [0.56, 0.98]	<del></del>
Total (95% CI)		1420		921	100.0%	1.30 [0.68, 2.47]	
Total events	147		89				
Heterogeneity: Tau <sup>2</sup> = 0.32; Chi <sup>2</sup> = 11.80, d	f= 4 (P =	0.02); (	l² = 66%			-	05 07 1 15 2
Test for overall effect: Z = 0.80 (P = 0.42)							Favours interferon Favours glatiramer acetat

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

	Interfe	ron	Glatiramer a	cetate		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Cadavid (IFNb-1a 44 µg tiw)	3	36	2	39	6.2%	1.63 [0.29, 9.17]	-
Calabrese 2012 (IFNb-1a im 30µg qwk)	6	55	2	28	7.9%	1.53 [0.33, 7.08]	
Calabrese 2012 (IFNb-1a sc 44µg tiw)	6	55	2	28	7.9%	1.53 [0.33, 7.08]	
/likol 2008 (IFNb-1a 44 μg tiw)	23	386	19	378	53.5%	1.19 [0.66, 2.14]	<del>-   •</del>
D'Conner 2009 (IFNb-1a 250 µg qad)	13	888	8	448	24.5%	0.82 [0.34, 1.96]	•
otal (95% CI)		1420		921	100.0%	1.15 [0.75, 1.77]	
otal events	51		33				
Heterogeneity: Tau² = 0.00; Chi² = 1.00, df	= 4 (P = 0)	).91); l²	= 0%			-	05 07 1 15 2
est for overall effect: Z = 0.63 (P = 0.53)							Favours interferon Favours glatiramer acetal

# 8. Alemtuzumab compared with interferon

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

	Alemtuz	umab	Interfe	ron		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
CAMMS223 2008 (Alemtuzumab 12mg	g) 86	112	57	111	19.6%	1.50 [1.21, 1.84]	
Cohen 2012 (Alemtuzumab 12mg)	292	376	110	187	48.7%	1.32 [1.16, 1.51]	<del>-</del>
Coles 2012 (Alemtuzumab 12mg)	279	426	94	202	31.7%	1.41 [1.20, 1.66]	<del></del>
Total (95% CI)		914		500	100.0%	1.38 [1.26, 1.51]	•
Total events	657		261				
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 1.07	', df = 2 (P = 0.	.59); l² =	0%			_	0.5 0.7 1 1.5 2
Test for overall effect: Z = 6.88 (P < 0.0	0001)						Eavours interferon Favours alemtuzumah

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

	Alemtuzu	ımab	Interfe	ron		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
CAMMS223 2008 (Alemtuzumab 12mg)	76	112	45	111	100.0%	1.67 [1.29, 2.17]	
Total (95% CI)		112		111	100.0%	1.67 [1.29, 2.17]	•
Total events	76		45				
Heterogeneity: Not applicable Test for overall effect: Z = 3.90 (P < 0.0001)	)						0.5 0.7 1 1.5 2 Favours interferon Favours alemtuzumab

# Disability progression<sup>8</sup> – number of participants worsened (104-156 weeks' follow-up)

	Alemtuzi	umab	Interfe	ron		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
CAMMS223 2008 (Alemtuzumab 12mg)	8	112	24	111	19.8%	0.33 [0.16, 0.70]	<del></del>
Cohen 2012 (Alemtuzumab 12mg)	30	376	20	187	32.1%	0.75 [0.44, 1.28]	<del></del>
Coles 2012 (Alemtuzumab 12mg)	54	426	40	202	48.1%	0.64 [0.44, 0.93]	
Total (95% CI)		914		500	100.0%	0.59 [0.40, 0.86]	-
Total events	92		84				
Heterogeneity: Tau <sup>2</sup> = 0.04; Chi <sup>2</sup> = 3.15, di	f = 2 (P = 0.	21); I2=	37%				05 07 1 15 2
Test for overall effect: $Z = 2.71$ (P = 0.007)							Favours alemtuzumab Favours interferon

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

	Alemtuzu	ımab	Interfe	ron		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	<b>Events</b>	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
CAMMS223 2008 (Alemtuzumab 12mg)	13	112	30	111	100.0%	0.43 [0.24, 0.78]	<del></del>
Total (95% CI)		112		111	100.0%	0.43 [0.24, 0.78]	
Total events Heterogeneity: Not applicable Test for overall effect: Z = 2.78 (P = 0.005)	13		30				0.5 0.7 1 1.5 2 Favours alemtuzumab Favours interferon

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

	Alemtuzi	ımab	Interfe	ron		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	<b>Events</b>	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Cohen 2012 (Alemtuzumab 12mg)	176	376	99	187	48.3%	0.88 [0.74, 1.05]	
Coles 2012 (Alemtuzumab 12mg)	186	403	127	187	51.7%	0.68 [0.59, 0.79]	
Total (95% CI)		779		374	100.0%	0.77 [0.60, 1.00]	-
Total events	362		226				
Heterogeneity: Tau <sup>2</sup> = 0.03; Chi <sup>2</sup> = 5.3	31, df = 1 (F	r = 0.02	; I² = 81%	5		-	05 07 1 15 2
Test for overall effect: Z = 1.96 (P = 0.	05)						U.S U.7 I I.S Z  Favours alemturumah Favours interferon

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

						1	,
	Alemtuzi	umab	Interfe	ron		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
CAMMS223 2008 (Alemtuzumab 12mg)	2	108	13	107	15.0%	0.15 [0.04, 0.66]	<del></del>
Cohen 2012 (Alemtuzumab 12mg)	5	376	11	187	28.5%	0.23 [0.08, 0.64]	•
Coles 2012 (Alemtuzumab 12mg)	14	435	15	202	56.6%	0.43 [0.21, 0.88]	<b>—</b>
Total (95% CI)		919		496	100.0%	0.31 [0.17, 0.55]	
Total events	21		39				
Heterogeneity: Tauz = 0.02; Chiz = 2.17, d	f = 2 (P = 0.	34); l² =	8%				05 07 1 15 2
Test for overall effect: Z = 3.99 (P < 0.000)	1)						Favours alemtuzumab Favours interferon

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

	Alemtuzi	umab	Interfe	ron		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
CAMMS223 2008 (Alemtuzumab 12mg)	22	113	45	111	32.9%	0.48 [0.31, 0.74]	
Cohen 2012 (Alemtuzumab 12mg)	24	386	31	195	28.4%	0.39 [0.24, 0.65]	
Coles 2012 (Alemtuzumab 12mg)	37	436	73	231	38.7%	0.27 [0.19, 0.39]	<b>←</b>
Total (95% CI)		935		537	100.0%	0.36 [0.25, 0.52]	-
Total events	83		149				
Heterogeneity: Tau <sup>2</sup> = 0.05; Chi <sup>2</sup> = 4.26, d	f = 2 (P = 0.	12); l² =	53%				0.5 0.7 1 1.5 2
Test for overall effect: $Z = 5.49$ (P < 0.0000	01)						Favours alemtuzumab Favours interferon

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

<sup>&</sup>lt;sup>8</sup> 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.

	Alemtuzu	ımab	Interfe	ron		Risk Ratio (Non-event)	Risk Ratio (Non-event)
Study or Subgroup	Events	Total	<b>Events</b>	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
CAMMS223 2008 (Alemtuzumab 12mg)	1	108	0	107	6.8%	0.99 [0.97, 1.02]	-+
Cohen 2012 (Alemtuzumab 12mg)	1	376	0	187	47.2%	1.00 [0.99, 1.01]	•
Coles 2012 (Alemtuzumab 12mg)	2	435	0	202	46.0%	1.00 [0.99, 1.01]	•
Total (95% CI)		919		496	100.0%	1.00 [0.99, 1.00]	•
Total events	4		0				
Heterogeneity: Tau² = 0.00; Chi² = 0.39, dt Test for overall effect: Z = 0.81 (P = 0.42)	f= 2 (P = 0.	82); I²=	0%				0.7 0.85 1 1.2 1.5 Favours interferon Favours alemtuzumab

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)

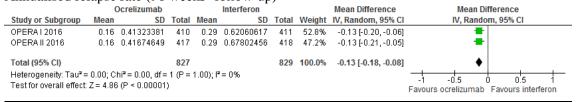
	Alemtuzi	umab	Interfe	ron		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
CAMMS223 2008 (Alemtuzumab 12mg)	71	108	50	107	25.6%	1.41 [1.10, 1.80]	_ <del>-</del>
Cohen 2012 (Alemtuzumab 12mg)	253	376	85	187	33.5%	1.48 [1.25, 1.76]	-
Coles 2012 (Alemtuzumab 12mg)	334	435	134	202	40.8%	1.16 [1.04, 1.29]	- <del>-</del>
Total (95% CI)		919		496	100.0%	1.32 [1.10, 1.58]	•
Total events	658		269				
Heterogeneity: Tauz = 0.02; Chiz = 6.78, d	f = 2 (P = 0.	03); l² =	71%			-	05 07 1 15 2
Test for overall effect: Z = 3.03 (P = 0.002)	)						0.5 0.7 1 1.5 2

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

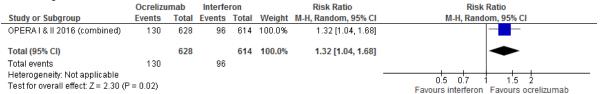
	Alemtuzi	umab	Interfe	ron		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
CAMMS223 2008 (Alemtuzumab 12mg)	2	108	1	107	43.5%	1.98 [0.18, 21.53]	<del></del>
Cohen 2012 (Alemtuzumab 12mg)	3	376	0	187	28.3%	3.49 [0.18, 67.23]	<del></del>
Coles 2012 (Alemtuzumab 12mg)	3	435	0	202	28.3%	3.26 [0.17, 62.80]	•
Total (95% CI)		919		496	100.0%	2.68 [0.56, 12.90]	
Total events	8		1				
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.11, dt	f = 2 (P = 0.	95); l² =	0%				05 07 1 15 2
Test for overall effect: Z = 1.23 (P = 0.22)							Favours alemtuzumab Favours interferon

# 9. Ocrelizumab compared with interferon

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

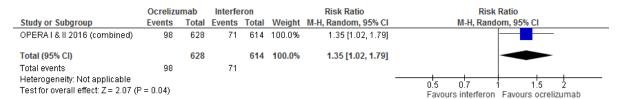


# Disability improvement<sup>9</sup> confirmed at 12 weeks – number of participants improved (96 weeks' follow-up)



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

<sup>&</sup>lt;sup>9</sup> 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<sup>10</sup> - number of participants worsened (96 weeks' follow-up)

	Ocrelizu	ımab	Interfe	ron		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	<b>Events</b>	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
OPERAI 2016	28	364	47	338	38.7%	0.55 [0.35, 0.86]	
OPERA II 2016	45	360	62	317	61.3%	0.64 [0.45, 0.91]	<del></del>
Total (95% CI)		724		655	100.0%	0.60 [0.46, 0.80]	•
Total events	73		109				
Heterogeneity: Tau <sup>2</sup> =	: 0.00; Chř	$^{2} = 0.25$	df = 1 (P	= 0.62	); I <sup>2</sup> = 0%		05 07 1 15 2
Test for overall effect:	Z = 3.57 (	P = 0.00	04)				0.5 U.7 1 1.5 Z  Favours occelizumab Favours interferon

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

	Ocrelizu	mab	Interfe	ron		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	<b>Events</b>	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
OPERA I 2016	42	410	69	411	40.8%	0.61 [0.43, 0.87]	<del></del>
OPERA II 2016	57	417	97	418	59.2%	0.59 [0.44, 0.79]	<del></del>
Total (95% CI)		827		829	100.0%	0.60 [0.48, 0.75]	•
Total events	99		166				
Heterogeneity: Tau2 =	= 0.00; Chř	$^{2} = 0.02$	df = 1 (P	= 0.88	); I² = 0%	-	05 07 1 15 2
Test for overall effect	: Z= 4.41 (	⊃ < 0.00	01)				0.5 0.7 1 1.5 2 Favours ocrelizumab Favours interferon

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

	Ocrelizu	mab	Interfe	ron		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	<b>Events</b>	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
OPERA I 2016	13	410	25	411	42.7%	0.52 [0.27, 1.00]	<del></del>
OPERA II 2016	16	417	39	418	57.3%	0.41 [0.23, 0.72]	<b>—</b>
Total (95% CI)		827		829	100.0%	0.46 [0.30, 0.70]	
Total events	29		64				
Heterogeneity: Tau² =	0.00; Chi <sup>2</sup>	= 0.29,	df = 1 (P	= 0.59	); l² = 0%		05 07 1 15 2
Test for overall effect:	Z = 3.60 (F	P = 0.00	03)				Eavours occelizumab Favours interferon

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

	Ocrelizu	ımab	Interfe	ron		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	<b>Events</b>	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
OPERA I & II 2016 (combined)	482	825	433	826	100.0%	1.11 [1.02, 1.22]	
Total (95% CI)		825		826	100.0%	1.11 [1.02, 1.22]	•
Total events	482		433				
Heterogeneity: Not applicable Test for overall effect: Z = 2.45 (F	9 = 0.01)						0.5 0.7 1 1.5 2 Favours ocrelizumab Favours interferon

#### Risk of influenza-like illness

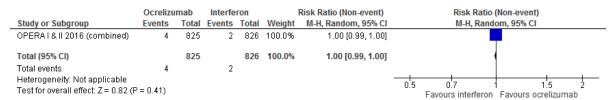
	Ocrelizu	lizumab Interferor		ron		Risk Ratio	Risk Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI			
OPERA I & II 2016 (combined)	38	825	177	826	100.0%	0.21 [0.15, 0.30]	H			
Total (95% CI)		825		826	100.0%	0.21 [0.15, 0.30]	<b>&gt;</b>			
Total events	38		177							
Heterogeneity: Not applicable Test for overall effect: Z = 8.94 (P	< 0.0000	1)					0.5 0.7 1 1.5 2 Favours ocrelizumab Favours interferon			

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

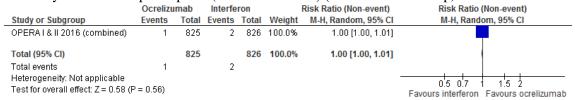
	Ocrelizu	mab	Interfe	ron		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	<b>Events</b>	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
OPERA I & II 2016 (combined)	57	825	72	826	100.0%	0.79 [0.57, 1.11]	
Total (95% CI)		825		826	100.0%	0.79 [0.57, 1.11]	-
Total events Heterogeneity: Not applicable Test for overall effect: Z = 1.36 (P	57 = 0.17)		72				0.5 0.7 1 1.5 2 Favours ocrelizumab Favours interferon

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

<sup>&</sup>lt;sup>10</sup> 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

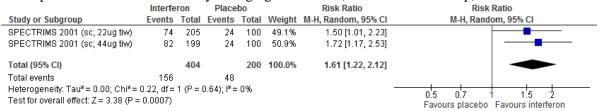
## Disability progression<sup>11</sup> confirmed at 6 months (156 weeks' follow-up)

	Interfe	ron	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Andersen 2004 (sc; 22ug qw)	77	186	68	178	24.7%	1.08 [0.84, 1.40]	
North American SG 2004 (sc; 250ug qad)	101	317	105	308	29.9%	0.93 [0.75, 1.17]	<del></del>
The European SG 1998 (sc; 8MIU qad)	147	360	174	358	45.4%	0.84 [0.71, 0.99]	<del></del> -
Total (95% CI)		863		844	100.0%	0.92 [0.80, 1.06]	•
Total events	325		347				
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 2.80, df =	2 (P = 0.)	25); l² =	28%			_	05 07 1 15 2
Test for overall effect: $Z = 1.10$ (P = 0.27)							0.5 0.7 1 1.5 2

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

	Interfe	ron	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Andersen 2004 (sc; 22ug qw)	114	186	110	178	41.1%	0.99 [0.84, 1.17]	<del>-</del>
North American SG 2004 (sc; 250ug qad)	226	317	192	308	58.9%	1.14 [1.02, 1.28]	-
Total (95% CI)		503		486	100.0%	1.08 [0.94, 1.24]	<b>*</b>
Total events	340		302				
Heterogeneity: Tau <sup>2</sup> = 0.01; Chi <sup>2</sup> = 2.02, df =	1 (P = 0.1)	16); l² =	50%			_	05 07 1 15 2
Test for overall effect: Z = 1.08 (P = 0.28)							Favours placebo Favours interferon

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



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

<sup>&</sup>lt;sup>11</sup> 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)

	Interfe	ron	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Andersen 2004 (sc; 22ug qw)	38	186	25	178	25.3%	1.45 [0.92, 2.31]	+
North American SG 2004 (sc; 250ug qad)	44	317	32	308	27.5%	1.34 [0.87, 2.05]	<del></del>
SPECTRIMS 2001 (sc; 22ug tiw)	14	209	10	103	12.2%	0.69 [0.32, 1.50]	•
SPECTRIMS 2001 (sc; 44ug tiw)	14	204	10	103	12.2%	0.71 [0.33, 1.54]	
The European SG 1998 (sc; 8MIU qad)	26	360	31	358	22.9%	0.83 [0.51, 1.38]	
Total (95% CI)		1276		1050	100.0%	1.05 [0.77, 1.42]	-
Total events	136		108				
Heterogeneity: Tau <sup>2</sup> = 0.04; Chi <sup>2</sup> = 6.00, df =	4 (P = 0.3	20); <b>I²</b> =	33%			-	0.5 0.7 1 1.5 2
Test for overall effect: Z = 0.29 (P = 0.77)							Favours interferon Favours placebo

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

	Interfe	ron	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Andersen 2004 (sc; 22ug qw)	16	186	6	178	46.5%	2.55 [1.02, 6.37]	-
SPECTRIMS 2001 (sc; 22ug tiw)	15	209	3	103	26.3%	2.46 [0.73, 8.32]	<del>-  </del>
SPECTRIMS 2001 (sc; 44ug tiw)	18	204	3	103	27.1%	3.03 [0.91, 10.05]	<del></del>
Total (95% CI)		599		384	100.0%	2.65 [1.42, 4.95]	
Total events	49		12				
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> =	_	05 07 1 15 2					
Test for overall effect; Z = 3.06 (P =	0.002)						Favours interferon Favours placebo

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

	interre	ron	Place	DO		RISK RATIO	RISK RATIO
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Andersen 2004 (sc; 22ug qw)	38	186	25	178	17.8%	1.45 [0.92, 2.31]	
North American SG 2004 (sc; 250ug qad)	79	317	75	308	45.5%	1.02 [0.78, 1.35]	<del></del>
The European SG 1998 (sc; 8MIU qad)	64	360	66	358	36.6%	0.96 [0.71, 1.32]	
Total (95% CI)		863		844	100.0%	1.07 [0.87, 1.30]	-
Total events	181		166				
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 2.23, df =	2 (P = 0.3	33); I² =	10%				0.5 0.7 1 1.5 2
Test for overall effect: $Z = 0.63$ (P = 0.53)							Favours interferon Favours placebo

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

•	·				`		
	Interfe	ron	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
North American SG 2004 (sc; 250ug qad)	30	317	12	308	43.0%	2.43 [1.27, 4.66]	
The European SG 1998 (sc; 8MIU qad)	45	360	15	358	57.0%	2.98 [1.69, 5.25]	
Total (95% CI)		677		666	100.0%	2.73 [1.78, 4.19]	
Total events	75		27				
Heterogeneity: Tau² = 0.00; Chi² = 0.22, df =	_	05 07 1 15 2					
Test for overall effect: Z = 4.61 (P < 0.00001	)						Favours interferon Favours placebo

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

	Interfe	ron	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Andersen 2004 (sc; 22ug qw)	2	186	2	178	27.0%	0.96 [0.14, 6.72]	+ -
North American SG 2004 (sc; 250ug qad)	4	317	1	308	21.5%	3.89 [0.44, 34.58]	
SPECTRIMS 2001 (sc; 22ug tiw)	1	209	1	103	13.4%	0.49 [0.03, 7.80]	+ -
SPECTRIMS 2001 (sc; 44ug tiw)	2	204	1	103	18.0%	1.01 [0.09, 11.01]	+
The European SG 1998 (sc; 8MIU qad)	3	360	1	358	20.1%	2.98 [0.31, 28.54]	-
Total (95% CI)		1276		1050	100.0%	1.50 [0.55, 4.13]	
Total events	12		6				
Heterogeneity: Tau2 = 0.00; Chi2 = 2.04, df =	4 (P = 0.1	73); l² =	0%				05 07 1 15 2
Test for overall effect: Z = 0.79 (P = 0.43)							Favours interferon Favours placeho

# **Review question 3**

### 1. Interferon compared with placebo for primary progressive multiple sclerosis

# Disability progression confirmed at three months<sup>12</sup> – number of participants worsened (104 weeks' follow-up)

	Interfe	ron	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	<b>Events</b>	Total	Weight	M-H, Random, 95% CI	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 = 0.6 Test for overall effect: Z = 0.15 (P = 0.8		-	0.5 0.7 1 1.5 2 Favours interferon Favours placebo				

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

	Interfe	ron	Place	bo		Risk Ratio (Non-event)	Risk Ratio (Non-event)
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Leary 2003 (IFNb1a im; 30ug)	1	15	2	20	28.0%	1.04 [0.85, 1.27]	<del>-</del>
Montalban 2004 (IFNb1b sc; 8 MIU)	2	36	3	37	72.0%	1.03 [0.91, 1.16]	<del>-</del>
Total (95% CI)		51		57	100.0%	1.03 [0.93, 1.14]	<b>*</b>
Total events	3		5				
Heterogeneity: Tauz = 0.00; Chiz = 0.0	1, df = 1 (	P = 0.9	4); $I^2 = 0.9$	%			05 07 1 15 3
Test for overall effect: Z = 0.56 (P = 0.9	58)						Eavours placebo Eavours interferon

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

•	Interfe	ron	Place	bo	`	Risk Ratio (Non-event)	Risk Ratio (Non-event)
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	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]	<b>+</b>
Total events	1		2				
Heterogeneity: $Tau^z = 0.00$ ; $Chi^z = 0.1$ Test for overall effect: $Z = 0.43$ (P = 0.		P = 0.7	1); I² = 09	%			0.5 0.7 1.5 2 Favours placebo Favours interferon

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

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.