Multiple sclerosis relapses following cessation of fingolimod

Clinical Drug Investigation

Supplementary Material

Charles B Malpas; CORe, Department of Medicine, University of Melbourne, Melbourne, Australia; Melbourne MS Centre, Department of Neurology, Royal Melbourne Hospital, Melbourne, Australia

Izanne Roos; CORe, Department of Medicine, University of Melbourne, Melbourne, Australia; Melbourne MS Centre, Department of Neurology, Royal Melbourne Hospital, Melbourne, Australia

Sifat Sharmin; CORe, Department of Medicine, University of Melbourne, Melbourne, Australia; Department of Neurology, Melbourne MS Centre, Royal Melbourne Hospital, Melbourne, Australia

Katherine Buzzard; Box Hill Hospital, Melbourne, Australia; Monash University, Melbourne, Australia; Melbourne MS Centre, Royal Melbourne Hospital, Melbourne, Australia

Olga Skibina; Box Hill Hospital, Melbourne, Australia; Monash University, Melbourne, Australia; The Alfred Hospital, Melbourne, Australia

Helmut Butzkueven; Central Clinical School, Monash University, Melbourne, Australia; Department of Neurology, The Alfred Hospital, Melbourne, Australia; Department of Neurology, Box Hill Hospital, Monash University, Melbourne, Australia

Ludwig Kappos; Neurologic Clinic and Policlinic, Departments of Medicine and Clinical Research, University Hospital and University of Basel, Basel , Switzerland

Francesco Patti; GF Ingrassia Department, University of Catania, Catania, Italy; Policlinico G Rodolico

Raed Alroughani; Division of Neurology, Department of Medicine, Amiri Hospital, Sharq, Kuwait

Dana Horakova; Department of Neurology and Center of Clinical Neuroscience, First Faculty of Medicine, Charles University in Prague and General University Hospital, Prague, Czech Republic

Eva Kubala Havrdova; Department of Neurology and Center of Clinical Neuroscience, First Faculty of Medicine, Charles University in Prague and General University Hospital, Prague, Czech Republic

Guillermo Izquierdo; Hospital Universitario Virgen Macarena, Sevilla, Spain

Sara Eichau; Hospital Universitario Virgen Macarena, Sevilla, Spain

Suzanne Hodgkinson; Liverpool Hospital, Sydney, Australia

Pierre Grammond; CISSS ChaudiËre-Appalache, Levis, Canada

Jeannette Lechner-Scott; School of Medicine and Public Health, University Newcastle, Newcastle, Australia; Department of Neurology, John Hunter Hospital, Hunter New England Health, Newcastle, Australia

Tomas Kalincik; CORe, Department of Medicine, University of Melbourne, Melbourne, Australia; Melbourne MS Centre, Department of Neurology, Royal Melbourne Hospital, Melbourne, Australia

on behalf of the MSBase Study Group

Table S1. Number of eligible patients contributed by each centre

Centre	*No. patients*
Hospital Fernandez, Capital Federal, Argentina	1
University of Western Australia, Nedlands, Australia	1
Brain and Mind Centre, Sydney, Australia	18
Melbourne MS Centre, Department of Neurology, Royal Melbourne Hospital, Melbourne, Australia	89
University Newcastle, Newcastle, Australia	20
St Vincents Hospital, Fitzroy, Melbourne, Australia	1
Monash Medical Centre, Melbourne, Australia	10
Liverpool Hospital, Sydney, Australia	24
Box Hill Hospital, Melbourne, Australia	60
Westmead Hospital, Sydney, Australia	6
Flinders University, Adelaide, Australia	6
University of Queensland, Brisbane, Australia	12
The Alfred Hospital, Melbourne, Australia	9
Austin Health, Melbourne, Australia	12
Concord Repatriation General Hospital, Sydney, Australia	1
Royal Brisbane and Women's Hospital, Brisbane, Australia	3
Cliniques Universitaires Saint-Luc, Brussels, Belgium	8
Universitary Hospital Ghent, Ghent, Belgium	5
Rehabilitation and MS-Centre Overpelt and Hasselt University, Hasselt, Belgium	3
CSSS Saint-Jérôme, Saint-Jerome, Canada	12
CHUM and Universite de Montreal, Montreal, Canada	6
CISSS Chaudière-Appalache, Levis, Canada	24
Neuro Rive-Sud, Quebec, Canada	7
St. Michael's Hospital, Canada	1
Geneva University Hospital, Switzerland	1
Universitatsspital Basel, Basel, Switzerland	46
Ospedale Civico Lugano	4
Charles University in Prague and General University Hospital, Prague, Czech Republic	33
Hospital Universitario Virgen de Valme, Seville, Spain	4
Hospital Universitario Donostia, San Sebastián, Spain	3
Hospital Universitario Virgen Macarena, Sevilla, Spain	32
Hospital de Galdakao-Usansolo, Galdakao, Spain	4
Hospital Germans Trias i Pujol, Badalona, Spain	4
University Hospital Reina Sofia, Cordoba, Spain	2
AHEPA University Hospital, Greece	1

University of Debrecen, Debrecen, Hungary	2
Isfahan University of Medical Sciences, Isfahan, Iran	3
University G. d'Annunzio, Chieti, Italy	11
Azienda Sanitaria Unica Regionale Marche - AV3, Macerata, Italy	3
University of Florence, Florence, Italy	1
IRCCS Mondino Foundation, Pavia, Italy	2
Ospedali Riuniti di Salerno, Salerno, Italy	1
University of Parma, Parma, Italy	10
Azienda Ospedaliera di Rilievo Nazionale San Giuseppe Moscati Avellino, Avellino, Italy	6
Azienda Ospedaliera Universitaria, Modena, Italy	3
ASL3 Genovese, Genova, Italy	1
Department of Medical and Surgical Sciences and Advanced Technologies, GF Ingrassia, Catania, Italy	37
Neurology Unit, Garibaldi Hospital, Catania, Italy	4
Amiri Hospital, Sharq, Kuwait	35
American University of Beirut Medical Center, Beirut, Lebanon	19
Zuyderland Ziekenhuis, Sittard, Netherlands	5
Groene Hart Ziekenhuis, Gouda, Netherlands	1
Medical Center Leeuwarden, Leeuwarden, Netherlands	1
Centro Hospitalar Universitario de Sao Joao, Porto, Portugal	2
Razi Hospital, Manouba, Tunisia	1
KTU Medical Faculty Farabi Hospital, Trabzon, Turkey	17
19 Mayis University, Samsun, Turkey	15
Hacettepe University, Ankara, Turkey	2
Dokuz Eylul University, Konak/Izmir, Turkey	17
Bakirkoy Education and Research Hospital for Psychiatric and Neurological Diseases, Istanbul, Turkey	8
Haydarpasa Numune Training and Research Hospital, Istanbul, Turkey	5

Table S2. Annualised relapse rates (ARR) [95% CI] excluding 72 patients with pregnancy (*n* = 613)

Cohort	*Before treatment*	*During treatment*	*After cessation*
All (*n* = 613)	1.74 [1.60, 1.88]	0.52 [0.46, 0.58]	0.42 [0.37, 0.48]
Switch to new therapy (12 months)			
None (*n* = 58)	1.39 [1.02, 1.84]	0.29 [0.13, 0.45]	0.26 [0.16, 0.37]
Low efficacy (*n* = 172)	1.36 [1.16, 1.58]	0.34 [0.25, 0.44]	0.49 [0.38, 0.62]
High efficacy (*n* = 383)	1.97 [1.78, 2.13]	0.64 [0.56, 0.71]	0.41 [0.34, 0.49]
Time to switch			
0-2 months (*n* = 308)	1.91 [1.72, 2.11]	0.60 [0.51, 0.69]	0.33 [0.26, 0.40]
2-4 months (*n* = 103)	1.74 [1.43, 2.10]	0.54 [0.40, 0.71]	0.49 [0.37, 0.60]
4-6 months (*n* = 44)	1.33 [0.73, 1.58]	0.31 [0.13, 0.49]	0.69 [0.44, 0.96]
6-8 months (*n* = 24)	1.72 [1.04, 2.64]	0.44 [0.16, 0.80]	0.80 [0.44, 1.32]
8-10 months (*n* = 14)	1.78 [1.11, 2.39]	0.33 [0.11, 0.61]	0.89 [0.33, 1.72]
10-12 months (*n* = 15)	1.00 [0.41, 2.24]	0.18 [0.00, 0.35]	0.59 [0.29, 1.00]
12+ months (*n* = 105)	1.65 [1.34, 1.98]	0.46 [0.33, 0.60]	0.30 [0.19, 0.40]

Note: All values are given as annualised relapse rates (ARRs) with 95% CI in square brackets. ARRs were computed as the total number of relapses observed over the specific 12-month period divided by the number of patients. 'Switch to new therapy' shows the ARRs stratified by the efficacy of the new therapy commenced within 12 months of fingolimod cessation. 'Time to switch' shows the ARRs stratified by the time to commencement of any new therapy following fingolimod cessation.

Table S3. Serious annualised relapse rates (ARR) [95% CI] excluding 72 patients with pregnancy (*n* = 613)

Cohort	*Before treatment*	*During treatment*	*After cessation*
All (*n* = 685)	0.05 [0.03, 0.07]	0.02 [0.01, 0.03]	0.02 [0.01, 0.03]
Switch to new therapy (12 months)			
None (*n* = 58)	0.05 [0.01, 0.12]	0.01 [0.00, 0.03]	0
Low efficacy (*n* = 172)	0.04 [0.01, 0.06]	0.01 [0.00, 0.02]	0.04 [0.01, 0.06]
High efficacy (*n* = 383)	0.06 [0.03, 0.09]	0.03 [0.01, 0.04]	0.01 [0.00, 0.03]
Time to switch			
0-2 months (*n* = 308)	0.04 [0.02, 0.07]	0.02 [0.01, 0.04]	0.02 [0.01, 0.04]
2-4 months (*n* = 103)	0.08 [0.02, 0.17]	0.04 [0.00, 0.08]	0.02 [0.00, 0.05]
4-6 months (*n* = 44)	0.02 [0.00, 0.07]	0.02 [0.00, 0.07]	0.02 [0.00, 0.07]
6-8 months (*n* = 24)	0	0	0.08 [0.00, 0.20]
8-10 months (*n* = 14)	0.11 [0.00, 0.28]	0.06 [0.00, 0.17]	0.06 [0.00, 0.17]
10-12 months (*n* = 15)	0.11 [0.00, 0.35]	0	0
12+ months (*n* = 105)	0.05 [0.01, 0.11]	0	0

Note: All values are given as annualised relapse rates (ARRs) with 95% CI in square brackets. ARRs were computed as the total number of relapses observed over the specific 12-month period divided by the number of patients. 'Switch to new therapy' shows the ARRs stratified by the efficacy of the new therapy commenced within 12 months of fingolimod cessation. 'Time to switch' shows the ARRs stratified by the time to commencement of any new therapy following fingolimod cessation.

Table S4. Annualised relapse rates (ARR) [95% CI] in patients who commenced therapy within 12 months (*n* = 544)

Cohort	*Before treatment*	*During treatment*	*After cessation*
All (*n* = 544)	1.75 [1.60, 1.90]	0.51 [0.46, 0.58]	0.47 [0.41, 0.54]
Switch to new therapy (12 months)			
Low efficacy (*n* = 166)	1.33 [1.10, 1.55]	0.33 [0.23, 0.42]	0.51 [0.39, 0.62]
High efficacy (*n* = 378)	1.93 [1.76, 2.12]	0.60 [0.53, 0.68]	0.45 [0.38, 0.54]
Time to switch			
0-2 months (*n* = 322)	1.87 [1.69, 2.07]	0.58 [0.50, 0.66]	0.34 [0.27, 0.41]
2-4 months (*n* = 108)	1.72 [1.42, 2.06]	0.52 [0.39, 0.67]	0.53 [0.40, 0.65]
4-6 months (*n* = 48)	1.21 [0.79, 1.71]	0.29 [0.15, 0.48]	0.71 [0.48, 0.98]
6-8 months (*n* = 25)	1.72 [1.00, 2.60]	0.44 [0.16, 0.80]	0.80 [0.44, 1.40]
8-10 months (*n* = 19)	1.74 [1.11, 2.32]	0.32 [0.11, 0.58]	0.84 [0.32, 1.63]
10-12 months (*n* = 22)	1.23 [0.68, 2.23]	0.23 [0.05, 0.36]	0.86 [0.46, 1.41]

Note: All values are given as annualised relapse rates (ARRs) with 95% CI in square brackets. ARRs were computed as the total number of relapses observed over the specific 12-month period divided by the number of patients. 'Switch to new therapy' shows the ARRs stratified by the efficacy of the new therapy commenced within 12 months of fingolimod cessation. 'Time to switch' shows the ARRs stratified by the time to commencement of any new therapy following fingolimod cessation.

Table S5. Serious annualised relapse rates (ARR) [95% CI] in patients who commenced therapy within 12 months

Cohort	*Before treatment*	*During treatment*	*After cessation*
All (*n* = 544)	0.05 [0.03, 0.07]	0.02 [0.01, 0.03]	0.03 [0.02, 0.05]
Switch to new therapy (12 months)			
Low efficacy (*n* = 166)	0.04 [0.01, 0.07]	0.01 [0.00, 0.02]	0.05 [0.02, 0.08]
High efficacy (*n* = 378)	0.05 [0.03, 0.09]	0.03 [0.01, 0.05]	0.02 [0.01, 0.04]
Time to switch			
0-2 months (*n* = 322)	0.04 [0.02, 0.07]	0.02 [0.01, 0.03]	0.03 [0.01, 0.04]
2-4 months (*n* = 108)	0.07 [0.02, 0.16]	0.04 [0.01, 0.07]	0.04 [0.01, 0.10]
4-6 months (*n* = 48)	0.02 [0.00, 0.06]	0.02 [0.00, 0.06]	0.02 [0.00, 0.06]
6-8 months (*n* = 25)	0	0	0.08 [0.00, 0.20]
8-10 months (*n* = 19)	0.11 [0.00, 0.26]	0.05 [0.00, 0.16]	0.05 [0.00, 0.16]
10-12 months (*n* = 22)	0.14 [0.00, 0.36]	0	0.05 [0.00, 0.14]

Note: All values are given as annualised relapse rates (ARRs) with 95% CI in square brackets. ARRs were computed as the total number of relapses observed over the specific 12-month period divided by the number of patients. 'Switch to new therapy' shows the ARRs stratified by the efficacy of the new therapy commenced within 12 months of fingolimod cessation. 'Time to switch' shows the ARRs stratified by the time to commencement of any new therapy following fingolimod cessation.

Table S6. Predictors of relapse after fingolimod cessation (excluding pregnancy)

Term	*B [95% CI]*	*IRR [95% CI]*
Clinicodemographic		
Sex (male)	**-0.50 [-0.87, -0.16]**	**0.60 [0.42, 0.85]**
Age at cessation	**-0.04 [-0.06, -0.03]**	**0.96 [0.94, 0.97]**
Disease duration at cessation	0.02 [-0.01, 0.04]	1.02 [0.99, 1.04]
Treatment duration	0.02 [-0.08, 0.12]	1.02 [0.93, 1.13]
ARR year before cessation	**0.2 [0.04, 0.37]**	**1.23 [1.04, 1.44]**
EDSS before cessation	0 [-0.07, 0.08]	1.00 [0.93, 1.08]
Switch to new therapy (12 months)[a]		
Switched to no treatment	0.00 [-0.73, 0.73]	1.00 [0.48, 2.07]
Switched to low efficacy	0.45 [0.16, 0.73]	1.57 [1.18, 2.07]
Time to switch[b]		
Switched 2-4 months	**0.42 [0.06, 0.77]**	**1.52 [1.06, 2.15]**
Switched 4-6 months	**0.83 [0.38, 1.24]**	**2.28 [1.47, 3.47]**
Switched 6-8 months	**0.81 [0.28, 1.30]**	**2.25 [1.32, 3.67]**
Switched 8-10 months	**0.83 [0.23, 1.37]**	**2.29 [1.26, 3.93]**
Switched 10-12 months	0.51 [-0.24, 1.15]	1.66 [0.78, 3.16]
Switched 12+ months	-0.18 [-0.76, 0.34]	0.84 [0.47, 1.41]

Note: Parameters are from negative binomial model predicting relapse count in the first 12 months after cessation of fingolimod. B = raw coefficient. IRR = incidence rate ratio. [a] Switch to high efficacy treatment is used as the reference class. [b] 0-2 months is used as the reference class. Bold values indicate confidence intervals that do not capture the null hypothesis value.

Table S7. Predictors of relapse after fingolimod cessation (patients who started treatment in first 12 months)

Term	*B [95% CI]*	*IRR [95% CI]*
Clinicodemographic		
Sex (male)	**-0.42 [-0.80, -0.06]**	**0.66 [0.45, 0.94]**
Age at cessation	**-0.05 [-0.07, -0.03]**	**0.96 [0.94, 0.97]**
Disease duration at cessation	0.01 [-0.01, 0.04]	1.01 [0.99, 1.04]
Treatment duration	0.03 [-0.08, 0.13]	1.03 [0.92, 1.14]
ARR year before cessation	**0.19 [0.02, 0.36]**	**1.21 [1.02, 1.44]**
EDSS before cessation	0.00 [-0.08, 0.08]	1.00 [0.92, 1.08]
Pregnancy following cessation	0.22 [-0.3, 0.70]	1.24 [0.74, 2.01]
Switch to new therapy (12 months)[a]		
Switched to low efficacy	**0.34 [0.05, 0.62]**	**1.40 [1.05, 1.86]**
Time to switch[b]		
Switched 2-4 months	**0.47 [0.13, 0.81]**	**1.60 [1.13, 2.24]**
Switched 4-6 months	**0.83 [0.40, 1.24]**	**2.29 [1.49, 3.45]**
Switched 6-8 months	**0.83 [0.29, 1.33]**	**2.30 [1.33, 3.79]**
Switched 8-10 months	**0.78 [0.17, 1.33]**	**2.18 [1.19, 3.77]**
Switched 10-12 months	**0.65 [0.07, 1.19]**	**1.92 [1.07, 3.29]**

Note: Parameters are from negative binomial model predicting relapse count in the first 12 months after cessation of fingolimod. B = raw coefficient. IRR = incidence rate ratio. [a] Switch to high efficacy treatment is used as the reference class. [b] 0-2 months is used as the reference class. Bold values indicate confidence intervals that do not capture the null hypothesis value.

Table S8. Severe relapses

#	*Sex*	*Pregnancy*	*Age at commencement of fingolimod (years)*	*Disease duration at commencement (years)*	*Disease duration at cessation (years)*	*Cessation reason*	*Treatment duration*	*Next therapy*	*Time to next therapy (days)*	*Time to first relapse (days)*	*Time to first serious relapse (days)*	*Number serious relapses after fingolimod*
1	F	Yes	28	5.85	8.72	Pregnancy planning	2.86	Natalizumab	28	194	194	1
2	F	Yes	18	1.57	3.47	Pregnancy planning	2.32	Natalizumab	112	98	98[a]	2
3	M	N/A	25	2.69	3.93	Non-adherence	1.23	Tecfidera	151	70	70[a]	1
4	F	No	37	13.59	14.84	Unknown	1.25	Natalizumab	100	331	331	1
5	F	No	20	6.44	8.78	Lack of improvement	2.34	Natalizumab	43	250	250	1
6	F	No	55	36.66	38.78	Lack of improvement	2.12	Tecfidera	36	21	21[a]	1
7	F	No	44	2.80	7.53	Scheduled stop	4.73	Teriflunomide	19	200	200	1
8	F	No	32	2.79	5.64	Lack of tolerance	2.85	Tecfidera	5	52	52	1
9	F	Yes	27	6.21	10.02	Pregnancy confirmed	3.82	Fingolimod	288	65	133[a]	1
10	F	No	25	2.60	4.98	Pregnancy planning	2.38	Copaxone	36	203	251	1
11	F	No	24	2.72	5.56	Pregnancy planning	2.85	Rebif	5	94	150	1
12	F	No	26	1.91	5.91	Convenience	4.00	Natalizumab	58	14	14[a]	1
13	F	Yes	31	9.74	10.76	Pregnancy confirmed	1.02	Fingolimod	235	65	212[a]	1
14	F	Yes	25	8.20	9.92	Pregnancy planning	1.72	Copaxone	326	103	103[a]	1
15	F	No	39	8.63	10.39	Unknown	1.76	Rebif	196	189	189[a]	1
16	M	N/A	37	17.43	19.09	Unknown	1.63	Fingolimod	91	309	309	1

Note: Pregnancy = became pregnancy within 12 months after fingolimod cessation. [a] = severe relapse occurred prior to new treatment commencement.

Table S9. Predictors of relapse after fingolimod cessation separated by treatment status at time of relapse

	IRR [95% CI]	
Term	*ARR prior to recommencement of therapy*	*ARR after recommencement of therapy*
Clinicodemographic		
Sex (male)	0.83 [0.46, 1.40]	0.61 [0.37, 0.97]
Age at cessation	0.97 [0.94, 0.99]	0.95 [0.93, 0.97]
Disease duration at cessation	1.02 [0.98, 1.06]	1.01 [0.97, 1.04]
Treatment duration	1.07 [0.92, 1.24]	0.99 [0.86, 1.14]
ARR year before cessation	1.21 [0.91, 1.57]	**1.27 [1.01, 1.58]**
EDSS before cessation	0.90 [0.80, 1.01]	1.10 [0.99, 1.21]
Pregnancy following cessation	1.75 [1.00, 3.02]	1.18 [0.56, 2.31]
Switch to new therapy (12 months) [a]		
Switched to low efficacy	0.94 [0.59, 1.45]	**1.86 [1.27, 2.70]**
Time to switch[b]		
Switched 2-4 months	**6.18 [3.31, 12.09]**	0.92 [0.58, 1.42]
Switched 4-6 months	**10.81 [5.49, 21.94]**	0.99 [0.51, 1.78]
Switched 6-8 months	**12.47 [5.87, 26.49]**	0.79 [0.30, 1.74]
Switched 8-10 months	**11.88 [5.33, 26.25]**	0.46 [0.11, 1.30]
Switched 10-12 months	**12.60 [6.01, 26.97]**	#

Note: Parameters are from negative binomial model predicting relapse count in the first 12 months after cessation of fingolimod. IRR = incidence rate ratio. [a] Switch to high efficacy treatment is used as the reference class. Patients who did not switch to a new therapy within 12 months were excluded to allow model convergence. [b] 0-2 months is used as the reference class. # The parameter for 10-12 months had to be dropped from this analysis due to the absence of recorded relapses in this cell. Bold values indicate confidence intervals that do not capture the null hypothesis value.

Table S10. Comparison of included versus excluded patients.

Variable	Included patients (*n* = 685)	Excluded patients (*n* = 1,184)	Standardised effect size	All patients treated with fingolimod (*n* = 1,869)
Age at fingolimod cessation	39.56 (9.88)	42.49 (10.79)	0.28	41.41 (10.56)
Female – *n* (%)	539 (79%)	904 (76%)	0.03[a]	1443 (77%)
Disease duration at cessation	12.31 (7.23)	13.47 (7.75)	0.15	13.05 (7.59)
Treatment duration at cessation	2.51 (1.32)	3.11 (1.78)	0.37	2.89 (1.65)
No. relapses year prior to cessation	0.54 (0.42)	0.15 (0.45)	0.61	0.27 (0.59)
Last EDSS prior to cessation	3.05 (2.03)	3.53 (2.13)	0.23	3.21 (2.07)
Pregnancy within 12 months – *n* (%)	72 (11%)	32 (3%)	0.16 [a]	104 (6%)

Point and interval estimates are mean and standard deviation, unless specified otherwise. Standardised effect sizes are Cohen's *d*, except where indicated with [a], which are given as Cramer's V.

Table S11. Predictors of increase in EDSS score in the first year following fingolimod cessation

Term	*B [95% CIs]*	*OR [95% CIs]*
Clinicodemographic		
Sex (male)	0.20 [-0.42, 0.71]	1.20 [0.68, 2.07]
Age at cessation	**0.05 [0.01, 0.08]**	**1.05 [1.01, 1.08]**
Disease duration at cessation	0.02 [-0.02, 0.06]	1.02 [0.98, 1.07]
Treatment duration	-0.09 [-0.29, 0.10]	0.91 [0.73, 1.09]
ARR year before cessation	0.26 [-0.06, 0.56]	1.30 [0.93, 1.73]
ARR year after cessation	**0.77 [0.51, 1.07]**	**2.17 [1.64, 3.00]**
EDSS before cessation	**-0.46 [-0.63, -0.33]**	**0.63 [0.55, 0.72]**
Pregnancy following cessation	-0.33 [-1.15, 0.37]	0.69 [0.29, 1.40]
Switch to new therapy (12 months) [a]		
Switched to high efficacy	-0.08 [-1.34, 1.08]	0.90 [0.26, 2.68]
Switched to low efficacy	-0.38 [-1.72, 0.81]	0.67 [0.19, 2.11]
Time to switch[b]		
Switched 2-4 months	0.09 [-0.57, 0.69]	1.09 [0.57, 1.95]
Switched 4-6 months	0.25 [-0.67, 1.07]	1.23 [0.50, 2.60]
Switched 6-8 months	-1.35 [-16.38, 0.20]	0.24 [0.00, 1.22]
Switched 8-10 months	0.88 [-0.38, 2.02]	2.40 [0.56, 7.51]
Switched 10-12 months	-0.86 [-15.27, 0.38]	0.42 [0.00, 1.50]
Switched 12+ months	0.29 [-0.81, 1.20]	1.31 [0.41, 3.27]

Note: Parameters derived from logistic regression model predicting EDSS increase of at least 1 point following cessation of fingolimod. OR = odds ratio. [a] Switch to no new treatment is used as the reference class. [b] 0-2 months is used as the reference class. Bold values indicate confidence intervals that do not capture the null hypothesis value.