Supplement

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eTable 1: Data quality procedure

- Duplicate patient records were removed.
- Centres with <10 patient records were excluded.
- Patients with missing date of birth were excluded.
- MS onset dates after the MSBase data extract date were removed.
- Patients with missing date of the first clinical presentation of MS were excluded.
- The dates of MS onset and the first recorded MS course were aligned.
- Patients with the age at onset outside the 0-100 range were excluded.
- A logical sequence of the MS courses (e.g. clinically isolated syndrome, relapsing-remitting MS, secondary progressive MS) was assured.
- Entries with the initiation of progressive MS prior to its clinical onset of MS were excluded.
- Visits with missing visit date or the recorded date before the clinical MS onset or after the date of MSBase data extract were removed.
- EDSS scores outside the range of possible EDSS values were removed.
- Duplicate visits were merged.
- MS relapses with missing visit date or the recorded date after the date of MSBase data extract were removed.
- Duplicate MS relapses were merged.
- Relapses occurring within 30 days of each other were merged.
- Visits preceded by relapses were identified and time from the last relapse was calculated for each visit.
- Therapies were labelled as discontinued or continuing.
- Therapies with erroneous date entries were removed (e.g. commencement date > termination date, commencement after the MSBase data extract date, commencement of disease modifying therapy before the year 1980).
- MS disease modifying therapies were identified and labelled.
- Duplicate treatment entries were removed.

eTable 2: Patient disposition per centre and country

Patient disposition per centre

Centre	Patients, n
Charles University in Prague and General University Hospital	1643
OF-012	1360
GF Ingrassia	689
OF-009	635
Hospital Universitario Virgen Macarena	617
OF-014	616
CHUM MS Center and Universite de Montreal	610
Dokuz Eylul University	592
CISSS Chaudière-Appalache	454
OF-027	426
OF-039	384
OF-033	383
University G. d'Annunzio, Chieti, Italy	376
OF-036	342
Royal Melbourne Hospital	317
University of Florence	293
OF-018	293
Amiri Hospital	288
Box Hill Hospital	279
19 Mayis University	274
OF-031	264
OF-038	258
Neuro Rive-Sud	254
OF-030	253
Azienda Sanitaria Unica Regionale Marche - AV3	247
KTU Medical Faculty Farabi Hospital	247
University Newcastle	215
OF-003	210
OF-037	206
Centro Hospitalar Universitario de Sao Joao	200
CSSS Saint-Jérôme	187
University Hospital and University of Basel	170
Buffalo General Medical Center	169
OF-019	162
Isfahan University of Medical Sciences	146
American University of Beirut Medical Center	137
Zuyderland Ziekenhuis	135
Azienda Ospedaliera di Rilievo Nazionale San Giuseppe Moscati Avellino	133
Cliniques Universitaires Saint-Luc	129
OF-011	119
Haydarpasa Numune Training and Research Hospital	116
OF-022	112
Ospedali Riuniti di Salerno	111
OF-005	108
ASL3 Genovese	105
University of Queensland	95
Bakirkoy Education and Research Hospital for Psychiatric and Neurological Diseases	92
Garibaldi Hospital	89
OF-032	88
Flinders University	87
Hospital Universitario Donostia	87
OF-001	85
Nemocnice Jihlava	82
Hospital Universitario Virgen de Valme	82
Monash Medical Centre	81
OF-010	79

Austin Health	77
University Hospital Reina Sofia, Cordoba, Spain	67
OF-017	66
Centro Hospitalar Universitario de Sao Joao	66
Rehabilitation and MS-Centre Overpelt and Hasselt University	62
OF-021	60
The Alfred Hospital	59
Universitary Hospital Ghent	59
Hospital Germans Trias i Pujol	59
OF-015	58
Liverpool Hospital	57
Hospital Clinico San Carlos	57
Hospital de Galdakao-Usansolo	57
Brain and Mind Centre	55
OF-029	51
Westmead Hospital	49
Razi Hospital	48
University of Debrecen	45
Hospital Universitari MútuaTerrassa, Barcelona, Spain	43
OF-028	40
Groene Hart Ziekenhuis	37
Sultan Qaboos University Hospital, Al-Khodh, Oman	37
Aarhus University Hospital	35
OF-004	35
Universidade Metropolitana de Santos	32
OF-016	24
Hacettepe University	23
Hospital Fernandez	22
Hospital Clinic de Barcelona	21
OF-006	21
OF-020	21
Jewish General Hospital	20
Koc University	20
OF-035	19
Ospedale Civico Lugano, Lugano, Switzerland	18
Assaf Harofeh Medical Center	18
South East Trust	17
OF-008	17
OF-024	16
INEBA - Institute of Neuroscience Buenos Aires	13
Royal Brisbane and Women's Hospital	12
St. Michael's Hospital	12
King Fahad Specialist Hospital-Dammam	12
Royal Hobart Hospital	11
Hospital Universitario de la Ribera	11
Jahn Ferenc Teaching Hospital	11
OF-025	11
Centro Internacional de Restauracion Neurologica	9
OF-034	9
University of Western Australia	8
Centro de Esclerosis Múltiple de Buenos Aires (CEMBA)	7
Geneva University Hospital, Geneva, Switzerland	7
Hospital General Universitario de Alicante	7
University Hospital Nijmegen	7
OF-013	7
Szent Imre Hospital	6
AZ Alma Ziekenhuis	5
AHEPA University Hospital, Thessaloniki, Greece	5
St Vincent's University Hospital	5
OF-007	5
St Vincents Hospital, Fitzroy	4

Semmelweis University Budapest	4
Bombay Hospital Institute of Medical Sciences	4
Waikato Hospital, Hamilton, New Zealand	4
OF-023	4
Emergency Clinical County Hospital "Pius Brinzeu", Timisoara, Romania	4
Veszprém Megyei Csolnoky Ferenc Kórház zrt.	3
Clinic of Neurology Clinical Center	3
Francicus Ziekenhuis	3
Royal Hospital	3
Geelong Hospital	2
Ain Shams University	2
Royal Victoria Hospital	2
Christchurch Hospital	2
OF-026	2
New York University Langone Medical Center	2
Townsville Hospital	1
Concord Repatriation General Hospital	1

OFSEP centres anonymised as per the data extract.

Patient disposition per country

Country	**Patients, n**
Argentina	42
Australia	1410
Belgium	255
Brazil	32
Canada	1537
Switzerland	195
Cuba	9
Czech Republic	1725
Denmark	35
Egypt	2
Spain	1108
Great Britain	19
Greece	5
Hungary	69
Israel	18
Ireland	5
India	4
Iran	146
Italy	2043
Kuwait	288
Lebanon	137
Macedonia	3
Netherlands	182
New Zealand	6
France	6849
Oman	40
Portugal	266
Romania	4
Saudi Arabia	12
Tunisia	48
Turkey	7225
USA	171

eTable 3: Disposition of RRMS patients, stratified by registry

Source	MSBase	OFSEP
Patients (% female)	8757 (75.0)	5456 (77.2)
Discontinuation epochs, n	11180	6849
Age, y	39.5 (10.3)	40.2 (10.5)
Disease duration, y	10.6 (7.2)	11.4 (7.2)
Disability, EDSS step	2.5 (1.7)	2.6 (1.7)
Relapse rate in 12 months before cessation	0.6 (0.8)	0.6 (0.9)
Disease modifying therapy		
Mitoxantrone	151 (1.4)	64 (0.9)
Natalizumab	1410 (12.6)	1163 (17.0)
Fingolimod	928 (8.3)	376 (5.5)
Dimethyl fumarate	291 (2.6)	264 (3.9)
Teriflunomide	219 (2.0)	170 (2.5)
Interferon	6345 (56.8)	3640 (53.1)
Glatiramer acetate	1836 (16.4)	1172 (17.1)
Duration of discontinued therapy, y	3.91 (3.14)	3.92 (3.14)
Time to next treatment, days	156.02 (370.09)	180.69 (454.91)
Pre-baseline follow up, y	5.82 (4.17)	6.43 (4.59)
Nr of previous DMTs	0.70 (1.01)	0.90 (1.15)
Postbaseline follow-up, y	5.33 (3.55)	5.94 (4.02)
Visit density	2.3 (1.43)	1.8 (1.15)

Note:
Values are presented as mean (standard deviation)

eTable 4: Characteristics of remitting-relapsing multiple sclerosis patients who were excluded from the analysis

	Excluded patients	**Included patients**
Source	**n**	**n**
Patients, n (% female)	35330 (72)	14213 (75.8)
Treatment epochs, n	70105	18029
Registry, n (%)		
MSBase	45343 (64)	11180 (62)
OFSEP	24762 (35)	6849 (38)
Age, years	43 (11.6)	40 (10.4)
MS duration, years	11.1 [6.2, 18]	9.3 [5.4, 14.7]
Disability, EDSS step	2.5 [1.5, 4.5]	2.0 [1.5, 4.0]
Discontinued therapy, n (%)		
Alemtuzumab	219 (0.31)	-
Mitoxantrone	2138 (3.0)	215 (1.2)
Natalizumab	6295 (9.0)	2573 (14.3)
Ocrelizumab	1093 (1.6)	-
Rituximab	1011 (1.4)	-
Cladribine	397 (0.6)	-
Fingolimod	7142 (10.2)	1304 (7.2)
Daclizumab	47 (0.07)	-
Dimethyl fumarate	3969 (5.7)	555 (3.1)
Teriflunomide	3120 (4.5)	389 (2.2)
Glatiramer acetate	10991 (15.7)	3008 (16.7)
Interferon beta-1a intramuscular	12318 (17.8)	
Interferon beta-1b	9180 (13.1)	9885 (55.4)
Pegylated interferon beta-1a	640 (0.9)	
Interferon beta-1a subcutaneous	11521 (16.4)	
Time to next treatment, days	30 [1, 139]	30 [1, 121]
Duration of discontinued therapy, years	2.6 [0, 5.5]	2.8 [1.7, 5.0]

Note:
Values are presented as mean (standard deviation) or median [quartiles] unless otherwise stated.
Patients in the excluded group are those with relapsing-remitting multiple sclerosis who ever discontinued a disease-modifying therapy but were excluded from the analysis based on insufficient treatment duration or inadequate follow-up.

Baseline characteristics of the excluded patients are reported at the visit closest to the date of treatment discontinuation.

eTable 5: Predictors of disability accumulation after cessation of therapy

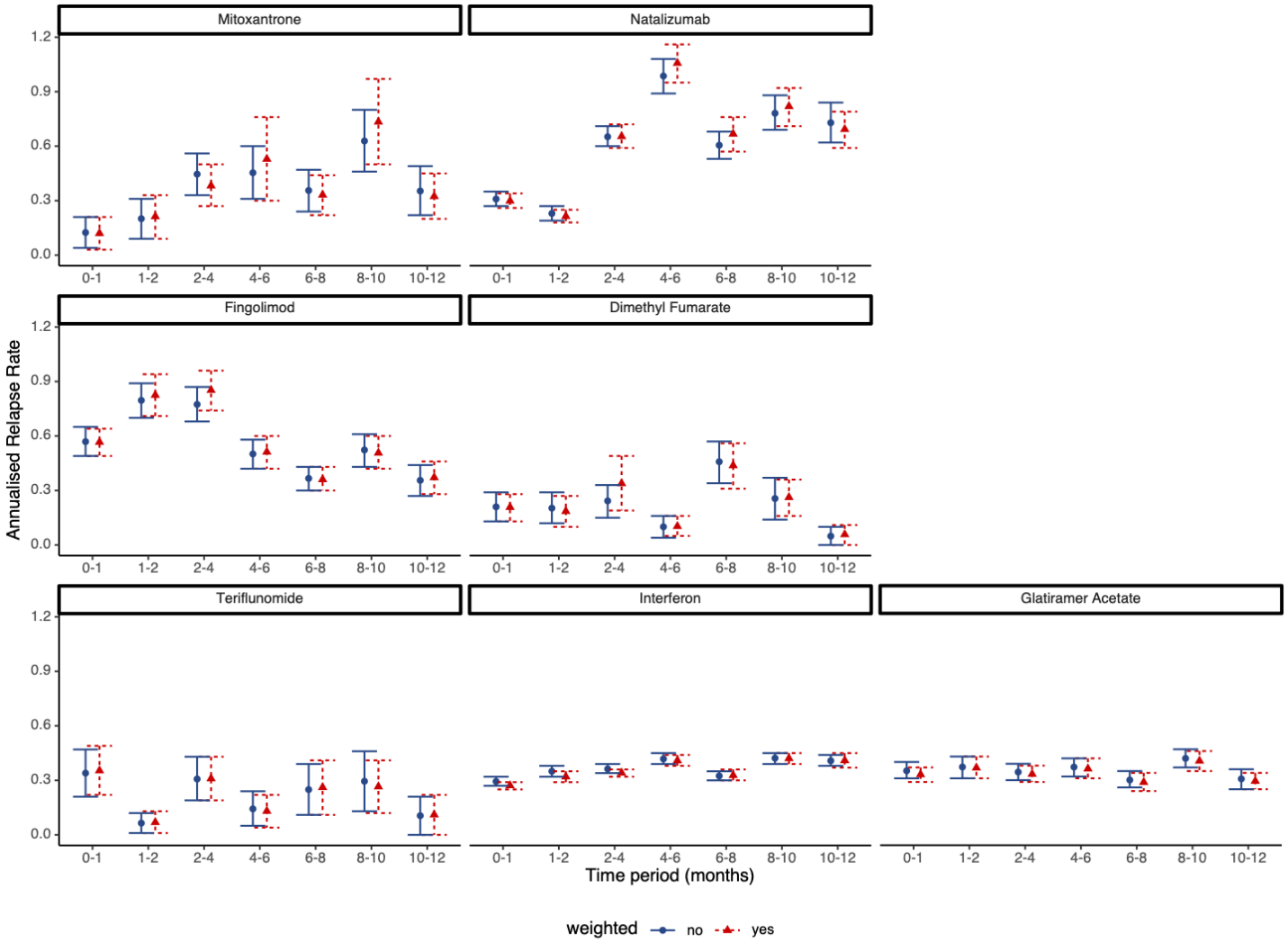
	First disability accumulation event	First disability accumulation event independent of relapse activity	First relapse associated disability accumulation event
Term		**HR (95% CI, p-value)**	
Therapy			
Interferon		Reference	
Mitoxantrone	1.12 (0.81-1.55, p=0.500)	0.95 (0.65-1.39, p=0.798)	1.06 (0.64-1.74, p=0.833)
Natalizumab	**2.06 (1.81-2.34, p<0.001)**	**1.63 (1.40-1.89, p<0.001)**	**2.77 (2.27-3.38, p<0.001)**
Fingolimod	**2.01 (1.67-2.43, p<0.001)**	**1.70 (1.36-2.12, p<0.001)**	**2.16 (1.59-2.95, p<0.001)**
Dimethyl fumarate	1.33 (0.97-1.81, p=0.079)	1.32 (0.92-1.89, p=0.135)	1.07 (0.60-1.91, p=0.808)
Teriflunomide	1.08 (0.74-1.57, p=0.699)	1.28 (0.85-1.92, p=0.237)	0.41 (0.14-1.15, p=0.090)
Glatiramer acetate	**1.17 (1.04-1.32, p=0.007)**	**1.16 (1.02-1.33, p=0.028)**	1.10 (0.91-1.33, p=0.316)
Age at cessation	**1.03 (1.02-1.03, p<0.001)**	**1.03 (1.03-1.04, p<0.001)**	1.01 (1.00-1.02, p=0.132)
Sex (male)	**1.32 (1.18-1.47, p<0.001)**	**1.39 (1.23-1.58, p<0.001)**	**1.23 (1.03-1.46, p=0.021)**
MS duration at cessation	**1.01 (1.00-1.02, p=0.004)**	**1.01 (1.00-1.02, p=0.002)**	1.00 (0.99-1.02, p=0.657)
EDSS at cessation	**0.95 (0.93-0.98, p=0.001)**	1.02 (0.99-1.05, p=0.274)	**0.88 (0.84-0.92, p<0.001)**
Number of relapses in prior 12 mo	0.98 (0.93-1.03, p=0.346)	**0.92 (0.87-0.98, p=0.009)**	**1.10 (1.02-1.19, p=0.013)**
Commencement of subsequent therapy	**0.73 (0.65-0.80, p<0.001)**	**0.73 (0.65-0.83, p<0.001)**	**0.73 (0.62-0.85, p<0.001**
Year at cessation	**0.98 (0.97-0.99, p=0.001)**	1.00 (0.99-1.02, p=0.592)	**0.95 (0.93-0.97, p<0.001)**

eTable 6: Time from treatment discontinuation to the point when the proportion of patients who experienced relapse was same as during year 2 pre-baseline.

	Proportion of treated patients who relapse in year-2	**Time from baseline to the point when proportion of patients with relapses equals the proportion of patients with relapses during year-2 pre-baseline, days (CI)**	**1st quartile survival time (i.e. time until 25% of patients experienced a relapse), days (CI)**
		Days, median (95% CI)	
Mitoxantrone	0.26	309 (248-513)	304 (240-496)
Natalizumab	0.17	147 (137-168)	211 (182-244)
Fingolimod	0.23	145 (120-211)	185 (134-270)
Dimethyl fumarate	0.14	231 (207-416)	564 (373-873)
Teriflunomide	0.18	375 (204-)	649 (297-)*
Glatiramer acetate	0.26	395 (335-473)	375 (320-458)
Interferon	0.28	372 (345-415)	305 (305-357)

*Insufficient numbers to calculate upper bounds of CI

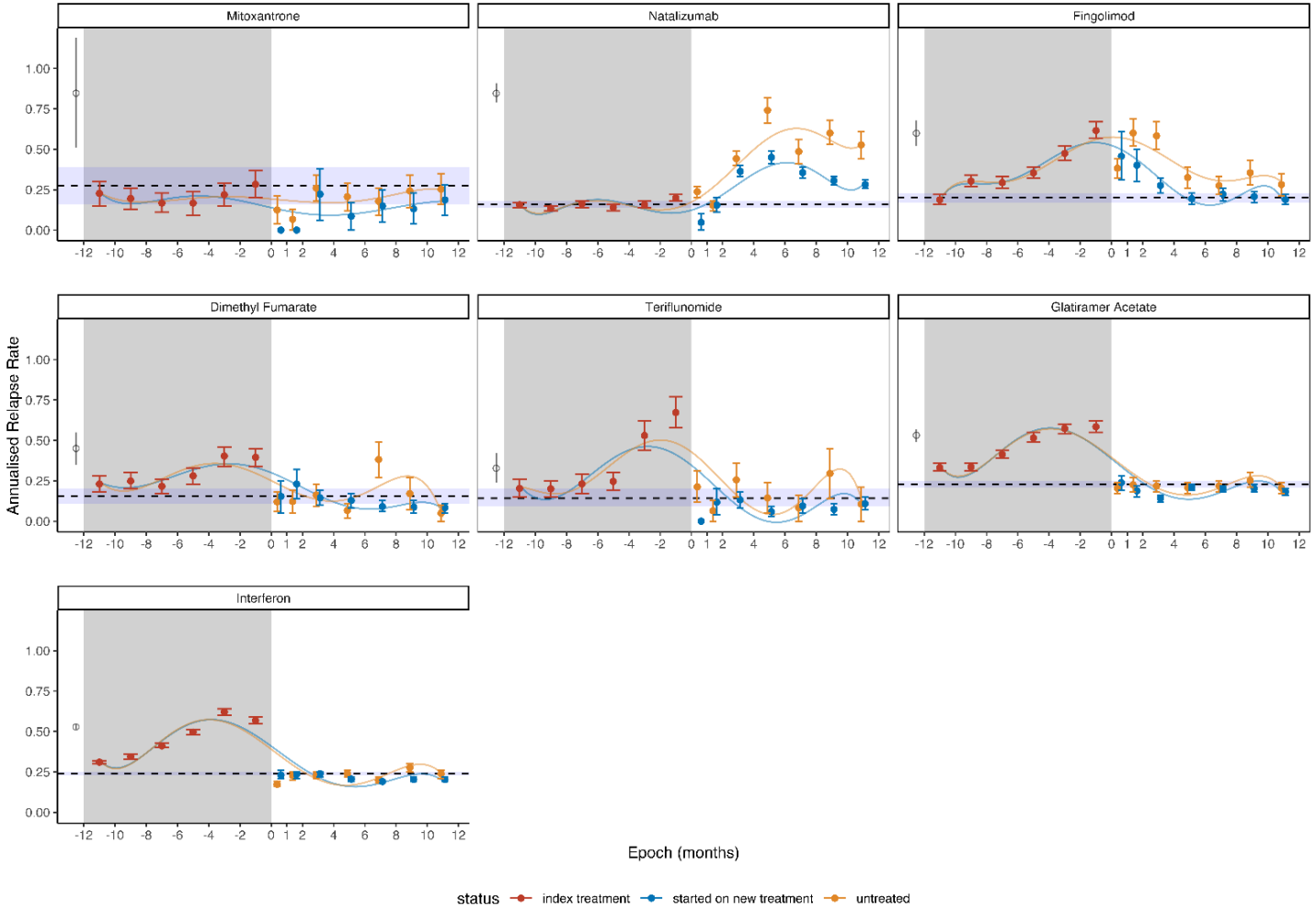
eFigure 1: Annualised relapse rate after treatment cessation in untreated patients: weighted, and unweighted, for the factors which determine start of a subsequent therapy



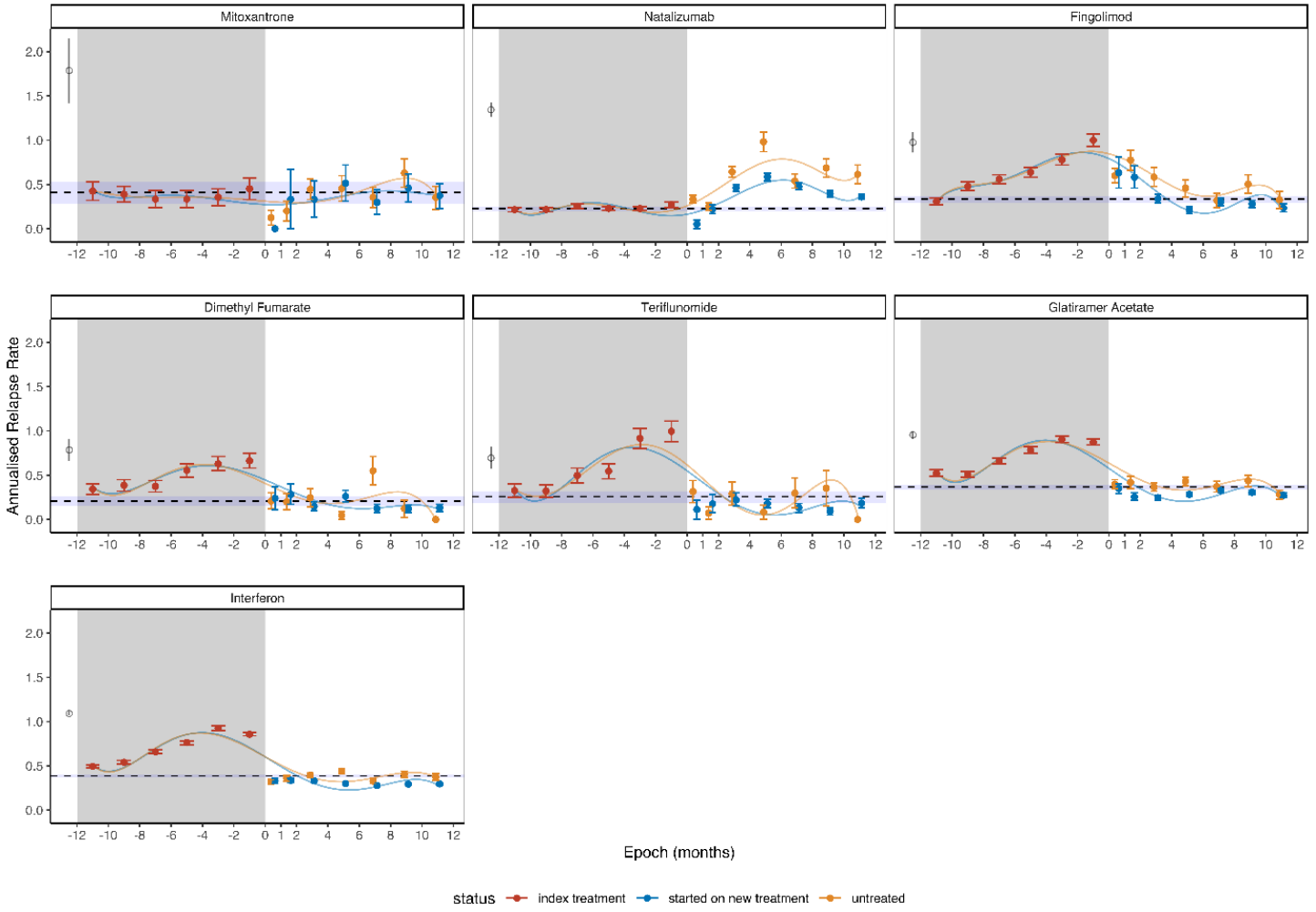
Baseline (treatment cessation) is indicated by timepoint 0, and represents the date of last treatment dose. Only includes patients who have not started a subsequent therapy.

eFigure 2:

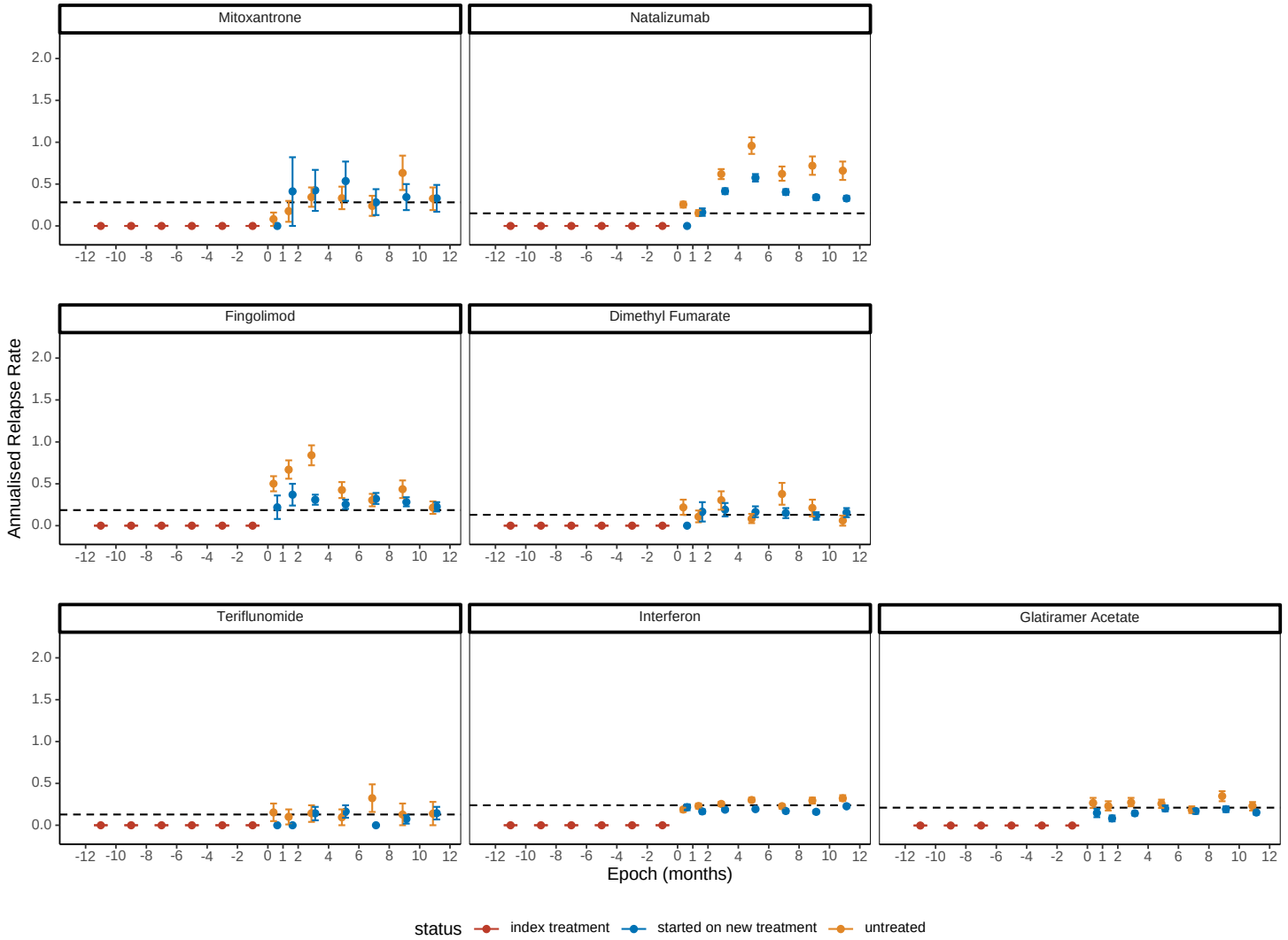
A: Annualised relapse rate in the 12 months before (during index treatment) and after treatment cessation in patients with a more stringent definition of relapses.



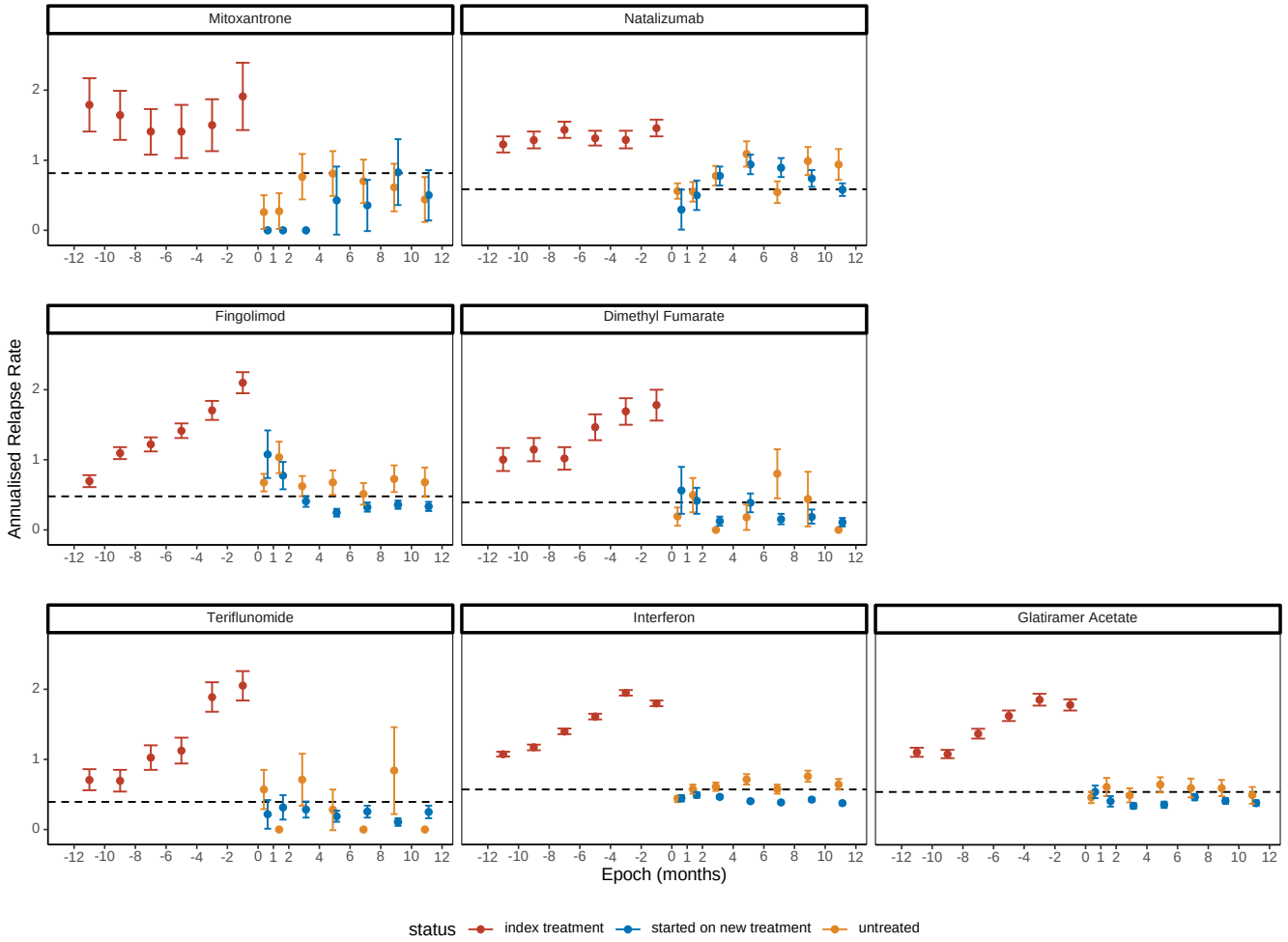
B: Annualised relapse rate in the 12 months before (during index treatment) and after treatment cessation (exclusion of patients who stopped treatment due to pregnancy or pregnancy planning).


Mitoxantrone
Natalizumab
Fingolimod
Dimethyl Fumarate
Teriflunomide
Glatiramer Acetate
Interferon
Annualised Relapse Rate
Epoch (months)
status
index treatment
started on new treatment
untreated

C: Annualised relapse rate in the 12 months before (during index treatment) and after treatment cessation in patients **without** relapses in the year before baseline.

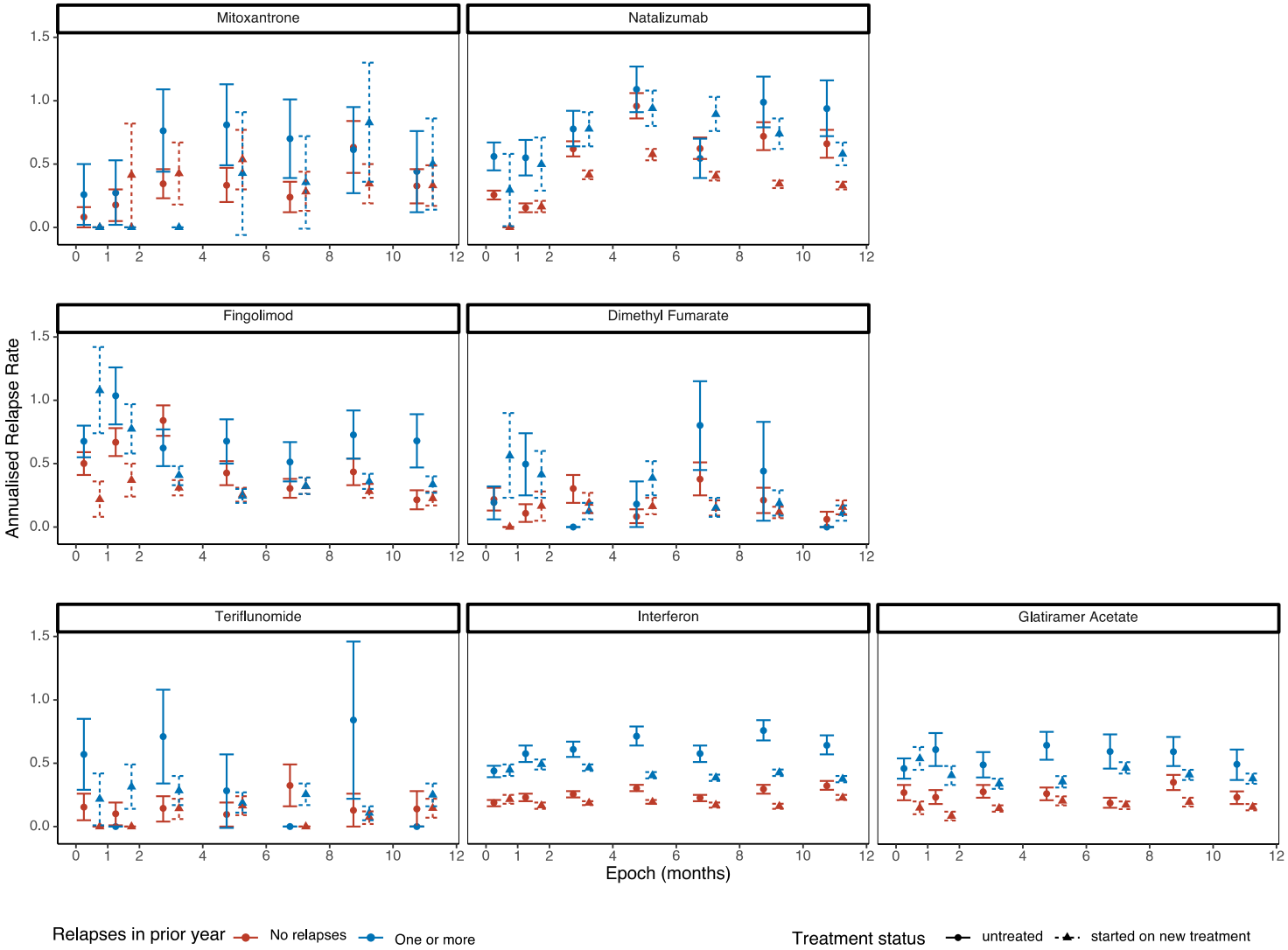


D: Annualised relapse rate in the 12 months before (during index treatment) and after treatment cessation in patients **with** relapses in the year before baseline.



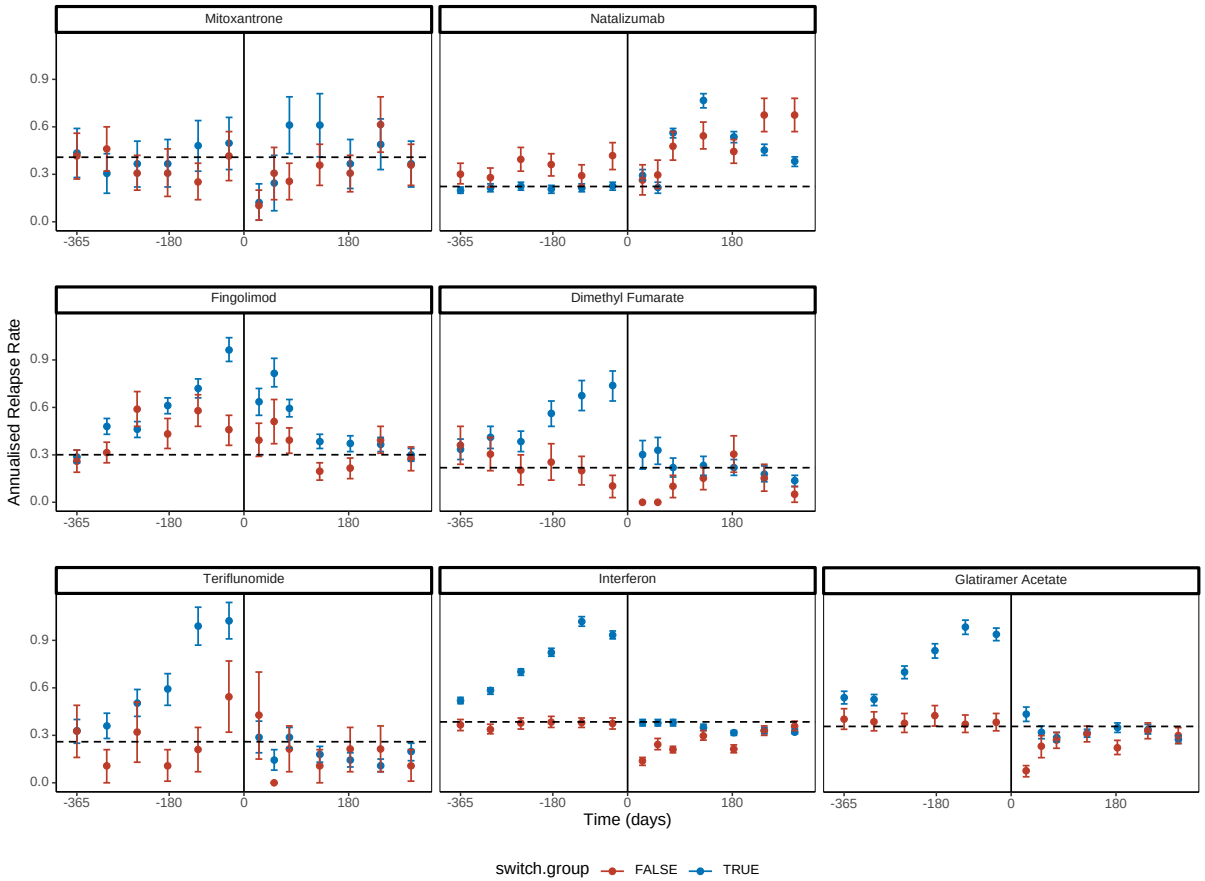
Baseline (treatment cessation) is indicated by timepoint 0, and represents the date of last treatment dose. The period after treatment cessation is stratified by patients who remain untreated, or have started a new treatment. The pre-treatment relapse rate, and 95% confidence interval, is indicated by the open circle and line. The on-treatment period is indicated by the grey shaded area. Point and whiskers show the relapse rates in each epoch. The black dashed line shows the mean relapse rate during the second year prior to treatment cessation, with the shaded area indicating 95% confidence intervals.

eFigure 3: Post-baseline relapse rates stratified by presence of relapses in the year before baseline



Baseline (treatment cessation) is indicated by timepoint 0, and represents the date of last treatment dose. The period after treatment cessation is stratified by (i) the presence of relapses in the year before baseline; (ii) patients who remain untreated, or have started a new treatment, in each time period.

eFigure 4: Visualisation of relapse trends in patients who will, and will not, commence another treatment within the first year after treatment discontinuation



The reader should refrain from comparing between these two groups for the following reasons:

1. Patients were categorized based on treatment decisions within an artificial cut-off of 1 year. This introduced conditioning on the future outcome.
2. The intention to switch/remain untreated more than 12 months after treatment discontinuation is inferred, as this data is not explicitly recorded. The categorization of patients at baseline into either group is therefore based on a future event (switching/remaining untreated). This introduces treatment indication bias, as the 'switch' group includes patients in whom the intent to remain untreated changed over the first year based on disease activity

3. Separating patients by future treatment decisions precludes differentiation of relapse activity before and after subsequent treatment commencement in the ‘switch’ group (ie – relapse rates in each time period would include patient who are still untreated, and patients who have started a new treatment)