Article:
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Supplementary Appendix

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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.
- Where multiple disease modifying therapies were recorded simultaneously, treatment end date of the previous therapy was imputed as the commencement date of the following therapy.
- Consecutive entries for certain disease modifying therapies were merged into a continuous treatment entry, given that the gap between the entries did not exceed 190 days for mitoxantrone, 365 days for cladribine, 90 days for other disease modifying therapies.
- The default duration of treatment effect was recorded as 190 days (mitoxantrone), 5 years (alemtuzumab) or 365 days (cladribine) from treatment commencement.

eTable 2
Summary of the study protocol (target trial)

Protocol component	Description
inclusion criteria	relapsing-remitting multiple sclerosis or clinically isolated syndrome
treatment strategies	AHSCT or fingolimod or ocrelizumab or natalizumab (secondary analysis: B-cell depleting therapies ocrelizumab and rituximab)
assignment procedures	non-random assignation of therapy by treating neurologists propensity score matching (1:10 variable matching ratio) with pairwise censoring
follow-up period	treatment persistence ≥3 months, ≥2 disability scores with ≥1 score recorded while on study therapy
outcomes	primary: annualised relapse rate secondary: cumulative hazard of relapses patients free from relapses cumulative hazard of 6-month confirmed disability worsening patients free from 6-month confirmed disability worsening cumulative hazard of 6-month confirmed disability improvement patients free from 6-month confirmed disability improvement
causal contrast of interest	per-protocol effect
analysis	weighted negative binomial model with cluster effect for matched patient pairs and adjusted for visit frequency weighted proportional hazards models of single event or multiple events (with robust estimation of variance)

eTable 3
Patient disposition per centre

Centre	Patients
Ottawa Hospital Research Institute, Ottawa, Canada	36
Sheffield Teaching Hospitals, Sheffield, UK	35
Uppsala University Hospital, Uppsala, Sweden	26
St Vincent's Hospital Sydney, Sydney, Australia	25
Charles University in Prague and General University Hospital, Prague, Czech Republic	430
Austin Health, Melbourne, Australia	70
The Royal Melbourne Hospital Neuroimmunology Centre, Melbourne, Australia	183
The Alfred Hospital, Melbourne, Australia	143
University of Queensland, Brisbane, Australia	52
Rehabilitation and MS-Centre Overpelt and Hasselt University, Hasselt, Belgium	51
Box Hill Hospital, Melbourne, Australia	204
University Newcastle, Newcastle, Australia	77
Antwerp University Hospital, Edegem, Belgium	25
Brain and Mind Centre, Sydney, Australia	51
Azienda Sanitaria Unica Regionale Marche - AV3, Macerata, Italy	26
Ospedali Riuniti di Salerno, Salerno, Italy	13
Royal Brisbane and Women's Hospital, Brisbane, Australia	8
Dokuz Eylul University, Konak/Izmir, Turkey	346
Amiri Hospital, Sharq, Kuwait	243
Hospital Universitario Virgen Macarena, Sevilla, Spain	214
KTU Medical Faculty Farabi Hospital, Trabzon, Turkey	177
University Hospital and University of Basel, Basel, Switzerland	170

GF Ingrassia, Catania, Italy	146
19 Mayis University, Samsun, Turkey	129
CHUM MS Center and Universite de Montreal, Montreal, Canada	117
CISSS Chaudière-Appalache, Levis, Canada	106
University G. d'Annunzio, Chieti, Italy	106
American University of Beirut Medical Center, Beirut, Lebanon	73
Bakirkoy Education & Research Hospital for Psychiatric & Neurological Diseases, Istanbul, Turkey	71
Flinders University, Adelaide, Australia	70
CSSS Saint-Jérôme, Saint-Jerome, Canada	69
Haydarpasa Numune Training and Research Hospital, Istanbul, Turkey	56
Liverpool Hospital, Sydney, Australia	49
Monash Medical Centre, Melbourne, Australia	48
Neuro Rive-Sud, Quebec, Canada	47
Isfahan University of Medical Sciences, Isfahan, Iran	47
Garibaldi Hospital, Catania, Italy	47
Centro Hospitalar Universitario de Sao Joao, Porto, Portugal	46
Cliniques Universitaires Saint-Luc, Brussels, Belgium	44
Zuyderland Medical Center, Sittard-Geleen, Netherlands	41
Universitary Hospital Ghent, Ghent, Belgium	40
Hacettepe University, Ankara, Turkey	40
Hospital Germans Trias i Pujol, Badalona, Spain	38
Azienda Ospedaliera di Rilievo Nazionale San Giuseppe Moscati Avellino, Avellino, Italy	37
University of Debrecen, Debrecen, Hungary	36
University of Florence, Florence, Italy	32
ASL3 Genovese, Genova, Italy	31
Razi Hospital, Manouba, Tunisia	31
Hospital Universitario Donostia, San Sebastián, Spain	28
Westmead Hospital, Sydney, Australia	25
Hospital de Galdakao-Usansolo, Galdakao, Spain	25
University Hospital Reina Sofia, Cordoba, Spain	25
Hospital Clinic de Barcelona, Barcelona, Spain	24
Sultan Qaboos University Hospital, Al-Khodh, Oman	24
Buffalo General Medical Center, Buffalo, United States	21
Royal Hobart Hospital, Hobart, Australia	20
Universidade Metropolitana de Santos, Santos, Brazil	20
Hospital Universitario Virgen de Valme, Seville, Spain	18
Groene Hart Ziekenhuis, Gouda, Netherlands	18
University of Western Australia, Nedlands, Australia	16
Ospedale Civico Lugano, Lugano, Switzerland	16
Aarhus University Hospital, Arhus C, Denmark	14
Jahn Ferenc Teaching Hospital, Budapest, Hungary	13
Geneva University Hospital, Geneva, Switzerland	12
Hospital Universitari MútuaTerrassa, Barcelona, Spain	11
Nemocnice Jihlava, Jihlava, Czech Republic	10
Hospital Clinico San Carlos, Madrid, Spain	9
Centro Hospitalar Universitario de Sao Joao, Porto, Portugal	9
Jewish General Hospital, Montreal, Canada	8
Semmelweis University Budapest, Budapest, Hungary	8
University Hospital Nijmegen, Nijmegen, Netherlands	8
Szent Imre Hospital, Budapest, Hungary	7
King Fahad Specialist Hospital-Dammam, Khobar, Saudi Arabia	7
University of Szeged, Szeged, Hungary	6
Hospital Universitario de la Ribera, Alzira, Spain	5
South Eastern HSC Trust, Belfast, United Kingdom	5
Townsville Hospital, Townsville, Australia	4
St. Michael's Hospital, Toronto, Canada	4
AHEPA University Hospital, Thessaloniki, Greece	4
Veszprém Megyei Csolnoky Ferenc Kórház zrt., Veszprem, Hungary	4
Royal Hospital, Muscat, Oman	4
INEBA - Institute of Neuroscience Buenos Aires, Buenos Aires, Argentina	3
Geelong Hospital, Geelong, Australia	3
AZ Alma Ziekenhuis, Sijsele - Damme, Belgium	3

Hospital General Universitario de Alicante, Alicante, Spain	3
Péterfy Sandor Hospital, Budapest, Hungary	3
Christchurch Hospital, Christchurch, New Zealand	3
Koc University, Istanbul, Turkey	3
Centro de Esclerosis Múltiple de Buenos Aires (CEMBA), Buenos Aires, Argentina	2
Sanatorio Allende, Cordoba, Argentina	2
St Vincents Hospital, Fitzroy, Melbourne, Australia	2
Concord Repatriation General Hospital, Sydney, Australia	2
AU-043, Australia	2
Royal Victoria Hospital, Belfast, United Kingdom	2
BAZ County Hospital, Miskolc, Hungary	2
St Vincent's University Hospital, Dublin, Ireland	2
Hospital Fernandez, Capital Federal, Argentina	1
Macquarie University Hospital, Sydney, Australia	1
Waikato Hospital, Hamilton, New Zealand	1
Emergency Clinical County Hospital \Pius Brinzeu\"	1
New York University Langone Medical Center, New York, United States	1

eTable 4
Characteristics of the included unmatched patients at baseline

	AHSCT	fingolimod	ocrelizumab	natalizumab
patients included	167	2558	700	1490
sex, M (%)	54 (32.3)	714 (27.9)	232 (33.1)	398 (26.7)
age (mean (SD))	35.0 (8.8)	38.4 (10.0)	41.8 (11.2)	36.8 (9.8)
MS duration, y (mean (SD))	7.88 (5.43)	9.56 (7.17)	10.89 (7.79)	8.74 (6.92)
relapses in prior 12 months (mean (SD))	0.77 (0.99)	0.75 (0.84)	0.52 (0.76)	1.26 (1.06)
relapses in prior 24 months (mean (SD))	1.07 (1.29)	1.17 (1.17)	0.87 (1.07)	1.93 (1.49)
baseline EDSS (mean (SD))	4.01 (1.73)	2.35 (1.61)	3.03 (1.89)	2.91 (1.75)
top pre-baseline DMT (%)				
low-efficacy	23(13.8)	991 (38.7)	120 (17.1)	603 (40.5)
medium-efficacy	12 (7.2)	63 (2.5)	176 (25.1)	156 (10.5)
high-efficacy	24 (14.4)	303 (11.8)	174 (24.9)	31 (2.1)
unknown	108 (64.7)	1201 (47.0)	230 (32.9)	700 (47.0)
Postbaseline follow-up, years (mean (SD))	4.07 (2.61)	2.80 (2.24)	1.64 (0.98)	2.50 (2.14)
region (%)				
Europe	82 (49.1)	1017 (39.8)	132 (18.9)	777 (52.1)
Middle East and Africa	0 (0.0)	826 (32.3)	228 (32.6)	219 (14.7)
North America	35 (21.0)	240 (9.4)	58 (8.3)	108 (7.2)
Asia-Pacific	50 (29.9)	461 (18.0)	282 (40.3)	371 (24.9)
South America	0 (0.0)	14 (0.5)	0 (0.0)	15 (1.0)
visit interval, months (mean (SD))	2.6 (6.0)	6.6 (9.8)	3.6 (3.5)	10.7 (17.3)

SD, standard deviation; DMT, disease modifying therapy
low-efficacy therapies: interferons β, glatiramer acetate, teriflunomide
medium-efficacy therapies: dimethyl fumarate, fingolimod, daclizumab, cladribine
high-efficacy therapies: natalizumab, alemtuzumab, ocrelizumab, rituximab. mitoxantrone

eTable 5
Logistic regression models used to estimate the propensity scores

AHSCT (reference) vs. fingolimod

	Coefficient	Std. Error	t	Pr(>|t|)	
(Intercept)	0.43067	0.40870	1.054	0.29209	
sex [male]	-0.08138	0.16631	-0.489	0.62466	
age	0.09619	0.01010	9.522	< 2e-16	***
baseline disability, EDSS	-0.76257	0.05124	-14.883	< 2e-16	***
relapses, previous 12 months	-0.25996	0.15271	-1.702	0.08881	.
relapses, previous 24 months	0.32227	0.11905	2.707	0.00683	**
disease duration	0.04752	0.01475	3.223	0.00129	**
the most active previous therapy	(reference: high-efficacy)				
low-efficacy	0.60609	0.29305	2.068	0.03871	*
medium-efficacy	-1.06055	0.38149	-2.780	0.00547	**
unknown	-0.48155	0.22383	-2.151	0.03153	*
region (reference: Asia-Pacific)					
Europe	0.78095	0.18548	4.210	2.63e-05	***
Middle East and Africa	18.63036	464.22888	0.040	0.96799	
North America	-0.10731	0.23330	-0.460	0.64557	
South America	17.59444	3841.58404	0.005	0.99635	

AHSCT (reference) vs. natalizumab

	Coefficient	Std. Error	t	Pr(>|t|)	
(Intercept)	-1.25430	0.48612	-2.580	0.009960	**
sex [male]	0.01002	0.18285	0.055	0.956294	
age	0.05171	0.01075	4.812	1.63e-06	***
baseline disability, EDSS	-0.44617	0.05062	-8.814	< 2e-16	***
relapses, previous 12 months	-0.07155	0.16893	-0.424	0.671953	
relapses, previous 24 months	0.57310	0.13167	4.353	1.43e-05	***
disease duration	0.04288	0.01578	2.718	0.006637	**
the most active previous therapy	(reference: high-efficacy)				
low-efficacy	2.79889	0.35961	7.783	1.24e-14	***
medium-efficacy	2.07821	0.40785	5.096	3.88e-07	***
unknown	1.75696	0.29889	5.878	5.01e-09	***
region (reference: Asia-Pacific)					
Europe	0.09309	0.19878	0.468	0.639609	
Middle East and Africa	17.37428	614.86489	0.028	0.977461	
North America	-0.92456	0.25547	-3.619	0.000305	***
South America	16.84731	2369.15464	0.007	0.994327	

AHSCT (reference) vs. ocrelizumab

	Coefficient	Std. Error	t	Pr(>|t|)	
(Intercept)	0.81743	0.48919	1.671	0.0951	.
sex [male]	-0.09207	0.21133	-0.436	0.6632	
age	0.09447	0.01223	7.726	3.12e-14	***
baseline disability, EDSS	-0.66487	0.06560	-10.136	< 2e-16	***
relapses, previous 12 months	-0.45783	0.19173	-2.388	0.0172	*
relapses, previous 24 months	0.18402	0.14820	1.242	0.2147	
disease duration	0.01249	0.01711	0.730	0.4657	
the most active previous therapy	(reference: high-efficacy)				
low-efficacy	-0.49302	0.36650	-1.345	0.1789	
medium-efficacy	0.68632	0.37390	1.836	0.0668	.
unknown	-1.12312	0.26533	-4.233	2.56e-05	***
region (reference: Asia-Pacific)					
Europe	-1.00692	0.22014	-4.574	5.49e-06	***
Middle East and Africa	18.13326	553.43475	0.033	0.9739	
North America	-1.25794	0.29350	-4.286	2.03e-05	***

eTable 6
Power analysis

	AHSCT vs. fingolimod	AHSCT vs. natalizumab	AHSCT vs. ocrelizumab
Annualised relapse rate	-	-	0.17
Relapse (difference in cumulative hazards)	-	-	62%
Disability worsening (difference in cumulative hazards)	50%	19%	69%
Disability improvement (difference in cumulative hazards)	-	-	54%

The table presents minimum detectable differences between the compared groups, estimated with 200 simulations per comparison and outcome at α=0.05 and 1-β=0.80. The power estimates were only calculated for analyses that did not find evidence of difference between groups.

eTable 7
Serious adverse events reported after AHSCT

serious adverse event	number of events
Infections	
Epstein-Barr virus	11
cytomegalovirus	11
herpes simplex or zoster	8
influenza	2
other viral infection	2
Bacterial infection	6
upper respiratory tract infection	3
lower respiratory tract infection	2
urinary tract infection	2
sepsis	2
Haematological	
thrombosis	3
thrombocytopenia	2
Gastrointestinal	
liver toxicity	1
colitis	1
Mallory-Weiss syndrome	1
Endocrinological	
hypothyroidism	1
ovarian failure	1
Fever of unknown aetiology	2
Lymphadenopathy	1
Arthralgia	1
Acute kidney injury	1
Atrial fibrillation	1
Other	13