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Table S1:
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The following collaborators contributed to the administration of the MSBase cohort study:

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From Rodanotech, Geneva, Switzerland; Mr Samir Mechati, Mr Matthieu Corageoud, Mr Alexandre Bulla.

Table S2:

Patients included per MSBase centre

Centre	City	Country	Patients
General University Hospital	Praha	Czech Republic	624
University of Bari	Bari	Italy	373
Hospital Universitario Virgen Macarena	Sevilla	Spain	304
CHUM - Hopital Notre Dame	Montreal	Canada	269
Ospedale Clinizzato (Ss. Annunziata)	Chieti	Italy	264
Centre de Réadaptation déficience Physique Chaudière-Appalache	Levis	Canada	209
Zuyderland Ziekenhuis	Sittard	Netherlands	102
Neuro Rive-Sud	Quebec	Canada	92
Nuovo Ospedale Civile Sant'Agostino/Estense	Modena	Italy	83
ASUR Marche - AV 3	Macerata	Italy	79
National Neurological Institute C. Mondino	Pavia	Italy	75
Hospital Universitario La Paz	Madrid	Spain	69
Cliniques Universitaires Saint-Luc	Brussels	Belgium	68
Royal Melbourne Hospital	Melbourne	Australia	65
Box Hill Hospital	Melbourne	Australia	61
University Hospital Nijmegen	Nijmegen	Netherlands	60
Centro Internacional de Restauracion Neurologica	Havana	Cuba	51
Hospital Germans Trias i Pujol	Badalona	Spain	49
AORN San Giuseppe Moscati Avellino	Avellino	Italy	41
Kommunehospitalet	Aarhus C	Denmark	40
Hospital Universitario Virgen de Valme	Sevilla	Spain	35
Ospedali Riuniti di Salerno	Salerno	Italy	35
Hospital São João	Porto	Portugal	32
Farabi Hospital	Trabzon	Turkey	32
Ospedale di Parma	Parma	Italy	31
John Hunter Hospital	Newcastle	Australia	28
Hospital Donostia	Donostia	Spain	21
Groene Hart Ziekenhuis	Gouda	Netherlands	21
Jahn Ferenc Teaching Hospital	Budapest	Hungary	19
19 Mayis University	Samsun	Turkey	17
Flinders Medical Centre	Adelaide	Australia	16
Hospital Italiano de Buenos Aires	Buenos Aires	Argentina	13
Liverpool Hospital	Sydney	Australia	13
Assaf Harofeh Medical Center	Beer-Yaakov	Israel	13
University of Florence	Florence	Italy	12
Hospital Fernández	Buenos Aires	Argentina	10
Hospital de Galdakao-Usansolo	Galdakao	Spain	9
Jewish General Hospital	Montreal	Canada	8
INEBA	Buenos Aires	Argentina	6
St Vincent’s Hospital	Melbourne	Australia	6
Westmead Hospital	Sydney	Australia	5
Royal Brisbane and Women's Hospital	Brisbane	Australia	5
Hôpital régional de Saint-Jérôme	Saint-Jérôme	Canada	5
Al-Zahra Hospital	Isfahan	Iran	5
Amiri Hospital	Kuwait City	Kuwait	5
Brain and Mind Research Institute	Camperdown	Australia	4
Craigavon Area Hospital	Craigavon	Northern Ireland	4
Royal Hobart Hospital	Hobart	Australia	3
Nemocnice Jihlava	Jihlava	Czech Republic	3
Petz A. County Hospital	Gyor	Hungary	3
Szent Imre Hospital	Budapest	Hungary	3
Geelong Hospital	Geelong	Australia	2
Bombay Hospital Institute of Medical Sciences	Mumbai	India	2
Francicus Ziekenhuis	Roosendaal	Netherlands	2
Central Clinical Emergency Military Hospital	Bucharest	Romania	2
Sir Charles Gairdner Hospital	Perth	Australia	1
The Alfred	Melbourne	Australia	1
Semmelweis University Budapest	Budapest	Hungary	1
University of Debrecen	Debrecen	Hungary	1
Péterfy Sandor Hospital	Budapest	Hungary	1
Neurology Clinical Center	Skopje	Macedonia	1
New York University Langone Medical Center	New York	United States	1

Table S3:

Sensitivity model 1 – outcome sustained for all available follow-up

	Study Epoch					
	EDSS 3-6		EDSS 4-6		EDSS 6-6.5	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Sex (Male)	1.10 (0.84-1.44)	0.48	1.31 (1.05-1.63)	0.02	1.25 (1.06-1.48)	0.009
Age at baseline (per year)	1.01 (1.00-1.03)	0.13	1.01 (1.00-1.03)	0.03	0.99 (0.98-1.00)	0.13
Disease duration at baseline (per year)	1.00 (0.89-1.13)	0.97	0.94 (0.85-1.03)	0.19	0.97 (0.90-1.04)	0.34
Annualised Relapse Rate						
- Pre-baseline (per relapse/year)	0.87 (0.70-1.08)	0.21	0.85 (0.69-1.05)	0.14	0.74 (0.62-0.88)	<0.001
- During epoch (per relapse/year)	3.01 (2.40-3.76)	<0.001	2.68 (2.28-3.16)	<0.001	1.84 (1.56-2.17)	<0.001
Rate of pre-baseline therapy initiation (per initiation/year)	1.39 (0.78-2.51)	0.27	1.17 (0.74-1.88)	0.50	0.95 (0.67-1.35)	0.77
Proportion of time on lower-efficacy therapies						
- Pre-baseline (per 25% increase)	1.00 (0.90-1.11)	1.00	0.96 (0.89-1.04)	0.31	1.06 (1.00-1.13)	0.07
- During epoch (per 25% increase)	0.99 (0.90-1.09)	0.84	1.00 (0.92-1.08)	0.96	1.00 (0.95-1.06)	0.98
Proportion of time on higher-efficacy therapies						
- Pre-baseline (per 25% increase)	0.74 (0.32-1.71)	0.48	1.44 (1.11-1.87)	0.006	1.06 (0.88-1.28)	0.52
- During epoch (per 25% increase)	0.80 (0.65-0.99)	0.04	0.82 (0.71-0.94)	0.006	0.89 (0.80-0.98)	0.02

Results of sensitivity analysis for each epoch. Unless stated otherwise, Cox proportional hazard models were utilised.

CI: confidence interval; HR: hazard ratio.

Table S4:

Sensitivity model 2 – patients with a baseline EDSS equal to or greater than the initial EDSS step for each epoch

	Study Epoch					
	EDSS 3-6		EDSS 4-6		EDSS 6-6.5	
	WAF (95% CI)	P-value	WAF (95% CI)	P-value	WAF (95% CI)	P-value
Sex (Male)	1.30 (1.03-1.63)	0.02	1.43 (1.10-1.88)	0.009	1.21 (0.88-1.65)	0.23
Age at baseline (per year)	1.01 (1.00-1.02)	0.17	1.01 (1.00-1.03)	0.08	0.97 (0.96-0.99)	0.003
Disease duration at baseline (per year)	1.02 (0.92-1.13)	0.71	0.92 (0.82-1.04)	0.20	0.92 (0.81-1.04)	0.18
Annualised Relapse Rate						
- Pre-baseline (per relapse/year)	1.13 (0.94-1.35)	0.21	1.16 (0.92-1.47)	0.20	0.77 (0.55-1.08)	0.12
- During epoch (per relapse/year)	1.47 (1.39-1.57)	<0.001	1.49 (1.35-1.64)	<0.001	0.84 (0.61-1.15)	0.27
Rate of pre-baseline therapy initiation (per initiation/year)	1.24 (0.74-2.05)	0.41	2.82 (1.58-5.03)	<0.001	1.59 (0.83-3.06)	0.17
Proportion of time on lower-efficacy therapies						
- Pre-baseline (per 25% increase)	0.98 (0.90-1.07)	0.68	0.95 (0.86-1.06)	0.36	0.99 (0.88-1.11)	0.85
- During epoch (per 25% increase)	0.90 (0.84-0.97)	0.009	0.84 (0.77-0.92)	<0.001	0.98 (0.88-1.08)	0.63
Proportion of time on higher-efficacy therapies						
- Pre-baseline (per 25% increase)	1.23 (0.82-1.86)	0.32	1.73 (1.23-2.43)	0.002	1.19 (0.85-1.67)	0.30
- During epoch (per 25% increase)	0.67 (0.57-0.79)	<0.001	0.53 (0.45-0.64)	<0.001	0.73 (0.61-0.87)	<0.001

Results of sensitivity analysis for each epoch. Weibull accelerated failure time models were utilised for all of the above. This sensitivity analysis included the following number of patients from the MSBase cohort: EDSS 3-6 epoch: 2,533; EDSS 4-6 epoch: 2,576; EDSS 6-6.5 epoch: 1,649.

CI: confidence interval; WAF: Weibull acceleration factor.

Table S5:

Sensitivity model 3 – results adjusted for patients' country of residence

	Study Epoch					
	EDSS 3-6[a]		EDSS 4-6		EDSS 6-6.5[a]	
	WAF (95% CI)	P-value	HR (95% CI)	P-value	WAF (95% CI)	P-value
Sex (Male)	1.06 (0.99-1.13)	0.09	1.33 (1.11-1.59)	0.002	1.20 (1.13-1.26)	<0.001
Age at baseline (per year)	1.01 (0.99-1.02)	0.41	1.01 (1.00-1.02)	0.04	0.99 (0.98-1.00)	0.003
Disease duration at baseline (per year)	1.00 (0.94-1.05)	0.87	0.91 (0.86 – 0.96)	0.001	0.96 (0.90-1.03)	0.27
Annualised Relapse Rate						
- Pre-baseline (per relapse/year)	0.98 (0.87-1.10)	0.71	0.93 (0.63-1.36)	0.70	0.79 (0.69-0.90)	<0.001
- During epoch (per relapse/year)	1.96 (1.76-2.18)	<0.001	2.41 (1.54-3.77)	<0.001	1.58 (1.44-1.74)	<0.001
Rate of pre-baseline therapy initiation (per initiation/year)	0.92 (0.57-1.49)	0.74	1.10 (0.86-1.40)	0.46	0.93 (0.73-1.17)	0.52
Proportion of time on lower-efficacy therapies						
- Pre-baseline (per 25% increase)	1.02 (0.93-1.12)	0.67	0.97 (0.91-1.04)	0.44	1.04 (0.98-1.10)	0.18
- During epoch (per 25% increase)	0.99 (0.96-1.02)	0.42	1.00 (0.94-1.06)	0.89	1.02 (0.96-1.07)	0.57
Proportion of time on higher-efficacy therapies						
- Pre-baseline (per 25% increase)	0.87 (0.56-1.35)	0.53	1.59 (1.22-2.07)	<0.001	1.10 (0.93-1.30)	0.25
- During epoch (per 25% increase)	0.80 (0.65-0.98)	0.03	0.79 (0.70-0.90)	<0.001	0.91 (0.85-0.97)	0.006

Results of sensitivity analysis for each epoch. Unless stated otherwise, Cox proportional hazard models were utilised.

[a]Weibull accelerated failure time models were utilised for these epochs.

CI: confidence interval; WAF: Weibull acceleration factor; HR: hazard ratio.

Full disclosures:

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