Supplementary material

Andersen-Gill model

Traditionally, in a randomized clinical trial setting, the disability related hypotheses are tested based on a time-to-first disability event analysis which is commonly carried out using Cox proportional hazard models where any worsening event after the first worsening are discarded. Our multiple sclerosis data pool NO.MS contains longitudinal long-term data, i.e., patients have repeated clinical worsening events, and indeed, we can apply the Andersen-Gill model which is an extension of Cox proportional hazard model and it formulated as follows:

$$\lambda_{ik}(t) = \lambda_0(t) \times \exp(\beta x_{ik})$$

Where $\lambda_{ik}(t)$ represents the instantaneous risk or hazard of individual i experiencing event k at the time t, $\lambda_0(t)$ is the baseline hazard (the same as in Cox modeling) and $\exp(\beta x_{ik})$ is the hazard ratio. The Andersen-Gill model uses a common baseline hazard function for all events and estimates a global parameter for the factors of interest. Furthermore, the model assumes that the correlation between event times for an individual can be explained by past events, which indeed implies that the time increments between events are conditionally uncorrelated, given the covariates.

In our study, the 6mCDW events were used as the response variable. Andersen-Gill models were adjusted for sex, baseline age and disability status (EDSS) as covariates, and the annual relapse rate 1 year (ARR_1) or 2 years (ARR_2) prior to time t as time-varying covariates. Censoring occurred in all patients who did not experience 6mCDW, or had an initial disability worsening but insufficient follow-up to either confirm or discard the worsening as a 6mCDW event. The censoring time for an individual patient was defined as the time from the first dose of study medication to the last available EDSS assessment (within the specific dataset [A, B, C]).

Estimating the time between milestone EDSS values using time continuous Markov models

To estimate time between milestone EDSS states, we employed a multistate continuous time Markov model for panel data. These models admit to the fact that exact time of transition to a new EDSS value is not precisely measured, but rather the new EDSS status is captured at the subsequent visit to the clinic. The model parameters in these models are transition intensities, which are akin to the hazard of transitioning from one EDSS state to another. We define these intensities as:

$$q_{ij} = \lim_{\delta t \to 0} \frac{\Pr\left(\text{transition } i \to j \text{ in } [t, \delta t) | \text{in state } i \text{ at time } t\right)}{\delta t}$$

Where i is the starting state, j is the state transitioned to, and t is the time of transition. In addition, we consider covariate effects that alter these "baseline" transition hazards through a proportional odds model:

$$q_{ij}\{\text{age,trt}\} = q_{ij} \exp(\beta_1 \text{age} + \beta_2 \text{trt}))$$

The continuous age and binary treatment variables are time-varying as they are set to their observed values at the time of transition. Treatment is set to $trt = 0$ if either placebo or no treatment is taken at the time of transition and $trt = 1$ if any disease-modifying therapy is being taken. By including time varying age in the model, we fit a time-inhomogeneous Markov model because the transition intensities are therefore a function of time.

Next, we used the model estimated transition intensities to predict EDSS progression given a patient's current EDSS score, age, and treatment status. These parameters can be used to draw survival curves to characterize time between milestone EDSS states due to the continuous time multistate model's close relationship to survival methods. Because of the time-inhomogeneous nature of our model, it is important when calculating the survival curves to update the transition intensities as these curves move through time. To estimate times between the EDSS states

1 to 4, 1 to 6, and 4 to 6 we drew three sets of survival curves corresponding to the three transitions between milestones values, we did this repeatedly for each value of age, across the age range observed in our dataset.

To summarize these curves, we utilize Restricted Mean Survival Time (RMST) to estimate the average time to a particular state. RMST is defined as:

$$E[\min(T, \tau)] = \int_0^{\tau} S(t)\mathrm{dt}$$

This is the area under the survival curve. For the Restricted Mean Survival Time (RMST) analysis, one needs to choose a cutoff (restriction) time (τ). In our models τ is 65, which approximately corresponds to the upper limit of where we have substantial data. For each model estimated survival curve starting from age 20 to 65, we calculated this RMST. Subsequently, we calculated a weighted average of the estimated time to milestone state where the weights are proportional to the age distribution at the starting EDSS state in our data. This provided us a one number summary of the time between milestone EDSS states for each value of age, up to age 65. Statistical inference was conducted via sampling from the asymptotic multivariate normal distribution of the transition intensities, re-calculating the survival curves and RMST. After resampling with B=1000 replicates we estimated confidence limits by calculating the 2.5% and 97.5% of the resulting statistics.

Supplementary Table 1 Composition of NO.MS datasets (A, B and C)

Study name and/or NCT code	Novartis study identifier	Period of enrolment	Study phase	Study type	Indication	Test compound	Total subjects, n	RRMS, n	SPMS, n	PPMS, n	Dataset
NCT00537082	CFTY720D1201	Oct 2007 – Feb 2010	2	Randomized, double-blind	RMS	Fingolimod/ placebo	168	168	0	0	A
Japan Post-marketing safety study	CFTY720D1401*	Nov 2011 – May 2013	4	Observational	MS	Fingolimod	1007	964	43	0	A
ACROSS NCT00333138	CFTY720D2201	May 2003 – Apr 2004	2	Randomized, double-blind	RMS	Fingolimod/ placebo	281	250	31	0	A
FREEDOMS I NCT00289978	CFTY720D2301	Jan 2006 – Aug 2007	3	Randomized, double-blind	RRMS	Fingolimod/ placebo	1272	1272	0	0	A, B, C
TRANSFORMS NCT00340834	CFTY720D2302	May 2006 – Sep 2007	3	Randomized, double-blind	RRMS	Fingolimod/ interferon beta-1a	1280	1280	0	0	A, B
INFORMS NCT00731692	CFTY720D2306	Sep 2008 – Aug 2011	3	Randomized, double-blind	PPMS	Fingolimod/ placebo	970	0	0	970	A ,B, C
FREEDOMS II NCT00355134	CFTY720D2309	Jun 2006 – Mar 2009	3	Randomized, double-blind	RRMS	Fingolimod/ placebo	1083	1083	0	0	A, B, C
PARADIGMS NCT01892722	CFTY720D2311	Jul 2018 – Aug' 2019	3	Randomized, double-blind	POMS***	Fingolimod/ interferon beta-1a	214	214	0	0	A, B
FIRST NCT01127750	CFTY720D2316*	May 2010 – Jul 2011	3	Open-label	RMS	Fingolimod	2367	2367	0	0	A
VERIFY NCT01199861	CFTY720D2320*	Aug 2010 – Dec 2010	2	Randomized, blinded	RMS	Fingolimod/ placebo	138	138	0	0	A
TOFINGO NCT01499667	CFTY720D2324	Sep 2011 – Mar 2012	3	Randomized, double-blind	RRMS	Fingolimod	121	121	0	0	A
FIRST LATAM NCT01497262	CFTY720D2325*	Feb 2012 – Jan 2014	3	Open-label	RRMS	Fingolimod	162	162	0	0	A
PASSAGE NCT01442194	CFTY720D2403*	Aug 2011 – Jun 2015	4	Observational	RMS	Fingolimod	3153	3121	19	13	A
TRANSITION Trial not registered	CFTY720D2405*	Feb 2012 – Jan 2015	4	Observational	RMS	Fingolimod	627	627	0	0	A
EU PASSAGE NCT01442194	CFTY720D2406*	Aug 2011 – present	4	Observational	MS	Fingolimod/ other DMTs	4389	4359	27	3	A
PANGAEA NCT02720107	CFTY720DDE02*	May 2012 – present	4	Open-label	RRMS	Fingolimod	4107	4107	0	0	A
EudraCT 2011-000770-60	CFTY720DIT03*	Apr 2011 – Apr 2013	4	Open-label	RRMS	Fingolimod	906	906	0	0	A
EPOC NCT01216072	CFTY720DUS01	Aug 2011 – Oct 2011	4	Randomized, open-label	RMS	Fingolimod/ first-line DMTs	1028	1028	0	0	A
BOLD NCT00879658	CBAF312A2201	Mar 20019 – Dec 2010	2	Randomized, double-blind	RRMS	Siponimod/ placebo	296	296	0	0	A
EXPAND NCT01665144	CBAF312A2304	Feb 2013 – Jun 2015	3	Randomized, double-blind	SPMS	Siponimod/ placebo	1645	0	1645	0	A, B, C
ASCLEPIOS I NCT02792218	COMB157G2301	Oct 2016 – Mar 2018	3	Randomized, double-blind	RMS	Ofatumumab/ teriflunomide	927	872	55	0	A, B
ASCLEPIOS II NCT02792231	COMB157G2302	Oct 2016 – Mar 2018	3	Randomized, double-blind	RRMS	Ofatumumab/ teriflunomide	955	902	53	0	A, B
MIRROR NCT01457924	COMS112831	Nov 2011 – Feb 2013	2	Randomized, double-blind	RMS	Ofatumumab/ placebo	232	232	0	0	A

Dataset A: Full dataset (N=27 328); Dataset B: Phase 3 trials plus extensions (N=8346); Dataset C: Phase 3 placebo-controlled trials (N=4970). MS; multiple sclerosis; POMS; pediatric-onset multiple sclerosis; PPMS = primary progressive multiple sclerosis; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis

Note: Studies marked with an asterisk (*) did not systematically assess the EDSS score at the time of investigator reported relapse; i.e. all relapses are investigator reported, but the information whether the relapse is confirmed by the EDSS score is not available for these studies (CFTY720D1401, CFTY720D2316, CFTY720D2320, CFTY720D2325, CFTY720D2403, CFTY720D2405, CFTY720D2406, CFTY720DDE02, CFTY720DIT03).

Supplementary Table 2a Criterion for disability worsening based on change in EDSS score

EDSS score at baseline[a]	"Disability worsening" criterion
0	≥ +1.5
1 to 5	≥ +1
≥5.5	≥ +0.5

EDSS=Expanded Disability Status Scale (i.e. the EDSS total score)
A 3-month confirmed disability worsening (3mCDW) can have an onset at any scheduled or unscheduled visit if the disability worsening criterion is met. A disability worsening can only be confirmed in another EDSS assessment if, over a period of 3 months (≥ 90 days=3*30) time interval, all assessments meet the worsening criterion.
A 6-month confirmed disability worsening (6mCDW) can have an onset at any scheduled or unscheduled visit if the disability worsening criterion is met. A disability worsening event can only be confirmed at a scheduled visit if, over a period of 6 months (≥ 166 days=6*30-14) time interval, all assessments meet the worsening criterion.
If a patients dies due to multiple sclerosis (EDSS=10 at any time), it will be considered a confirmed disability worsening regardless of the baseline EDSS score or the change in EDSS score.
[a]Baseline EDSS score is defined as the last EDSS assessment prior to the first dose of study medication, or in exceptional cases the first available EDSS assessment after the first dosing date if no pre-dose assessment is available.

EDSS; Expanded Disability Status Scale

Supplementary Table 2b Disease definitions

Relapse definitions	
MS relapse[1]	An MS relapse is defined as the appearance of a new neurological abnormality or worsening of previously stable or improving pre-existing neurological abnormality (present for at least 24 hours in the absence of fever or known infection), separated by at least 30 days from onset of a preceding clinical demyelinating event in the central nervous system (McDonald *et al*. 2001[4]) present for at least 24 hours.
Confirmed MS relapse[1]	A ***confirmed*** MS relapse is one accompanied by a clinically relevant change in the EDSS score performed by an Independent EDSS Rater, i.e. an increase of at least 0.5 points on the EDSS score, or an increase of 1 point on two functional scores (FSs) or 2 points on one FS, excluding changes involving bowel/bladder or cerebral FS compared to the previous available rating (the last EDSS rating that did not occur during a relapse). Confirmation of MS relapse based on these definitions was done centrally.
Disability worsening definitions	
Confirmed disability worsening[2]	A 3-month (or 6-month) confirmed disability worsening (3mCDW or 6mCDW) is defined as a clinically meaningful increase of the EDSS score (by criteria described in S2b) from baseline EDSS score confirmed by an EDSS assessment at least 3 months (or 6 months) apart from the onset of the worsening. This means that after a scheduled or unscheduled visit at which the patient fulfills the disability worsening criterion, all EDSS assessments (scheduled or unscheduled) need to also fulfill the worsening criteria until the worsening can be confirmed at the first scheduled visit that occurs 3 months (or 6 months) after the onset of the worsening, outside the influence of a (confirmed or unconfirmed) relapse. The influence of a relapse is defined by the Investigator-reported start and end-date of a relapse, and is considered to last for a maximum of 90 days from the onset date of the relapse. If the confirmation date would fall on an EDSS assessment that is influenced by a relapse, confirmation is delayed until the next scheduled EDSS assessment that is not influenced by a relapse. **<u>Repeated CDW events:</u>** To identify repeated 3- or 6-month confirmed disability worsening events, the EDSS baseline value is reset after each 3- or 6-months confirmed disability worsening event, i.e. the new baseline EDSS is reset to the EDSS score at the confirmation visit for the previous 3- or 6-month confirmed disability worsening event.
Relapse-associated worsening (RAW 3-month or 6-month confirmed)[2]	A 3- or 6-month confirmed relapse-associated disability worsening event (RAW) is defined as a 3- or 6-month CDW event that has its onset *within 90 days* from the onset of a (confirmed or unconfirmed) relapse.
Progression independent of relapse activity (PIRA 3-month or 6-month confirmed)[2,3]	A 3- or 6-month CDW event with either no prior relapse, or an onset *more than 90 days* after the onset of the last relapse (confirmed or unconfirmed). No relapse must occur within 30 days before or after the EDSS-confirmation to qualify as PIRA. For the detection of PIRA events, the baseline EDSS score is reset after each relapse if the patient was worse after the relapse than before to the next scheduled EDSS value >90 days after the onset of the relapse.
Sustained progression independent of relapse activity (sustained PIRA; 3-month or 6-month confirmed)[2,3]	A PIRA event from which the patient never recovered in all the available longitudinal data.

A schematic representation of the definitions is given in Fig. 1.

[1]All studies collected investigator reported relapses. Unless specifically noted, all investigator-reported relapses are included in the statistical analyses.

[2]CDW events are not a union of PIRA and RAW events, due to the re-baselining of the EDSS score after relapses in the PIRA (but not the CDW) definition; i.e. some CDW events are neither PIRA nor RAW due to the timing of the relapses relative to the worsening. In addition, some patients can have RAW and PIRA events sequentially.

[3]For the detection of PIRA events, the baseline EDSS score is reset after each relapse to the level no less than the original baseline. Relapses prior to or after a PIRA event, and superimposed relapses are allowed within the definition of PIRA.

[4]McDonald W.I. *et al*., Recommended Diagnostic Criteria for Multiple Sclerosis: Guidelines from the International Panel on the Diagnosis of Multiple Sclerosis. Ann Neurol 2001;50:121–127.

CDW = confirmed disability worsening; EDSS; Expanded Disability Status Scale; MS; multiple sclerosis; PIRA = progression independent of relapse activity; PPMS = primary progressive multiple sclerosis; RAW = relapse-associated worsening RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis

Supplementary Table 3 6-Month confirmed disability worsening events

Full dataset	**RRMS**	**SPMS**	**PPMS**
CDW, n	1761	373	320
All PIRA, n	1175	307	310
Sustained PIRA, n (%)	833 (70.9)	286 (93.2)	267 (86.1)
Reversible PIRA, n (%)	342 (29.1)	21 (6.8)	43 (13.9)
Phase 3 dataset, n (%)	**RRMS**	**SPMS**	**PPMS**
CDW, n	611	354	320
All PIRA, n	394	295	310
Sustained PIRA, n (%)	211 (53.6)	275 (93.2)	267 (86.1)
Reversible PIRA, n (%)	183 (46.4)	20 (6.8)	43 (13.9)

All PIRA= 6-month confirmed PIRA events (regardless of whether they were sustained or not; sustained PIRA= 6-month confirmed PIRA sustained in all follow-up assessments; reversible PIRA=6-month confirmed PIRA, unsustained in the longitudinal follow-up data. CDW = confirmed disability worsening; PIRA = progression independent of relapse activity; PPMS = primary progressive multiple sclerosis; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis

Supplementary Table 4 Baseline characteristics of RRMS patients with sustained PIRA and RAW events (at any time), Full dataset

	Patients with PIRA (N=833)		Patients with RAW (N= 474)	Total (N=24,469)
	With relapse (N= 244)	**Without relapse (N= 589)**		
Age (years)	*N`=244 (100%)* ***41.8 ± 9.3***	*N`=588 (99.8%)* ***42.7 ± 9.3***	*N`=473 (99.8%)* ***38.4 ± 9.9***	*N`=24,440 (99.9%)* ***39.4 ± 10.5***
Females (%)	*N`=244 (100%)* ***162 (66.4%)***	*N`=589 (100%)* ***410 (69.6%)***	*N`=474 (100%)* ***342 (72.2%)***	*N`=24,467 (99.99%)* ***17,490 (71.5%)***
Caucasian (%)	*N`=170 (69.7%)* ***151 (88.8%)***	*N`=448 (76.1%)* ***399 (89.1%)***	*N`=379 (80.0%)* ***353 (93.1%)***	*N`=19,218 (78.5%)* ***16,400 (85.3%)***
Years since first symptoms, (%)	*N`=230 (94.3%)*	*N`=556 (94.4%)*	*N`=466 (98.3%)*	*N`=21,943 (89.7%)*
0 to < 2	***14 (6.1%)***	***53 (9.5%)***	***66 (14.2%)***	***3213 (14.6%)***
2 to < 5	***40 (17.4%)***	***91 (16.4%)***	***83 (17.8%)***	***4397 (20.0%)***
5 to < 10	***56 (24.3%)***	***137 (24.6%)***	***126 (27.0%)***	***5867 (26.7%)***
10 to < 30	***115 (50.0%)***	***258 (46.4%)***	***179 (38.4%)***	***8033 (36.6%)***
>= 30	***5 (2.2%)***	***17 (3.1%)***	***12 (2.6%)***	***433 (2.0%)***
Previously treated (%)	*N`=161 (66.0%)* ***126 (78.3%)***	*N`=320 (54.3%)* ***244 (76.2%)***	*N`=339 (71.5%)* ***234 (69.0%)***	*N`=15,935 (65.1%)* ***12,343 (77.5%)***
Relapses in previous year	*N'=230 (94.3%)* ***1.53 ± 0.99***	*N'=548 (93.0%)* ***1.14 ± 0.90***	*N'=457 (96.4%)* ***1.61 ± 1.02***	*N'=22,040 (90.1%)* ***1.2 ± 1.0***
EDSS at baseline	***3.25 ± 1.72***	***3.28 ± 1.87***	***3.01 ± 1.60***	***2.7 ± 1.6***
Proportion with Gd-enhancing lesions (%)	*N`=152 (62.3%)* ***58 (38.2%)***	*N`=269 (45.7%)* ***98 (36.4%)***	*N`=309 (65.2%)* ***120 (38.8%)***	*N`=10,227 (41.8%)* ***3,884 (38.0%)***
T2 lesion volume at baseline	*N'=79 (32.4%)* ***7576 ± 7896***	*N'= 140 (23.8%)* ***9699 ± 12,557***	*N'=211 (44.5%)* ***10,306 ± 13,393***	*N'=6178 (25.2%)* ***8375 ± 10`764***

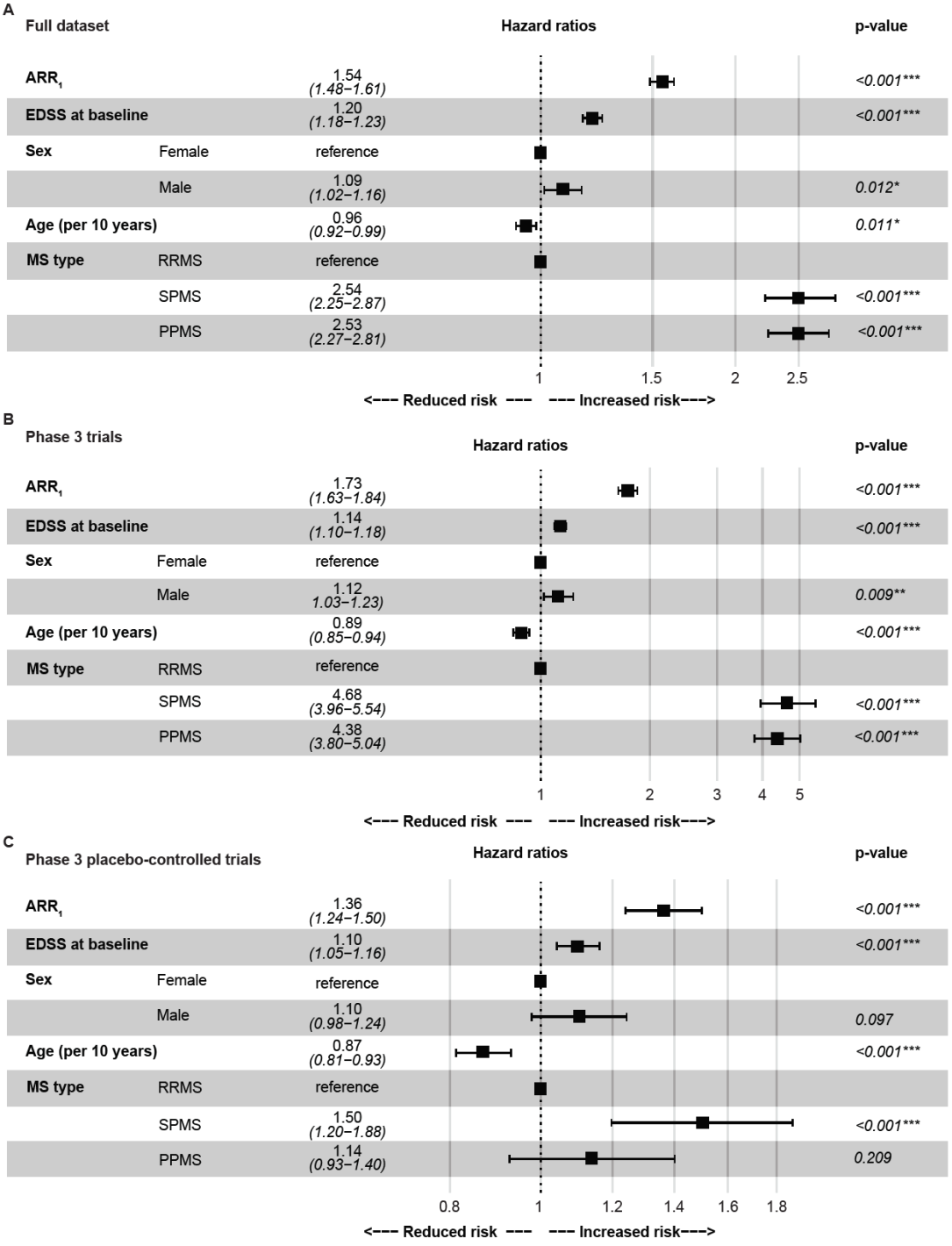
EDSS = Expanded Disability Status Scale; Gd = gadolinium; PIRA = progression independent of relapse activity; RAW = relapse-associated worsening RRMS = relapsing-remitting multiple sclerosis

Supplementary Table 5 MRI on-study activity in patients with at least one PIRA or RAW event, Dataset C (phase 3 double-blind, placebo-controlled trials). PIRA events are sustained until the end of the follow up.

		RRMS (N=2,355)	SPMS (N=1,645)	PPMS (N=970)
Number of Gd-enhancing lesions (per scan)	**PIRA**			
	Placebo	*N'=27 (1.2%)* ***0.98 (0.49; 1.98)***	*N'=91 (5.5%)* ***0.57 (0.34; 0.96)***	*N'=138 (14.2%)* ***0.22 (0.14; 0.34)***
	Treated	*N'=65 (2.8%)* ***0.12 (0.06; 0.22)***	*N'=161 (9.8%)* ***0.09 (0.05; 0.15)***	*N'=124 (12.8%)* ***0.04 (0.02; 0.07)***
	RAW			
	Placebo	*N'=58 (2.5%)* ***1.35 (0.90; 2.03)***	*N'=25 (1.5%)* ***0.70 (0.38; 1.32)***	[a]*N'=6 (0.6%)* ***0.38***
	Treated	*N'=50 (2.1%)* ***0.38 (0.23; 0.63)***	*N'=21 (1.3%)* ***0.09 (0.03; 0.27)***	[a]*N'=2 (0.2%)* ***0.0***
Patients free of Gd-enhancing lesions	**PIRA**			
	Placebo	*N'=27 (1.2%)* ***12 (44.4%)***	*N'=91 (5.5%)* ***57 (62.6%)***	*N'=138 (14.2%)* ***109 (79.0%)***
	Treated	*N'=65 (2.8%)* ***52 (80.0%)***	*N'=161 (9.8%)* ***138 (85.7%)***	*N'=124 (12.8%)* ***110 (88.7%)***
	RAW			
	Placebo	*N'=58 (2.5%)* ***16 (27.6%)***	*N'=25 (1.5%)* ***11 (44.0%)***	[a]*N'=6 (0.6%)* ***4 (66.7%)***
	Treated	*N'=50 (2.1%)* ***34 (68.0%)***	*N'=21 (1.3%)* ***18 (85.7%)***	[1]*N'=2 (0.2%)* ***2 (100.0%)***

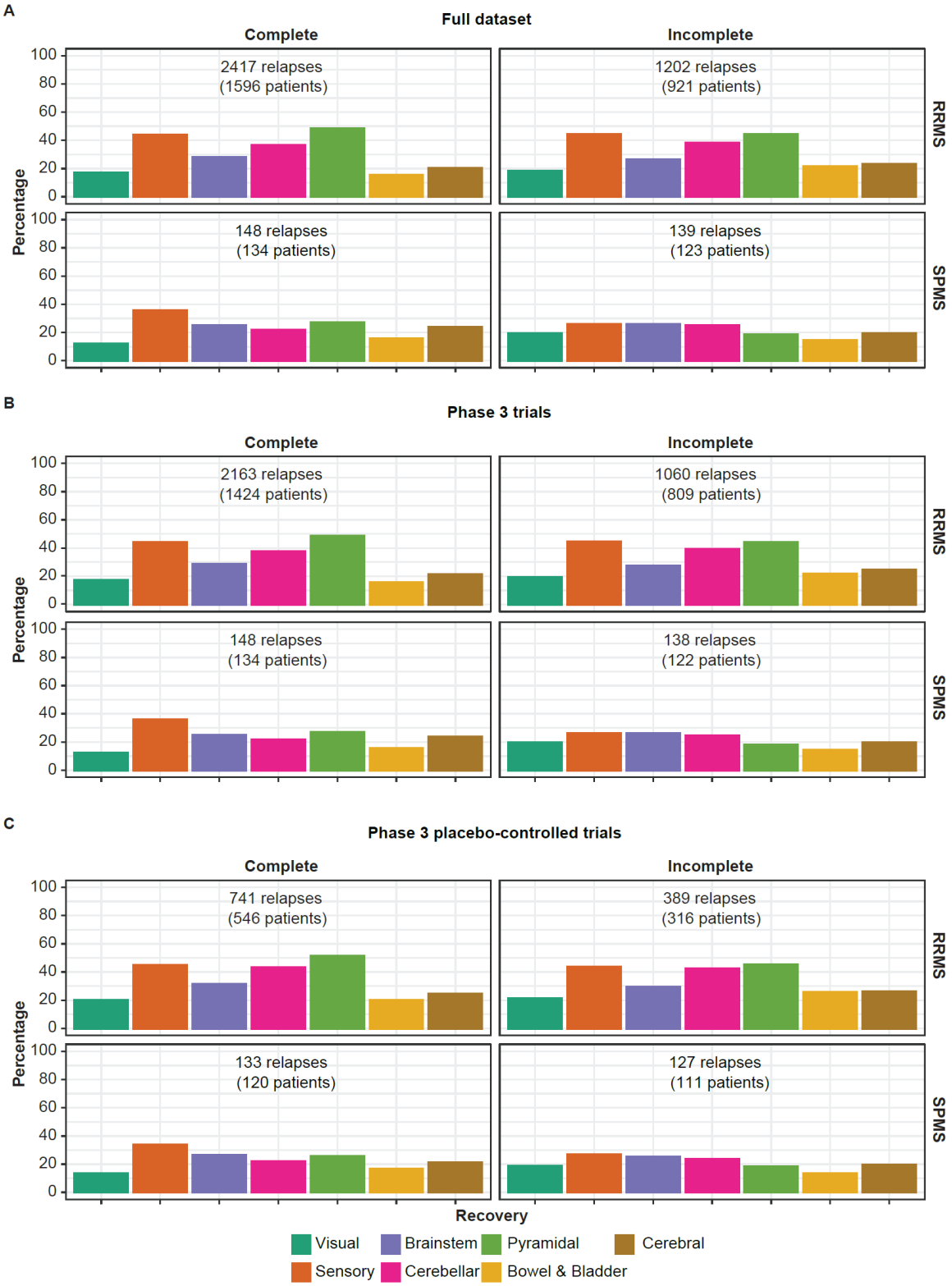
Estimates of the number of Gd-enhancing lesions with confidence limit were obtained from negative binomials with baseline number of Gd-enhancing lesions and age at baseline as covariates, and treatment as factor. The number of evaluable scans was used as the offset.
[a]Estimates without confidence limits are reported where a model could not be fitted due to low sample (i.e. not point estimates of the negative binomial model). Patients had to have at least one PIRA event to be included in the PIRA column, and at least one RAW event to be included in the RAW column. Gd = gadolinium; PIRA = progression independent of relapse activity; PPMS = primary progressive multiple sclerosis; RAW = relapse-associated worsening RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis

Supplementary Figure 1 Effect size of different covariates on the speed of all-cause disability worsening (CDW) in the full, phase 3 and phase 3 placebo controlled data

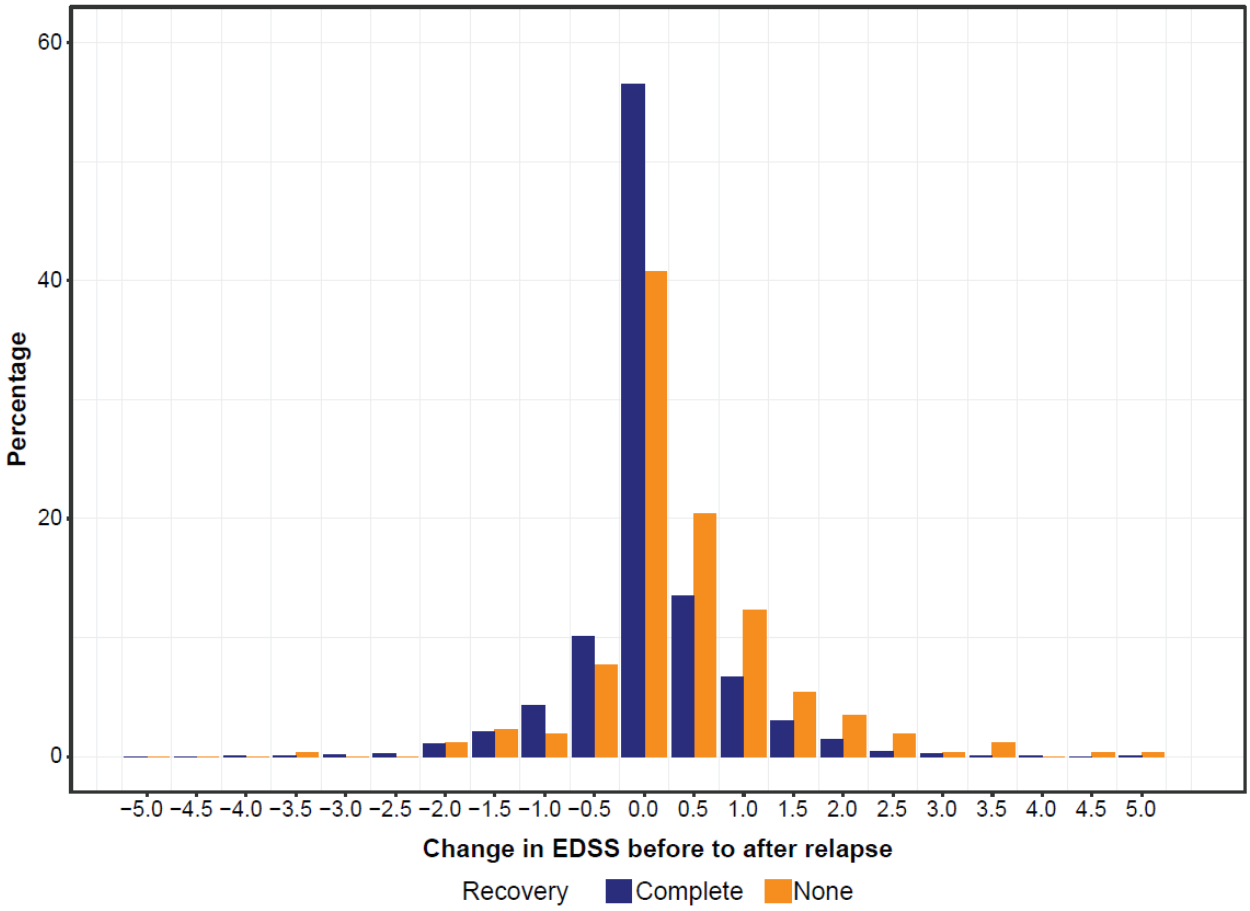


The Andersen-Gill model is fitted, controlling for ARR_1, EDSS score at baseline, treatment, sex, age at baseline and MS type measured at baseline. Sex and MS type are specified as factors, with 'female' and 'RRMS' as the reference categories; comparisons for males or patients with progressive MS are relative to the reference levels. Covariates with values greater than 1 increase the probability of worsening and those less than 1 decrease the probability of worsening. Notice that in this setting ARR_1 and Treatment are time varying covariates and the rest are time independent ones. Similar results were observed across phase 3 and placebo-controlled phase 3 trials. ARR_1 = annualized relapse rate-1 year; CDW = confirmed disability worsening; EDSS = Expanded Disability Status Scale; MS = multiple sclerosis; RRMS = relapsing-remitting multiple sclerosis

Supplementary Figure 2 Functional systems involved in relapses with complete or incomplete recovery (as judged by the Investigator)

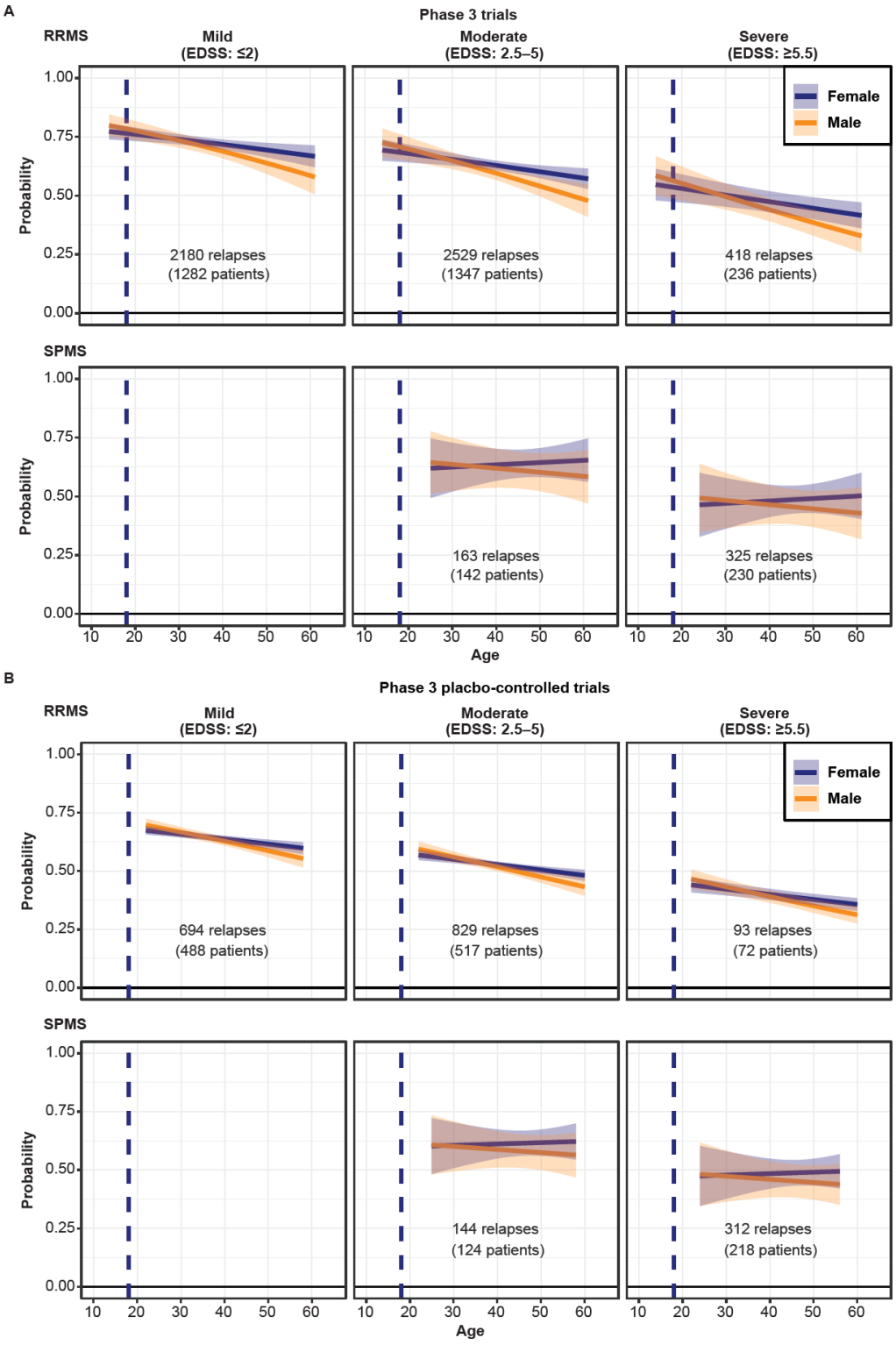


Supplementary Figure 3 Differences between the EDSS "before onset" and "after completion" of a relapse for each functional system and for the total EDSS for relapses that were judged by the investigator as "complete recovery" vs "no recovery"



EDSS; Expanded Disability Status Scale

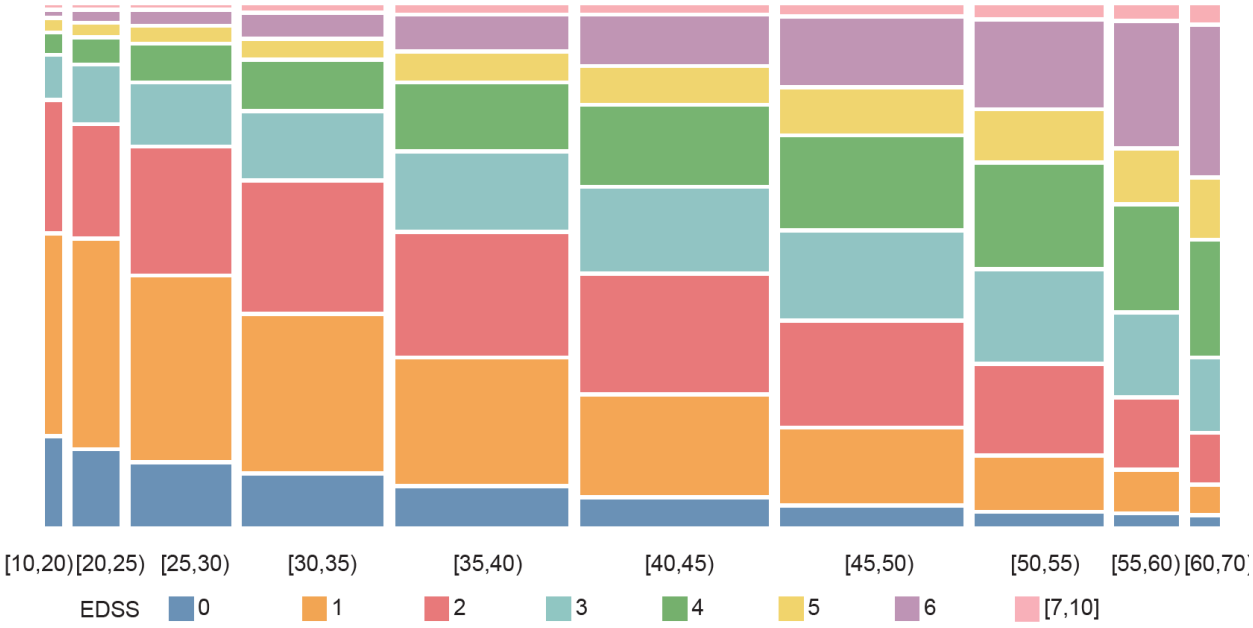
Supplementary Figure 4 Relapse recovery by phenotype, sex, and as a function of the patient's age



The mean probability of a complete recovery from relapse displayed as a function of the patient's sex, EDSS category and age prior to relapse. The number of patients noted in each panel corresponds to the number of patients with relapses. Relapse recovery was analyzed in a logistic regression model with adjustments for sex, age, and EDSS score (prior to relapse). EDSS; Expanded Disability Status Scale; multiple; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis

Supplementary Figure 5 Baseline distribution of disability stages (EDSS scores) as a function of the patient's age in the NO.MS Data Pool (A) EDSS distribution by age (B) Markov Model Estimated Annualized Probability Transition Matrix for a placebo patient at age 40, for illustration*

A



B

EDSS	0	1	2	3	4	5	6	[7,10]
0	0.378	0.423	0.159	0.032	0.007	0.001	0	0
1	0.144	0.468	0.283	0.079	0.022	0.003	0.001	0
2	0.055	0.287	0.391	0.180	0.072	0.012	0.003	0
3	0.017	0.123	0.275	0.302	0.221	0.052	0.020	0.001
4	0.004	0.039	0.128	0.247	0.358	0.137	0.081	0.005
5	0.001	0.009	0.038	0.104	0.235	0.254	0.331	0.029
6	0	0.001	0.004	0.016	0.056	0.133	0.693	0.098
[7,10]	0	0	0	0.002	0.010	0.037	0.308	0.643

Markov Model Estimated Annualized Probability Transition Matrix for a placebo patient at age 40, for illustration. For a specific patient, the row labels indicate the starting EDSS value, the column labels the EDSS values transitioned to, and the value contained in the cell is the probability of that particular transition within the next year. For each value of age (and for treated or placebo-treated patients), a different transition matrix, as estimated from the data, is used. In simulations, long-term patient trajectories can be simulated taking into account aging and the accumulation of disability over time. EDSS; Expanded Disability Status Scale

Supplementary Figure 6 Unequal stay times at different values of the EDSS as estimated based on the full analysis set