Figure S1: SPI2 Study Design

Double Blind Period for 15 to 27 Months

Open Label Extension

Mean=20·1 Months

Once the last M15 evaluation is completed, patients switched to the active drug between M15 and M27

Group 1: Placebo TID

Placebo ➔ MD1003 100mg TID

MD1003 100mg TID

n=642 patients

1:1

Group 2: MD1003 100mg TID

MD1003 100mg TID

Eligibility Criteria

- SPMS or PPMS
- EDSS 3·5 to 6·5
- Progression evidence prior 2 years
- TW25 <40 seconds
- No relapse prior 2 years
- No fampridine but all DMT allowed

| M0 | M3 | M6 | M9 | M12 | M15 | M18 | M21 | M24 | M27 |

EDSS, TW25, FitBit®, AEs, C-SSRS

MRI, Lab test

Biotin assay

ECG, SMDT, MSQoL-54 ; CAREQoL-MS

CGI / SGI

Primary endpoint (composite)

Decreased EDSS (M12 confirmed at M15)
Or
Decreased TW25 ≥20% (M12 confirmed at M15)

Secondary endpoints

Time to EDSS progression confirmed at 12 weeks
TW25: change from baseline
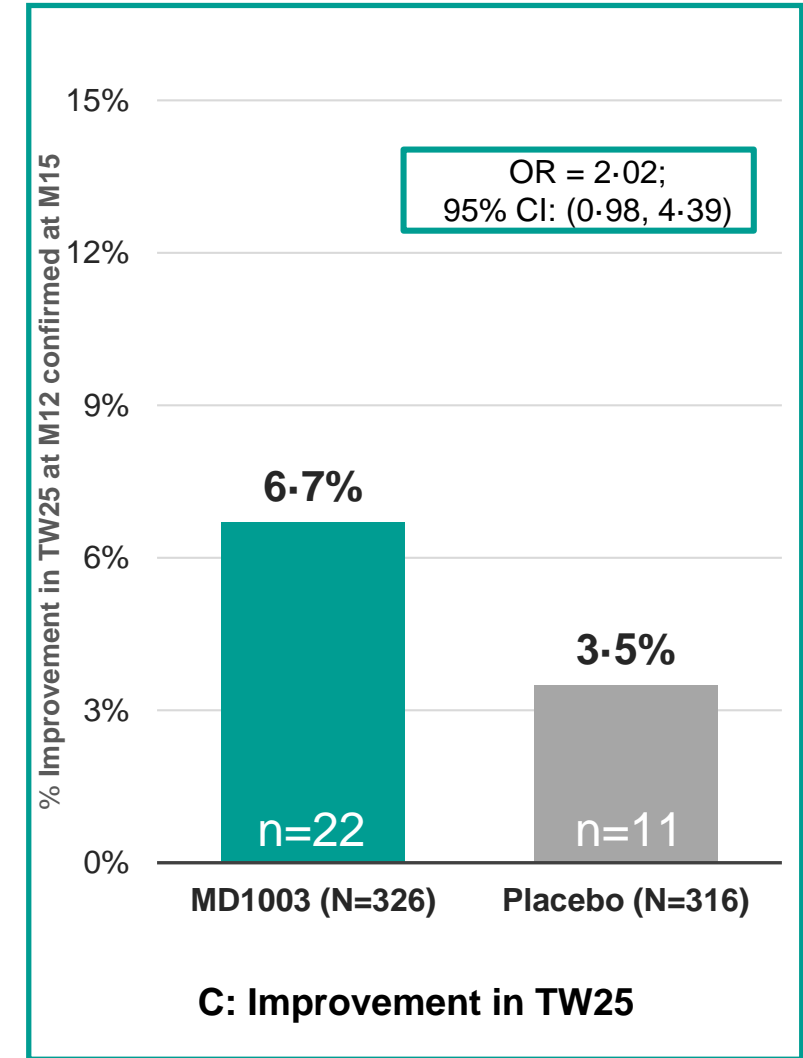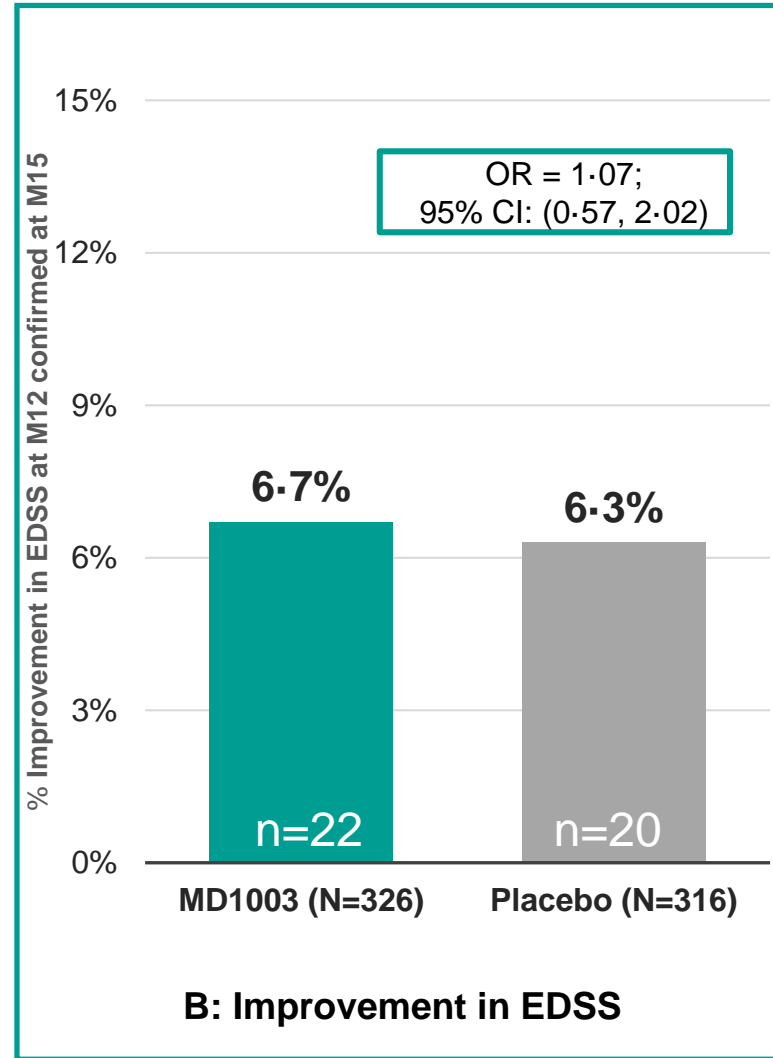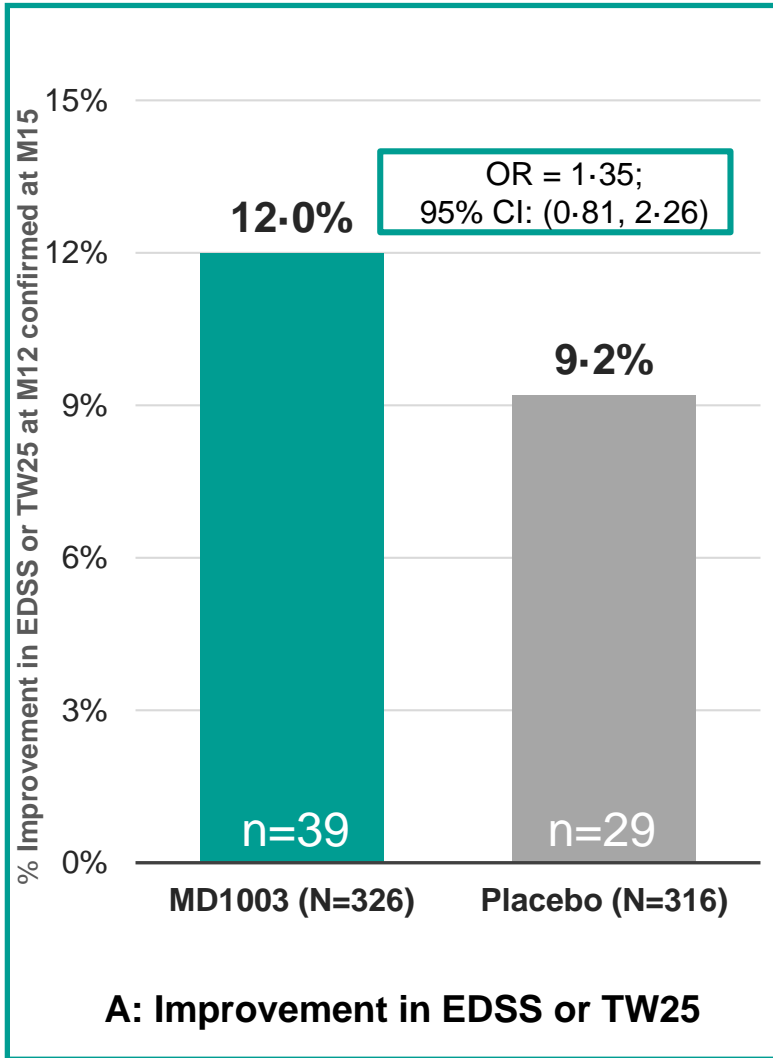CGI / SGI

EDSS: Expanded Disability Status Scale; MRS: Magnetic Resonance Spectroscopy; MSQoL-54: Multiple Sclerosis Quality of Life-54; SGI: subject-assessed Clinical Global Impression Scale; SDMT: Symbol Digit Modalities Test; TW25: timed 25-foot walk; Aes: Adverse events; CAREQoL-MS: caregiver health-related quality of life in multiple sclerosis; CGI: clinician-assessed Clinical Global Impression Scale; ECG: electrocardiogram;* ≥ 1 point if initial EDSS from 3·5 to 5·5; ≥ 0.5 point if initial EDSS from 6 to 6·5

Figure S2: Primary endpoint– Improvement in EDSS or TW25 at M12 confirmed at M15

A: Improvement in EDSS or TW25

Panel A (y-axis: % Improvement in EDSS or TW25 at M12 confirmed at M15):
- MD1003 (N=326): 12·0%, n=39
- Placebo (N=316): 9·2%, n=29
- OR = 1·35; 95% CI: (0·81, 2·26)

B: Improvement in EDSS

Panel B (y-axis: % Improvement in EDSS at M12 confirmed at M15):
- MD1003 (N=326): 6·7%, n=22
- Placebo (N=316): 6·3%, n=20
- OR = 1·07; 95% CI: (0·57, 2·02)

C: Improvement in TW25

Panel C (y-axis: % Improvement in TW25 at M12 confirmed at M15):
- MD1003 (N=326): 6·7%, n=22
- Placebo (N=316): 3·5%, n=11
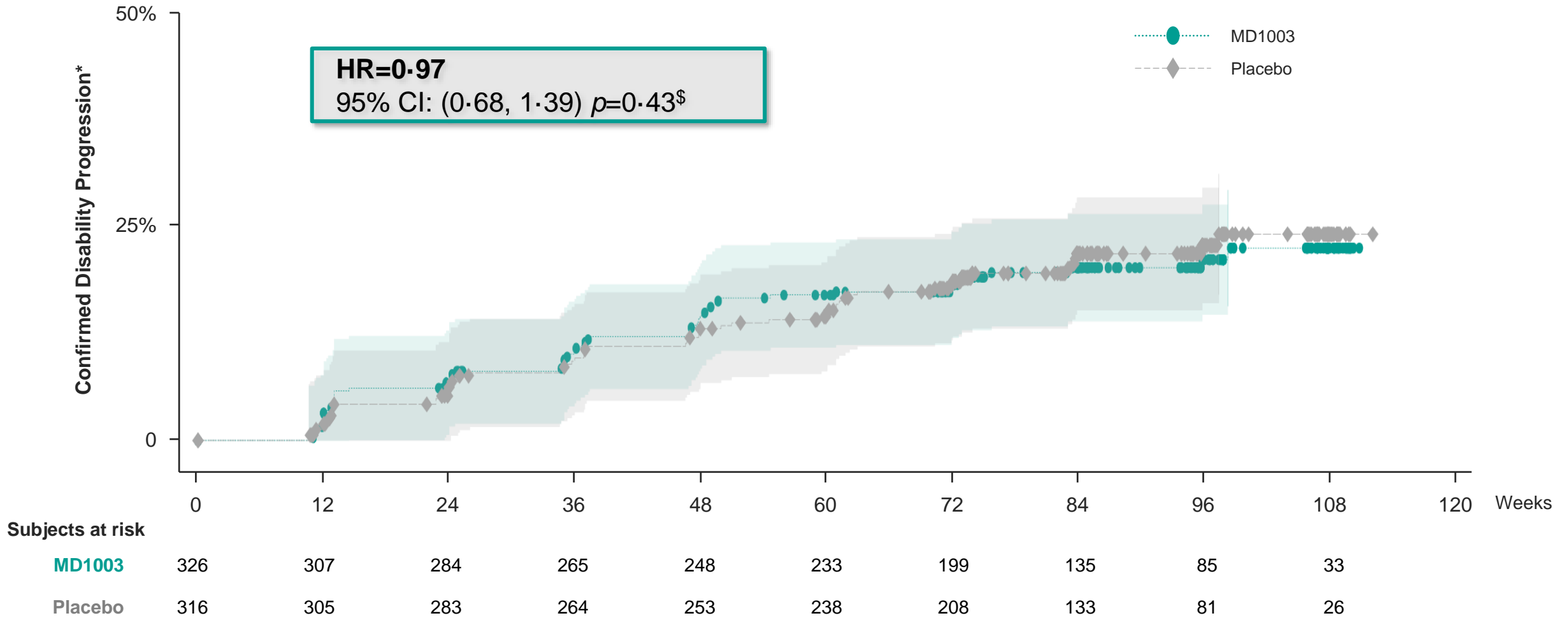- OR = 2·02; 95% CI: (0·98, 4·39)

EDSS response is defined as: decrease of at least 1 point if baseline EDSS 3·5 to 5·5 and of at least 0·5 points if baseline EDSS 6 to 6·5 compared to the lowest EDSS at inclusion and randomization visits.
TW25 response is defined as: decrease of at least 20% compared to the lowest mean of TW25 attempts at inclusion and randomization visits.
Asymptotic logistic regression analysis for the primary efficacy endpoint with study treatment group, disease history, and geographical region as factors; ITT Analysis Set – single imputation of missing values as non-response.
CI: confidence interval; EDSS: Expanded Disability Status Scale; OR: odds ratio; TW25: timed 25-foot walk.

Figure S3: First secondary endpoint – Time to 12-week confirmed EDSS progression

HR=0·97
95% CI: (0·68, 1·39) p=0·43$

Confirmed Disability Progression*

- MD1003
- Placebo

Subjects at risk	0	12	24	36	48	60	72	84	96	108
MD1003	326	307	284	265	248	233	199	135	85	33
Placebo	316	305	283	264	253	238	208	133	81	26

ITT analysis set; analysis was performed with a Proportional Hazards model stratified for geographical region and disease history. $Wald-test p-value.
*12-week confirmed EDSS progression is defined by an increase of at least 1 point if baseline EDSS 3·5 to 5·5 and of at least 0·5 point if baseline EDSS 6 to 6.5 with respective confirmation 12 weeks later Patients with initial disability progression who discontinued treatment early with no confirmatory EDSS assessment were considered as having confirmed disability progression
EDSS = Expanded Disability Status Scale; HR = hazard ratio; ITT = intention-to-treat

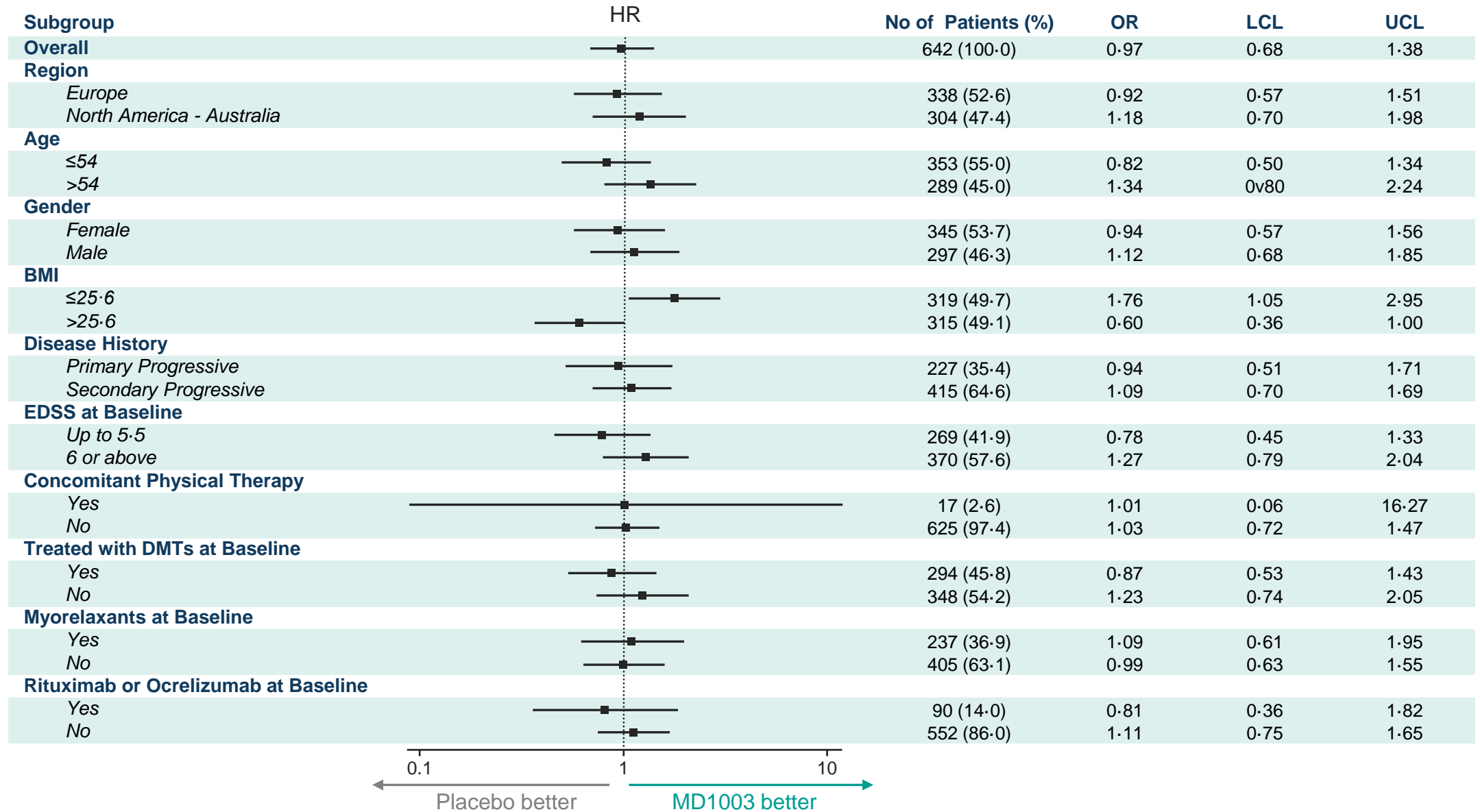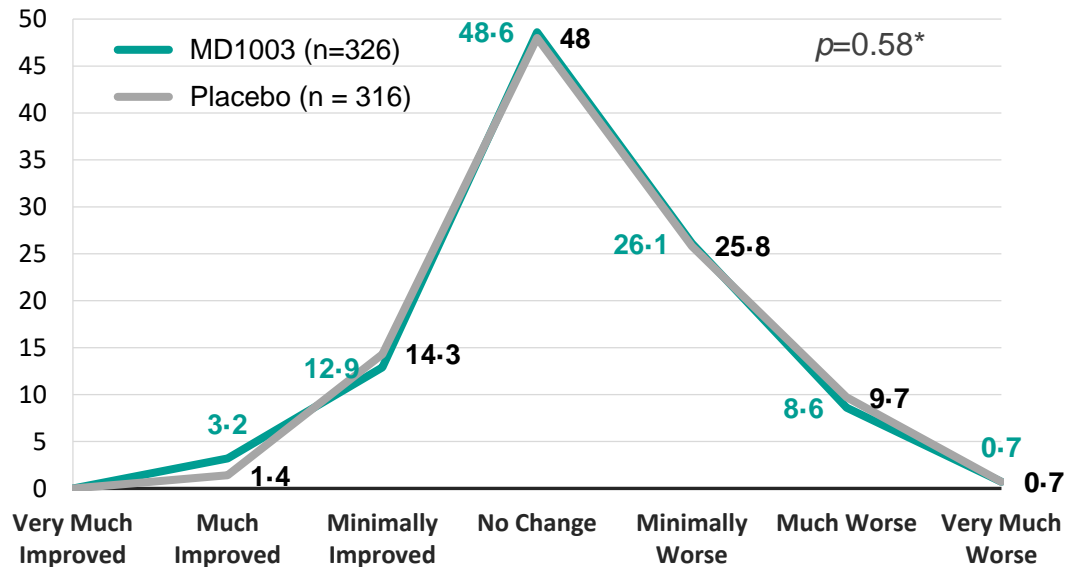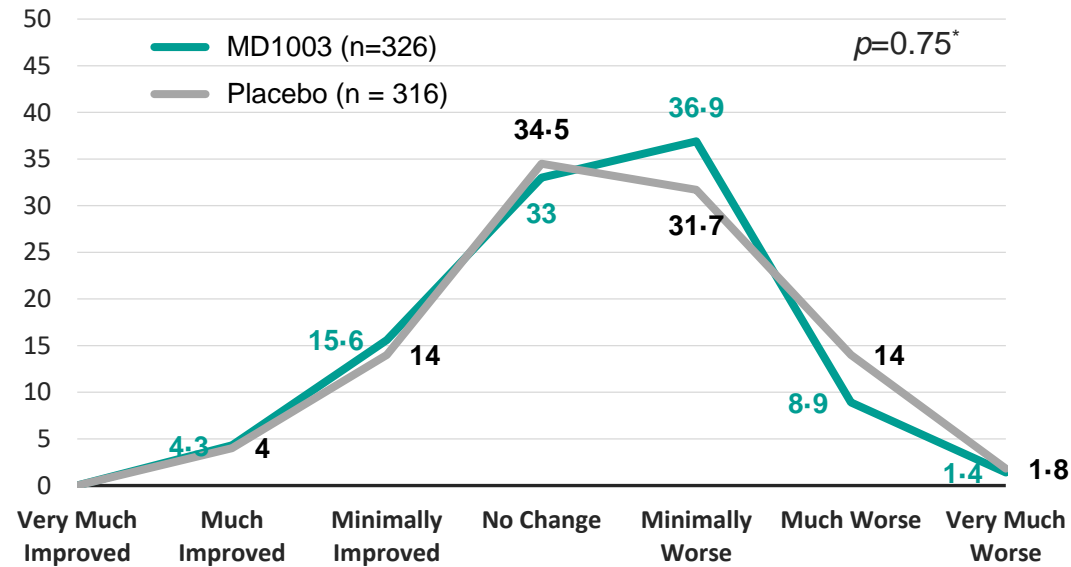# Figure S4: First Secondary Endpoint – Subgroup Analysis

Subgroup	HR	No of Patients (%)	OR	LCL	UCL
Overall		642 (100·0)	0·97	0·68	1·38
Region					
Europe		338 (52·6)	0·92	0·57	1·51
North America - Australia		304 (47·4)	1·18	0·70	1·98
Age					
≤54		353 (55·0)	0·82	0·50	1·34
>54		289 (45·0)	1·34	0v80	2·24
Gender					
Female		345 (53·7)	0·94	0·57	1·56
Male		297 (46·3)	1·12	0·68	1·85
BMI					
≤25·6		319 (49·7)	1·76	1·05	2·95
>25·6		315 (49·1)	0·60	0·36	1·00
Disease History					
Primary Progressive		227 (35·4)	0·94	0·51	1·71
Secondary Progressive		415 (64·6)	1·09	0·70	1·69
EDSS at Baseline					
Up to 5·5		269 (41·9)	0·78	0·45	1·33
6 or above		370 (57·6)	1·27	0·79	2·04
Concomitant Physical Therapy					
Yes		17 (2·6)	1·01	0·06	16·27
No		625 (97·4)	1·03	0·72	1·47
Treated with DMTs at Baseline					
Yes		294 (45·8)	0·87	0·53	1·43
No		348 (54·2)	1·23	0·74	2·05
Myorelaxants at Baseline					
Yes		237 (36·9)	1·09	0·61	1·95
No		405 (63·1)	0·99	0·63	1·55
Rituximab or Ocrelizumab at Baseline					
Yes		90 (14·0)	0·81	0·36	1·82
No		552 (86·0)	1·11	0·75	1·65

0.1   1   10

← Placebo better   MD1003 better →

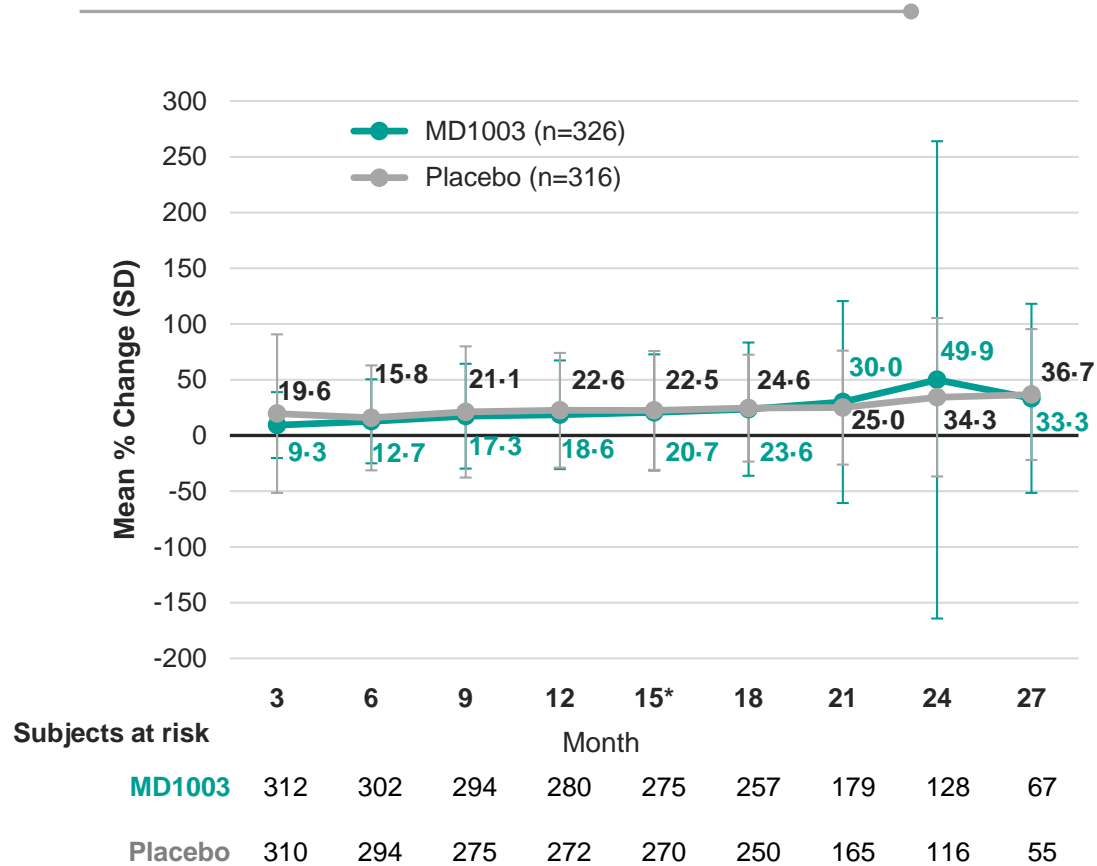# Figure S5: Secondary endpoint – CGI/SGI

Clinician rating (CGI)

MD1003 (n=326)
Placebo (n = 316)

p=0.58*

| Very Much Improved | Much Improved | Minimally Improved | No Change | Minimally Worse | Much Worse | Very Much Worse |

MD1003: 3·2, 12·9, 48·6, 26·1, 8·6, 0·7
Placebo: 1·4, 14·3, 48, 25·8, 9·7, 0·7

Improvement

Subject rating (SGI)

MD1003 (n=326)
Placebo (n = 316)

p=0.75*

| Very Much Improved | Much Improved | Minimally Improved | No Change | Minimally Worse | Much Worse | Very Much Worse |

MD1003: 4·3, 15·6, 33, 36·9, 8·9, 1·4
Placebo: 4, 14, 34·5, 31·7, 14, 1·8

Improvement

ITT analyses set , * One-sided Van Elteren test stratified for disease history (SPMS/PPMS) and geographical region (North America-Australia/Europe) comparing the two study treatment groups

Figure S6: Secondary Endpoint – Change in T25W

Mean change from Baseline in TW25 % (SD)

MD1003 (n=326)
Placebo (n=316)

Mean % Change (SD)

	3	6	9	12	15*	18	21	24	27
Placebo	19·6	15·8	21·1	22·6	22·5	24·6	25·0	34·3	36·7 / 33·3
MD1003	9·3	12·7	17·3	18·6	20·7	23·6	30·0	49·9	

Month

Subjects at risk

	3	6	9	12	15*	18	21	24	27
MD1003	312	302	294	280	275	257	179	128	67
Placebo	310	294	275	272	270	250	165	116	55

Mean TW25 seconds (SD)

MD1003 (n=326)
Placebo (n=316)

Mean Seconds (SD)

	Baseline	3	6	9	12	15*	18	21	24	27
Placebo	11·9	14·5	13·2	14·4	14·2	14·4	14·3	15·7	16·7	16·5
MD1003	11·5	12·6	13·0	13·7	13·5	13·8	14·3	14·5	16·0	15·9

Month

Subjects at risk

	Baseline	3	6	9	12	15*	18	21	24	27
MD1003	324	314	304	290	282	277	259	179	128	67
Placebo	315	311	295	276	273	271	251	165	116	55

*One-sided p=0·52
Hodges-Lehmann Point estimate for location shift of distributions (95% CI): 0.30 (-5·89 , 6·49)

ITT analyses set; Descriptive summary
*One-sided Van Elteren test stratified for disease history (SPMS/PPMS) and geographical region (North America-Australia/Europe) comparing the two study treatment groups.

Figure S7: Confirmed Relapses by Clinical Adjudication Committee
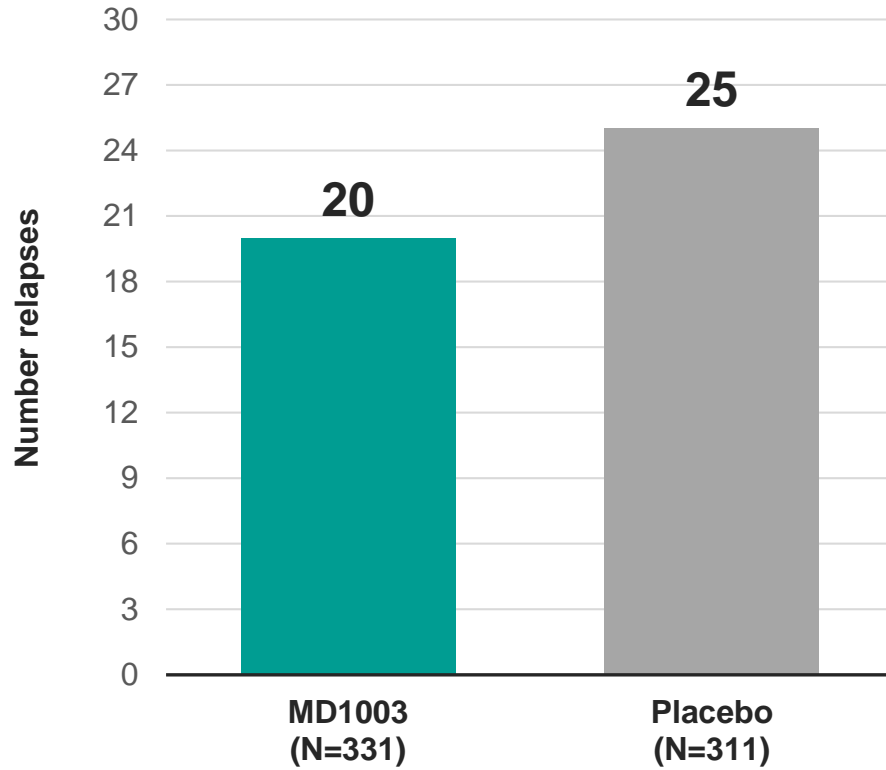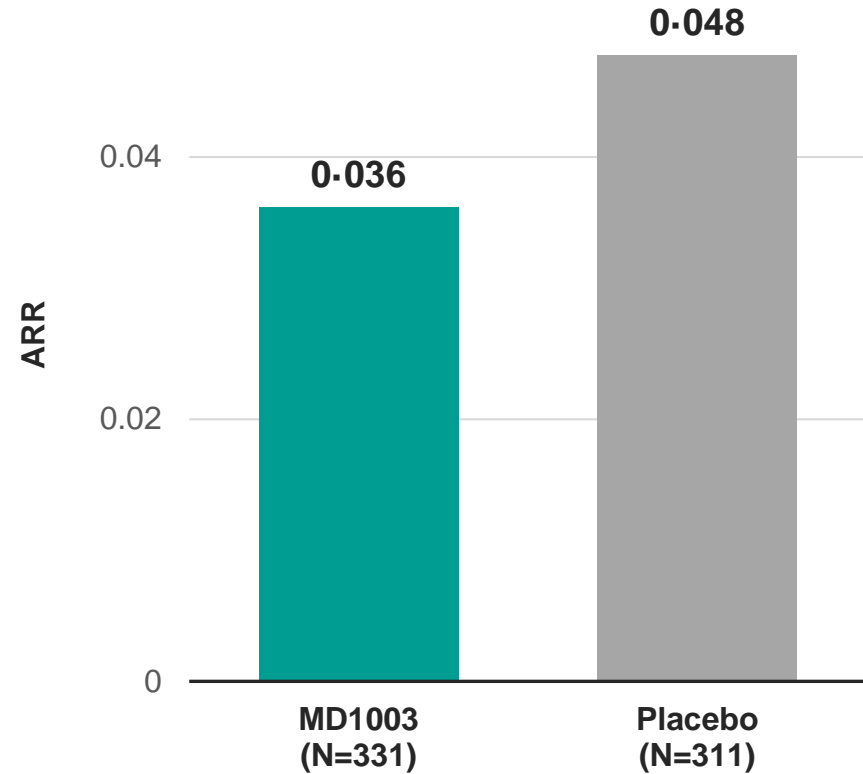
Figure S8: Time to First Relapse Confirmed by the Adjudication Committee
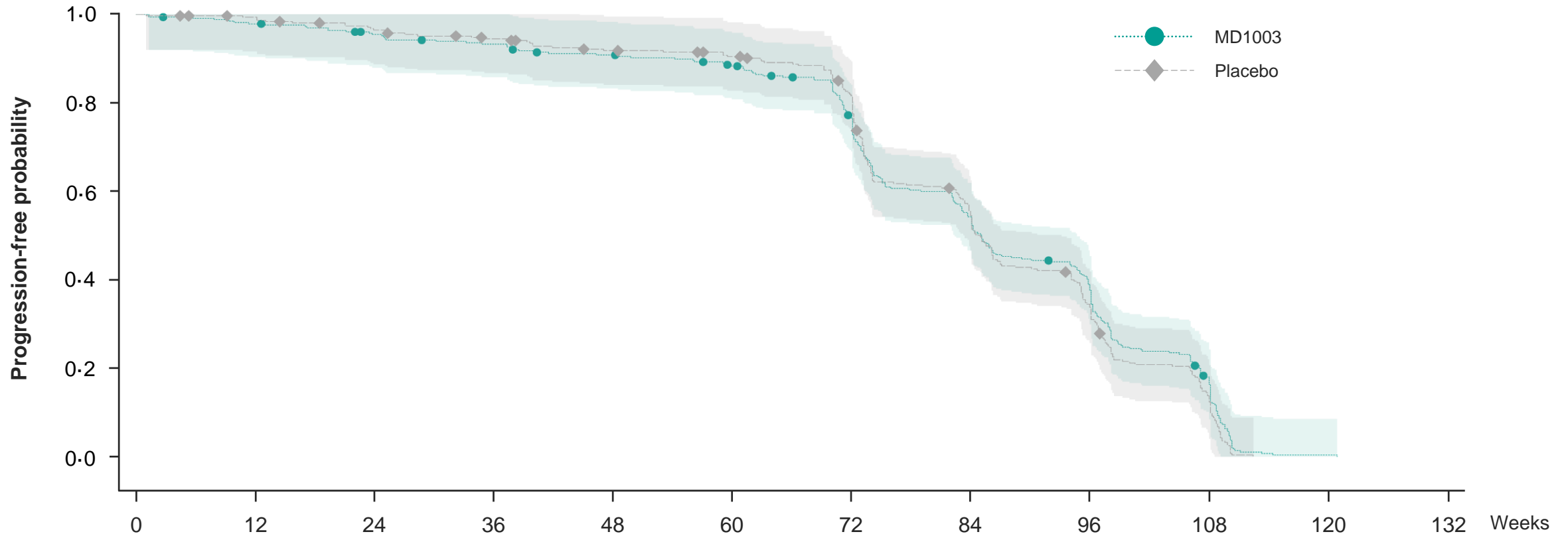
Subjects at risk												
MD1003	331	322	311	303	292	281	228	164	107	37	1	0
Placebo	311	306	295	286	275	268	227	149	89	28	0	0

Figure S9: SPI2 Primary Endpoint at Different Timepoints
Improvement in EDSS or Improvement in TW25 confirmed at + 3 months

EDSS or TW25 responder at different timepoints

Figure S10: Time to Confirmed Disease Improvement on EDSS or TW25

KAPLAN MEIER survival curve

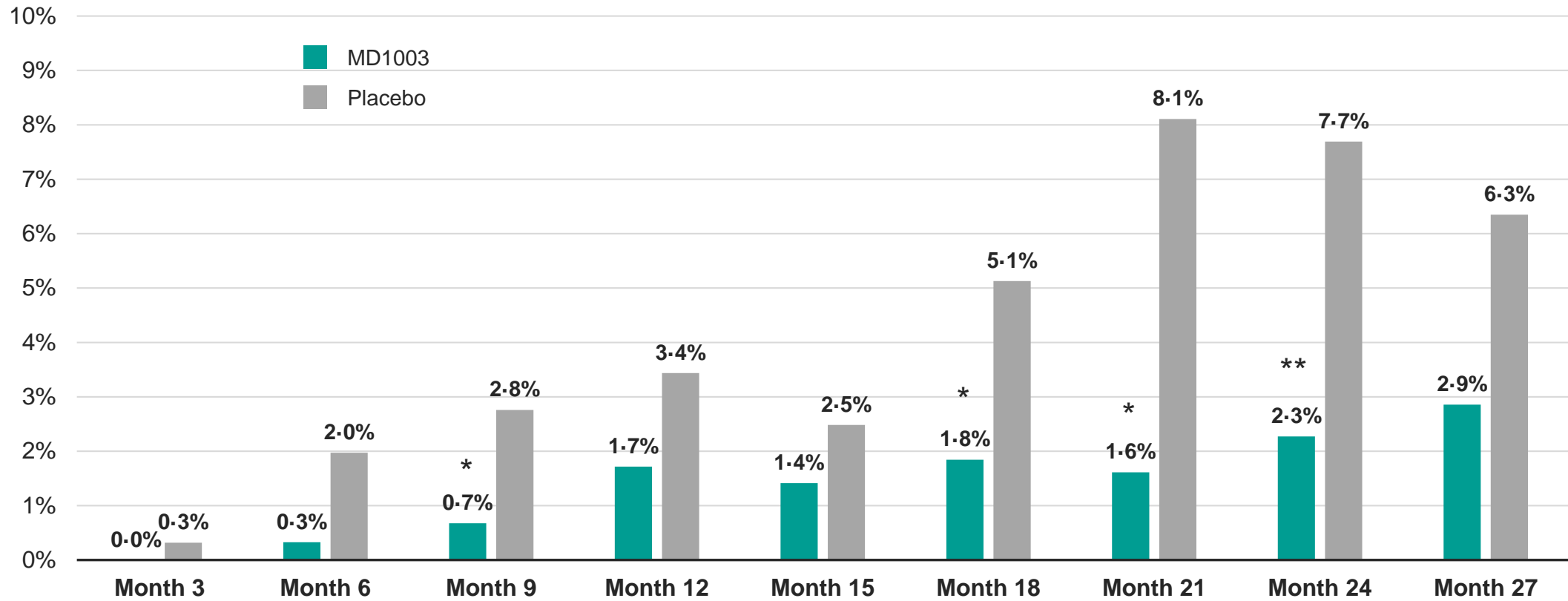**Time to 3 month confirmed disease improvement on EDSS or TW25**

test	*p*-value
Log-rang	0·10
Wilcoxon	0·08
-2Log(LR)	0·09

— Survival (MD1003)

— Survival (Placebo)

▲ Censor (MD1003)

▲ Survival (Placebo)

Figure S11: The Proportions of Patients Unable to Perform the TW25 Because of MS Worsening

TW25 missing assessement due to MS worsening (per visit view)

* p<0·05; ** p<0·01, Fisher exact test

Figure S12: The Proportions of Participants with an EDSS of at least 7

Patients with EDSS ≥ 7 - Visit wise (per visit view)
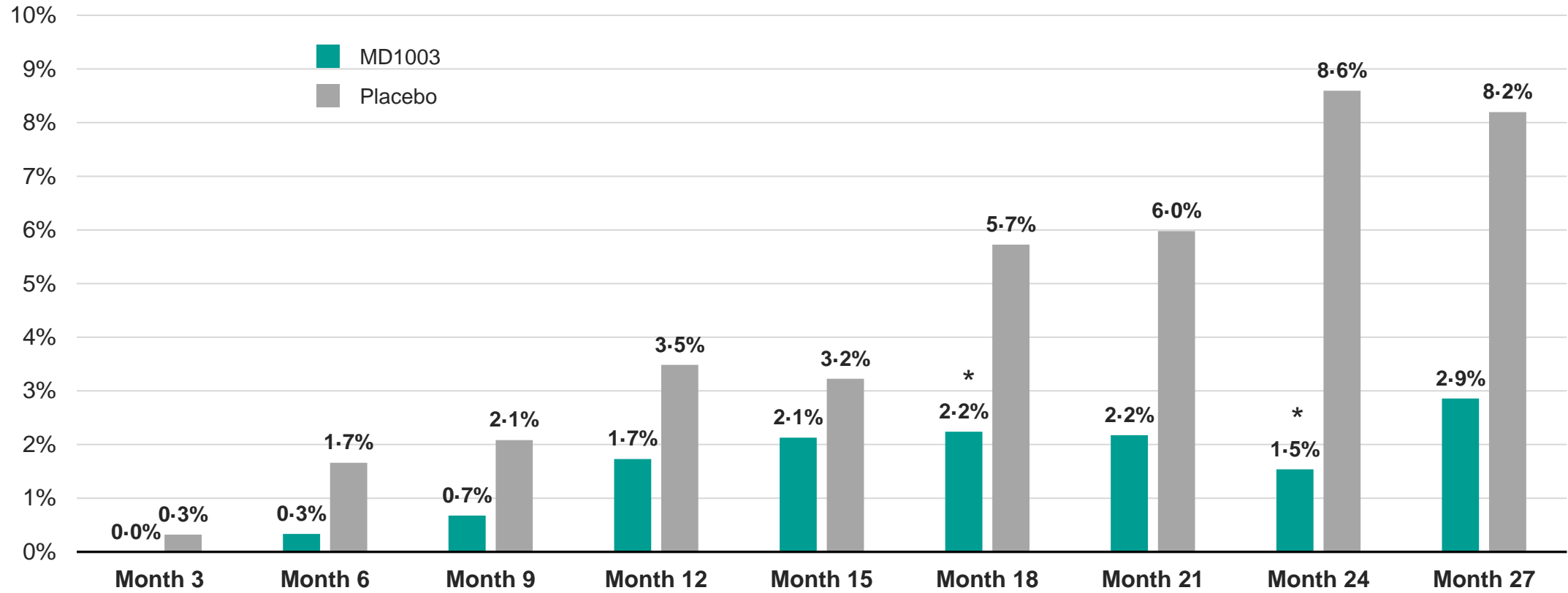
* p<0·05; Fisher exact test
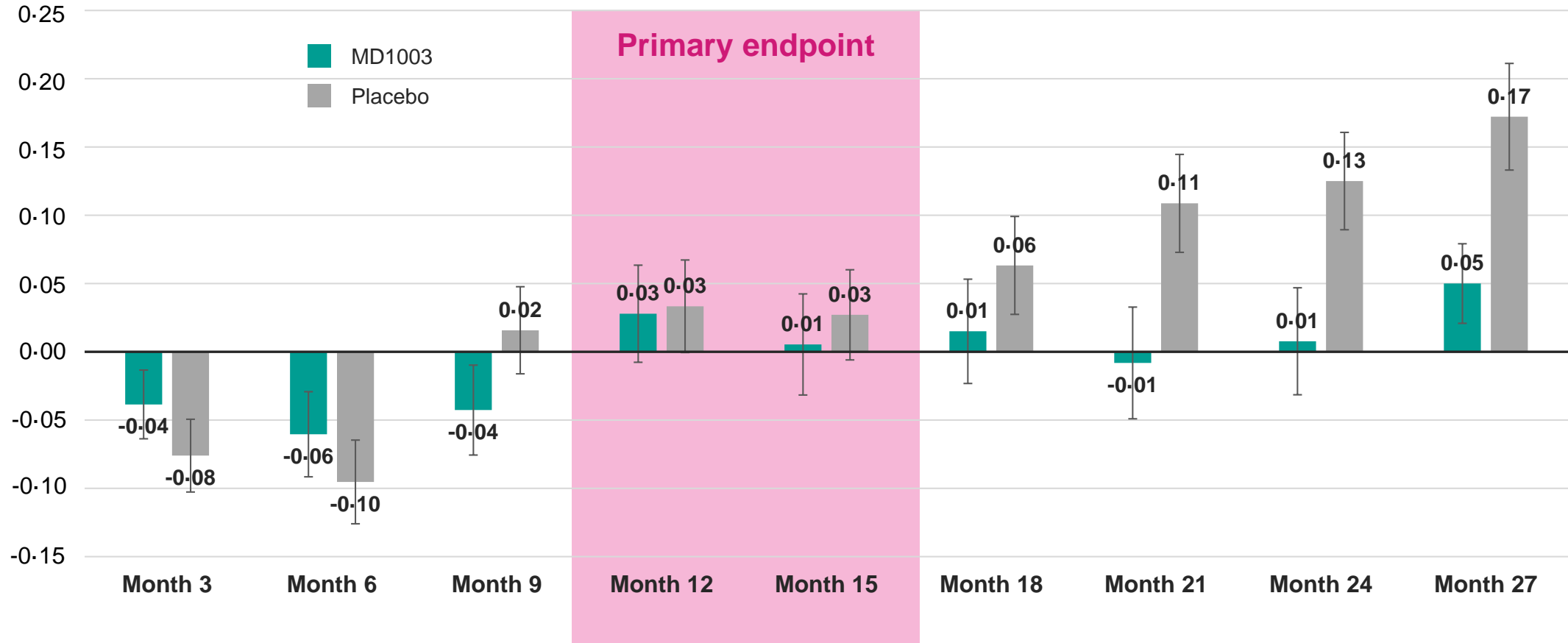
Figure S13: EDSS Mean Change versus M0

Figure S14: Disability Progression in SPI2, MS-SPI and Other Progressive MS Studies