

Table 1 - Target Trial 1 baseline weighted cohort characteristics

Characteristic <i>Median and (IQR) presented unless otherwise specified</i>	EXPAND emulation		Active SPMS EXPAND emulation		Inactive SPMS EXPAND emulation	
	No treatment	Siponimod	No treatment	Siponimod	No treatment	Siponimod
Number of unique individuals, n=	901	310	279	163	261	82
Total n=	1,050		379		314	
Number of sequentially emulated trials (i.e. non-unique individuals)	8,114	4,729	1,620	1,881	1,869	846
Number of trials per unique individual	6 (2, 14)	15 (6, 23)	3 (1, 8)	11 (5, 17)	5 (2, 10)	9 (4, 15)
Trial duration (years)	1.2 (0.5, 2.4)	1.5 (0.7, 2.2)	0.9 (0.4, 2.0)	1.7 (0.9, 2.4)	1.2 (0.5, 2.2)	1.3 (0.7, 2.0)
Female (number, %)	628 (69.7%)	204 (65.8%)	204 (73.1%)	107 (65.6%)	174 (66.7%)	46 (56.1%)
Weighted covariates						
Age at baseline (years)	51 (46, 56)	52 (47, 56)	51 (45, 56)	51 (46, 56)	52 (47, 56)	52 (45, 56)
Baseline EDSS	5.5 (4.5, 6.5)	6.0 (5.0, 6.5)	5.5 (4.5, 6.0)	6.0 (5.0, 6.5)	6.0 (4.5, 6.5)	6 (5.0, 6.5)
Disease duration (at baseline; years)	17 (11, 24)	18 (12, 26)	16 (10, 23)	18 (12, 24)	18 (12, 25)	18 (11, 24)
SPMS duration (at baseline; years)	1.7 (0.5, 4.3)	2.1 (1.0, 4.4)	1.7 (0.5, 4.1)	1.9 (0.8, 3.9)	1.6 (0.6, 4.1)	2.0 (0.8, 4.0)
Duration of current treatment state (at baseline; years)	0.3 (0.1, 2.4)	1.0 (0.4, 1.8)	0.2 (0.1, 0.9)	0.7 (0.3, 1.3)	0.4 (0.1, 2.3)	1.0 (0.3, 1.9)
Number of previous DMTs	2 (1, 3)	3 (2, 3)	2 (2, 3)	3 (2, 3)	2 (1, 3)	3 (2, 3)
Any relapses in the 2 years preceding baseline (%)	24%	23%	71%	75%	0%	0%
Any inflammatory activity in the preceding 2 years (%)	32%	31%	100%	100%	0%	0%
Time since last relapse (years)	6 (2, 10)	5 (2, 10)	0 (0, 0)	0 (0, 0)	7 (4, 11)	6 (3, 11)

Baseline weighted cohort characteristics for target trial 1 (emulation of EXPAND under the original conditions, and had only active or inactive SPMS participants been recruited). Sex is presented prior to weighting to report actual numbers (but was also balanced with weighting procedure). Final weights at baseline (combined treatment, non-adherence, and loss-to-follow-up weights), with additional down-weighting for multiple representations of the same individual, are utilised here.

IQR: interquartile range. EDSS: expanded disability status scale. SPMS: secondary progressive multiple sclerosis. DMT: disease-modifying therapies.

Table 2 - Target Trial 2 cohort characteristics after propensity score matching

Characteristic <i>Median and (IQR) presented unless otherwise specified</i>	Treatment Group		
	HET n=192	Siponimod n=192	SMD
Female (%)	134 (70%)	135 (70%)	0.01
Age at baseline (years)	53 (46, 59)	52 (46, 58)	0.01
Treatment commenced (number, %)	Ocrelizumab: 109 (57%) Ofatumumab: 39 (20%) Natalizumab: 26 (14%) Rituximab: 16 (8.3%) Alemtuzumab: 2 (1.0%)	Siponimod: 192 (100%)	-
Baseline EDSS	5.5 (4.5, 6)	5.5 (4.5, 6)	0.06
Calendar year	2022 (2021, 2023)	2022 (2021, 2023)	0.00
Disease duration (at baseline; years)	17 (11, 23)	18 (12, 24)	0.10
SPMS duration (at baseline; years)	1.6 (0.5, 4.3)	1.7 (0.4, 4.5)	0.03
Number of previous DMTs	2 (1, 3)	2 (1, 2)	0.06
Highest preceding DMT class (number, %)	High-efficacy: 38 (20%)	High-efficacy: 37 (19%)	0.00
	Medium-efficacy: 62 (32%)	Medium-efficacy: 61 (32%)	0.01
	Low-efficacy: 75 (39%)	Low-efficacy: 71 (37%)	0.01
	None: 16 (8.3%)	None: 23 (12%)	0.03
	RCT: 1 (0.5%)	RCT: 0 (0%)	0.01
Any relapses in the 2 years preceding baseline (number, %)	76 (40%)	74 (39%)	0.02
New/enhancing lesions on MRI recorded in the preceding 2 years (number, %)	43 (22%)	35 (18%)	0.10
Any inflammatory activity in the preceding 2 years (number, %)	106 (55%)	101 (53%)	0.05
Worsening of EDSS in the year prior to baseline (number, %)	138 (72%)	132 (69%)	0.07
Follow-up duration after baseline (years) ^a	2.02 (1.45, 2.98)	2.55 (1.71, 3.43)	0.23

Baseline cohort characteristics for target trial 2 (commencement of HET vs siponimod in SPMS) after propensity-score matching.

HET: high-efficacy therapies. IQR: interquartile range. DMT: disease-modifying therapies. EDSS: expanded disability status scale. SMD: standardised mean difference.

^aMatching was not undertaken on this covariate as eventual follow-up duration is not known at time of baseline

Table 3 - Target Trial 3 baseline weighted cohort characteristics

Characteristic <i>Median and (IQR) presented unless otherwise specified</i>	All participants	Participants who later switched to siponimod within grace period
Number of unique individuals, n=	3,002	49
Number of sequentially emulated and cloned trials (i.e. non-unique individuals)	100,078	1,138
Female (number, %)	2,039 (67.9%)	32 (65.3%)
Weighted covariates		
Age at baseline (years)	48 (41, 55)	48 (41, 55)
Baseline EDSS	6.0 (4.5, 6.5)	6.0 (5.0, 6.5)
Disease duration (at baseline; years)	15 (9, 22)	14 (9, 20)
SPMS duration (at baseline; years)	1.6 (0.0, 5.2)	0.5 (0.0, 4.6)
Number of previous DMTs	2 (1, 3)	2 (1, 3)
Any relapses in the 2 years preceding baseline (%)	19%	43%
Any inflammatory activity in the preceding 2 years (%)	25%	46%
Time since last relapse (years)	5 (3, 9)	2.7 (0.9, 5.0)

Baseline weighted cohort characteristics for target trial 3 (continuation of high-efficacy therapy vs switch to siponimod). Sex is presented prior to weighting to report actual numbers (but was also balanced with weighting procedure). Final weights at baseline (combined treatment, non-adherence, and loss-to-follow-up weights), with additional down-weighting for multiple representations of the same individual, are utilised here. Note that, as weights are time varying and depend significantly on treatment-dependent grace periods, covariates would not be expected to necessarily be balanced at baseline.

IQR: interquartile range. EDSS: expanded disability status scale. SPMS: secondary progressive multiple sclerosis. DMT: disease-modifying therapies.