Effect of Siponimod on MSWS-12 and MSIS-29 in Patients With SPMS From the EXPAND Study

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Introduction

- In the EXPAND Phase 3 study in SPMS patients, siponimod significantly reduced 3mCDP by 21% and 6mCDP by 26% versus placebo and showed significant benefits on CPS as measured by clinically meaningful confirmed changes in SDMT (confirmed or sustained ≥4 points)[1,2]
- In previous analysis, siponimod also showed favourable treatment effect on change from baseline in MSWS-12 scores in the overall EXPAND SPMS population[1]
- Treatment effect on change from baseline in MSIS-29 physical score was also seen[3], however the clinical meaningfulness of the results of these analyses was difficult to assess
- There is a need for outcome measures that reliably reflect accrual of disability in MS. Therefore, confirmed progression over 3- or 6-months endpoints are included in most MS trials using relevant cutoffs
- A similar approach could also be considered for PROs to better understand the impact of disease progression from the patients' perspective by evaluating confirmed minimal clinically important difference (MCID)

Introduction (contd.)

- Therefore, we further investigated the risk reduction in clinically meaningful worsening on MSIS-29 and MSWS-12 by evaluating confirmed MCID using cutoffs previously reported in the literature[4–7]

Objective

- To investigate the effect of siponimod treatment on
  - change from baseline in MSIS-29 and MSWS-12 (prespecified per protocol)
  - risk reduction in confirmed clinically meaningful worsening defined as[4–7]
    - a 6-month confirmed increase of ≥7.5 points in MSIS-29
    - a 6-month confirmed increase in MSWS-12, evaluated over clinically meaningful cutoffs of 4, 6, 8 and 10 points

3mCDP, 3-month confirmed disability progression; 6mCDP, 6-month confirmed disability progression; CPS, cognitive processing speed; M, month; MSIS-29, 29-item Multiple Sclerosis Impact Scale; MS, multiple sclerosis; MSWS-12, 12-item Multiple Sclerosis Walking Scale; PRO, patient-reported outcome measure; SDMT, Symbol Digit Modalities Test; SPMS, secondary progressive multiple sclerosis

1. Kappos L, et al. Lancet 2018;391:1263–1273; **2**. Benedict RHB, et al. Neurology 2021;96:e376-e386; **3.** Adlard N, et al. Poster presented at IPSOR Europe 2018: PRM197; **4.** Phillips GA, et al. Mult Scler 2014;20(13):1753–1760; **5.** Baert I, et al. Neurorehabilit Neural Repair 2014;28(7):621–631; **6.** Mehta L, et al. Mult Scler J Exp Transl Clin 2015;1:2055217315596993; **7.** Motl RW, et al. Eur Neurol 2014;71:196–202.

Methods

- EXPAND core part was a multicentre, randomised (2:1), double-blind, parallel-group, placebo-controlled, variable treatment duration, event-driven study in patients with SPMS[1]
  - Of the 1651 patients randomised, 1327 completed the core part (median duration, 21 months)
- The present analyses included all randomised subjects with assigned treatments who took at least one dose of study medication
  - The analyses comprised 1645 patients: 1099 in the siponimod group and 546 in the placebo group

Statistical analysis

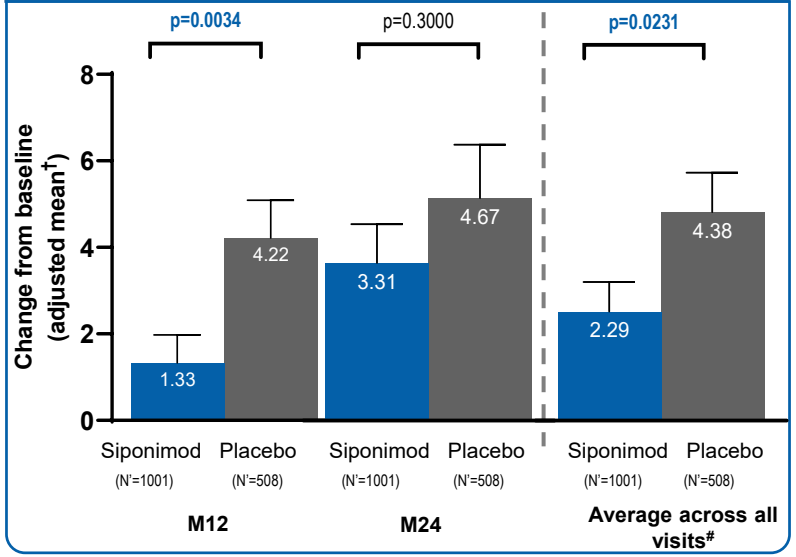
- MSIS-29 and MSWS-12 were assessed every 6 months in the EXPAND study
- Change from baseline for MSIS-29 (physical/psychological) and MSWS-12 scores was assessed using a repeated measures model adjusted for treatment, country and the respective baseline scores
- Risk reduction in clinically meaningful worsening for MSIS-29 (physical/psychological) and MSWS-12 scores was analysed using a Cox regression model* in the
  - Overall SPMS population
  - Subset of patients with active/nonactive SPMS, and patients aged ≤/>45 years
- Ceiling effect was not accounted for in the analysis

*The Cox regression model was adjusted for treatment, baseline MSIS-29 physical/psychological impact score or MSWS-12, baseline EDSS and superimposed relapses at baseline (yes or no)
EDSS, Expanded Disability Status Scale; MSIS-29, 29-item Multiple Sclerosis Impact Scale; MSWS-12, 12-item Multiple Sclerosis Walking Scale; SPMS, secondary progressive multiple sclerosis

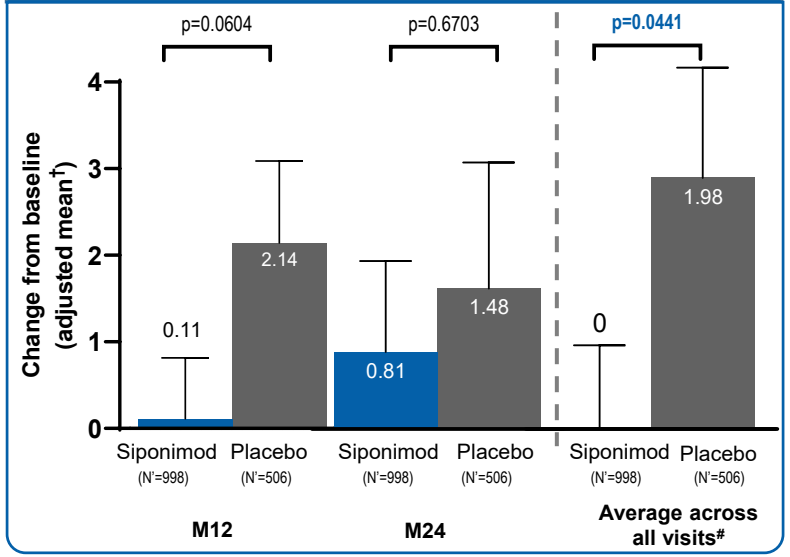
1. Kappos L, et al. Lancet 2018;391:1263–1273.

Siponimod reduced worsening in the MSIS-29 and MSWS-12 scores from baseline in the overall SPMS population*

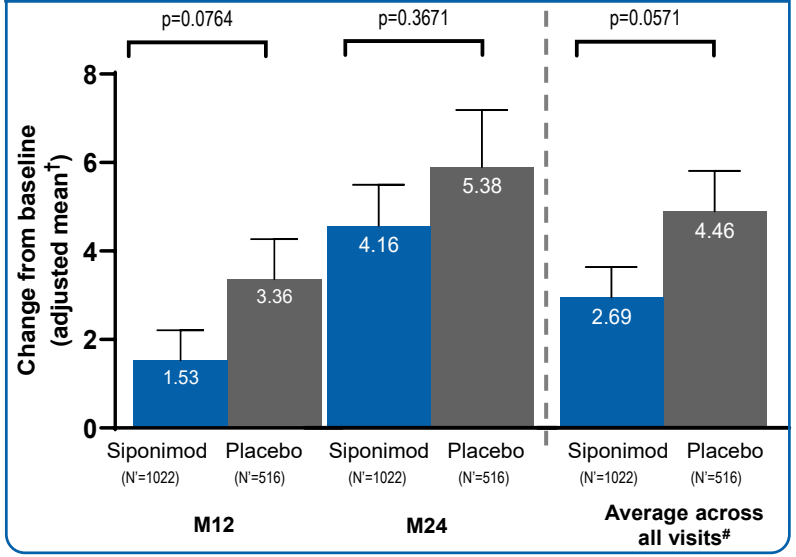
MSIS-29 Physical Impact



MSIS-29 Psychological Impact



MSWS-12[1]



Siponimod significantly reduced the increase from baseline in MSIS-29 physical and psychological scores (average across all visits up to M30) as compared to placebo, with a similar trend in MSWS-12 scores; however, the clinical meaningfulness of these results is difficult to assess

*Prespecified analyses using a mixed-effect repeated measures model (full analysis set). #Includes all post-baseline visits up to and including Month 30. Obtained from fitting a repeated measures model for normally distributed data, with visit as categorical factor
The model was adjusted for treatment, region/country, and MSIS-29 physical/psychological impact imputed converted total score or MSWS-12 converted scores as baseline scores
†Adjusted mean refers to the change from baseline in MSIS-29 physical/psychological impact imputed converted total score or MSWS-12 converted scores. Subjects who had completed version 1 of MSIS-29 instead of version 2 had been excluded from the analysis
M, month; MSIS-29, 29-item Multiple Sclerosis Impact Scale; MSWS-12, 12-item Multiple Sclerosis Walking Scale; N', number of subjects included in the analysis (i.e., with at least one result at baseline and post-baseline)

1. Kappos L, et al. Lancet 2018; 391:1263–1273.

Siponimod reduced the risk of clinically meaningful worsening in the MSIS-29 physical score in patients with SPMS

	Siponimod n/N'	Placebo n/N'	HR (95% CI)	p value	Risk reduction
Overall population	260/1063	158/529	0.78 (0.64, 0.95)	**0.0147**	21.8%
Active SPMS	125/501	81/255	0.73 (0.55, 0.97)	**0.0301**	26.6%
Nonactive SPMS	132/540	73/262	0.87 (0.65, 1.16)	0.3437	12.9%
Age ≤45 years	84/378	65/193	0.63 (0.45, 0.87)	**0.0053**	37.0%
Age >45 years	176/685	93/336	0.90 (0.70, 1.15)	0.3936	10.4%

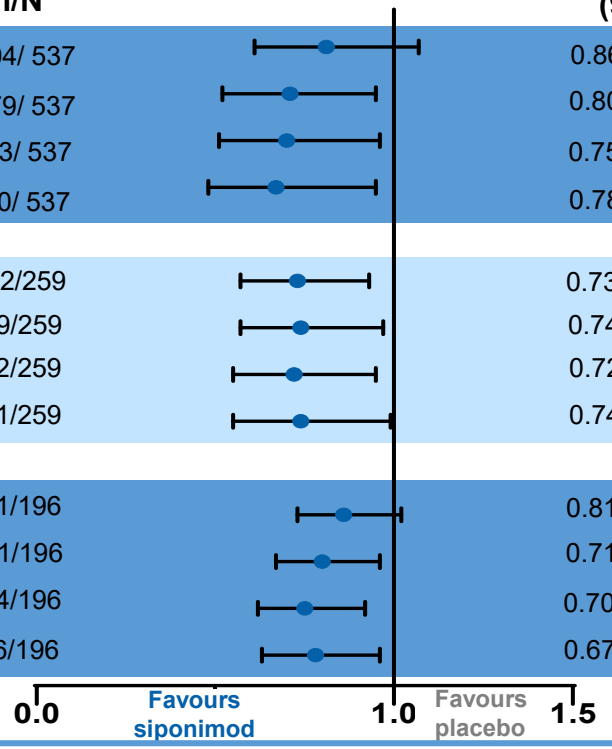
- Siponimod significantly reduced the risk of confirmed clinically meaningful worsening of ≥7.5 points in the MSIS-29 physical score by 21.8% in the overall population; the effect was most pronounced in subgroup of patients with active SPMS and patients aged ≤45 years
- A favourable trend was observed for MSIS-29 psychological score (applying the same ≥7.5 points cutoff as for physical) in the overall population (HR 0.87, p=ns), and in the active SPMS (HR 0.81, p=ns) and patients aged ≤45 years (HR 0.72, p=ns) subgroups

The Cox regression model (full analysis set) includes the predictors treatment, baseline MSIS physical impact score, baseline EDSS and superimposed relapses at baseline (yes/no). Analyses in the 'active'/'nonactive' SPMS subgroups were not adjusted for relapses at baseline. Confirmed progression in MSIS-29 is defined as an increase of 7.5 points

CI, confidence interval; EDSS, Expanded Disability Status Scale; HR, hazard ratio; MSIS-29, 29-item Multiple Sclerosis Impact Scale; n, number of patients with an event; N', number of patients included in the analysis (i.e., with nonmissing covariates); ns, nonsignificant; SPMS, secondary progressive multiple sclerosis

Siponimod reduced the risk of clinically meaningful worsening in the MSWS-12 score in patients with SPMS

	MCID	Siponimod n/N'	Placebo n/N'	HR (95% CI)	p value	Risk reduction
Overall population	4 points	370/1086	204/ 537	0.86 (0.73, 1.02)	0.0902	13.7%
	6 points	304/1086	179/ 537	0.80 (0.67, 0.96)	0.0184	19.9%
	8 points	264/1086	163/ 537	0.75 (0.62, 0.92)	0.0047	24.5%
	10 points	230/1086	140/ 537	0.78 (0.63, 0.96)	0.0183	22.4%
Active SPMS	4 points	164/511	102/259	0.73 (0.57, 0.93)	0.0121	27.2%
	6 points	144/511	89/259	0.74 (0.57, 0.97)	0.0284	25.6%
	8 points	130/511	82/259	0.72 (0.55, 0.95)	0.0211	27.8%
	10 points	114/511	71/259	0.74 (0.55, 0.99)	0.0430	26.4%
Age ≤45 years	4 points	136/386	81/196	0.81 (0.61, 1.07)	0.1380	18.9%
	6 points	108/386	71/196	0.71 (0.52, 0.95)	0.0236	29.4%
	8 points	97/386	64/196	0.70 (0.51, 0.96)	0.0273	30.1%
	10 points	80/386	56/196	0.67 (0.48, 0.95)	0.0243	32.7%



- Siponimod significantly reduced the risk of confirmed clinically meaningful worsening with more stringent cutoffs of 6–10 points in the overall population, as well as in the subgroups of patients with active SPMS and in patients aged ≤45 years
- A favorable trend was observed for MSWS-12 in the nonactive SPMS subgroup and patients aged >45 years (HR 0.82–0.89 and HR 0.80–0.87, respectively, for cutoffs of 6–10 points, both p=ns)
- In the EXPAND study, patients with 6mCDP on EDSS experienced a change of 8.3 (median)/9.89 (mean) in MSWS-12, suggesting an MCID of 8 or 10 points may be most appropriate

The Cox regression model (full analysis set) includes the predictors treatment, baseline MSWS, baseline EDSS and superimposed relapses at baseline (yes/no). Analyses in the 'active'/'nonactive' SPMS subgroups were not adjusted for relapses at baseline.
Confirmed progression in MSWS-12 is defined as an increase of 4–10 points
CI, confidence interval; 6m CDP, 6-month confirmed disability progression; EDSS, Expanded Disability Status Scale; HR, hazard ratio; MCID, minimal clinically important difference; MSWS-12, 12-item Multiple Sclerosis Walking Scale; n, number of patients with event; N', number of patients included in the analysis (i.e., with nonmissing covariates); ns, nonsignificant; SPMS, secondary progressive multiple sclerosis

Conclusions

- Siponimod reduced the increase from baseline in MSIS-29 and MSWS-12 scores, as well as the risk of confirmed clinically meaningful worsening of these PRO measures in patients with SPMS
- In the overall SPMS population, a more pronounced siponimod effect was observed with more stringent cutoffs (6–10 points) in MSWS-12 (20–25% risk reduction)
- Siponimod's effect for both PROs was more prominent in younger patients and in patients with active SPMS, showing a risk reduction in clinically meaningful worsening of 26% to 33% for MSWS-12 (6–10 points) and 27% to 37% for MSIS-29 physical score
- MCID analyses of PRO measures enables a more precise understanding of the nature of the PRO results described, mirroring reported clinically meaningful benefits of siponimod on disability and cognitive outcomes in SPMS patients

Disclosures

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MCID, minimal clinically important difference; MSIS-29, 29-item Multiple Sclerosis Impact Scale; MSWS-12, 12-item Multiple Sclerosis Walking Scale; PRO, patient-reported outcome measure; SPMS, secondary progressive multiple sclerosis