Effect of Siponimod on Disability Progression as Measured by the Ambulation Score, a Subscore of the Neurostatus-EDSS: Post hoc Analysis of the EXPAND Trial in SPMS

M. D`Souza[1,2], J. Gavin Giovannoni[3], Patrick Vermersch[4], Jeff Maca[5], Soudeh Ansari[6], Goeril Karlsson[7], Daniela Piani-Meier[7], Ludwig Kappos[1,2]

[1]Neurology, University Hospital Basel, Basel, Switzerland, [2]Neurology, VU University Medical Center, Amsterdam, The Netherlands, [3]Microsoft Research, Cambridge, United Kingdom, [4]Novartis Pharma AG, Basel, [5]Neurology, University Hospital Bern, Bern, Switzerland

Background

- More than 50% of patients with RRMS transition to SPMS within 15–20 years, and disability continues to gradually worsen. Majority of currently available treatments did not consistently show efficacy in slowing disability progression independent of relapses
- Neurostatus-eEDSS is a standardized electronic neurological assessment to quantify disease related impairment and disability in patients with MS. It includes an automated real-time consistency-check and a digital expert-based review system. As part of Neurostatus.eEDSS the Ambulation Score (AS) provides a numerical score from 0 to 16, based on walking distance as assessed during the site visit and type of assistance required for walking[1]
- In the Phase 3 EXPAND study in patients with SPMS, siponimod significantly reduced the Neurostatus-EDSS-measured risk of 3/6-month confirmed disability progression versus placebo by 21%/26%, with more pronounced effects (31%/37%) in patients with active SPMS[2]

EDSS, Expanded Disability Status Scale; RRMS, relapsing remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis

[1]D'Souza M et al. Mult Scler. 2020 Jul;26(8):993-996
[2]Kappos L, et al., Lancet. 2018;391(10127):1263-1273;

Objective

- To perform a post hoc analysis of the EXPAND trial data to assess the effect of siponimod on the AS of the Neurostatus-EDSS in patients with SPMS

Methods

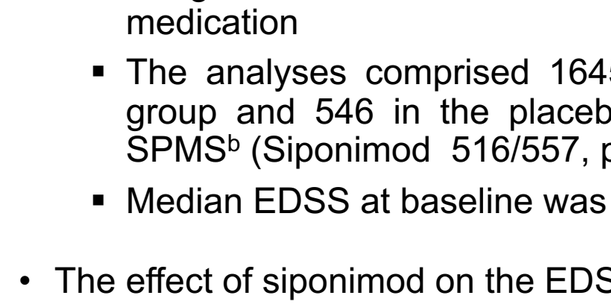
- EXPAND core part was a multi-center, randomized (2:1), double-blind, parallel-group, placebo-controlled, variable treatment duration, event-driven study in patients with SPMS[1] ([median (range) duration: 21 (0.2–37.0) months]):
  - The present analyses included all randomized subjects with assigned 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; active SPMS[a]/non-active SPMS[b] (Siponimod 516/557, placebo 267/270)
  - Median EDSS at baseline was 6.0
- The effect of siponimod on the EDSS and AS was evaluated by:
  - Difference in mean change in EDSS and AS from baseline was assessed using Jonckheere Terpstra test
  - Time-to-3 month and 6 month confirmed worsening on AS by ≥1/≥2-points was assessed by Cox regression adjusted for treatment and baseline AS
  - Categorical changes: Mantel Haenszel chi-square test was used to assess the effect of treatment on proportion of patients with 6 month confirmed worsening or confirmed improvement by ≥1-point during the core study

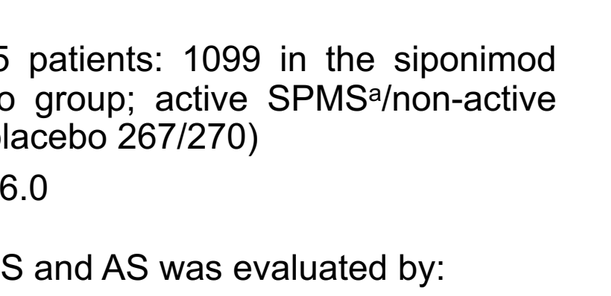
[a]presence of relapses in the 2 years prior to screening and/or ≥1 T1 gadolinium-enhancing lesion at baseline
[b]patients with no relapse in prior 2 years and no gadolinium-enhancing lesions at baseline .

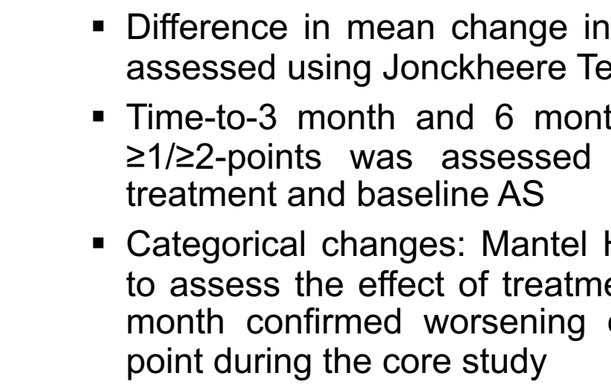
[1]Kappos L, et al., Lancet. 2018;391(10127):1263-1273;

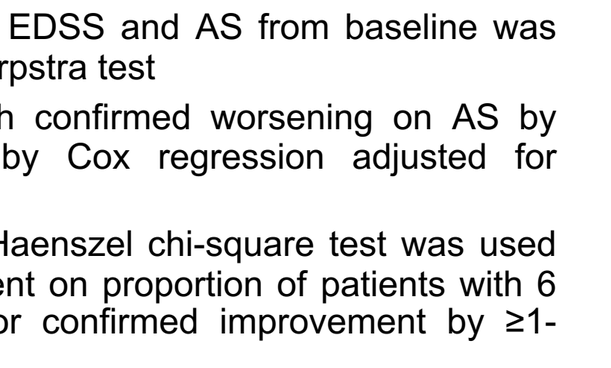
Results 1

Effect of siponimod on change in EDSS and AS from baseline in overall SPMS and in patients with active SPMS









M, month; N, number of subjects; OP, overall population;

Disclosures
● **Marcus D'Souza** received travel support from Bayer AG, Teva and Genzyme and research support from the University Hospital Basel ● **Gavin Giovannoni** is a steering committee member on the daclizumab trials for AbbVie, the BG12 and daclizumab trials for Biogen, the fingolimod and siponimod trials for Novartis, the laquinimod trials for Teva and the ocrelizumab trials for Roche. He has also received consultancy fees for advisory board meetings for oral cladribine trials for Merck KGaA, Sanofi Genzyme, and in relation to DSMB activities for Synthon BV, as well as honoraria for speaking at the Physicians' summit and several medical education meetings. He is also the Co-Chief Editor of Multiple Sclerosis and Related Disorders (Elsevier) ● **Patrick Vermersch** received honoraria and consulting fees from Biogen, Sanofi-Genzyme, Novartis, Teva, Merck, Roche, Imcyse, AB Science and BMS-Celgene and research supports from Novartis, Sanofi-Genzyme and Roche ● **Jeff Maca** is an employee of Novartis and may hold Novartis stocks ● **Soudeh Ansari** is an employee of Novartis and may hold Novartis stocks ● **Goeril Karlsson** is an employee of Novartis and may hold Novartis stocks ● **Daniela Piani-Meier** is an employee of Novartis and may hold Novartis stocks ● **Ludwig Kappos** has received the following exclusively for research support: Steering committee, advisory board, and consultancy fees (Actelion, Bayer HealthCare, Biogen, BMS, Genzyme, Janssen, Japan Tobacco, Merck, Novartis, Roche, Sanofi, Santhera, TG Therapeutics); Speaker fees (Bayer HealthCare, Biogen, Merck, Novartis, Roche, and Sanofi); Support of educational activities (Allergan, Bayer HealthCare, Biogen, CSL Behring, Desitin, Genzyme, Merck, Novartis, Roche, Pfizer, Sanofi, Shire, and Teva); License fees for Neurostatus products; And grants (Bayer HealthCare, Biogen, European Union, InnoSwiss, Merck, Novartis, Roche, Swiss MS Society, and Swiss National Research Foundation).
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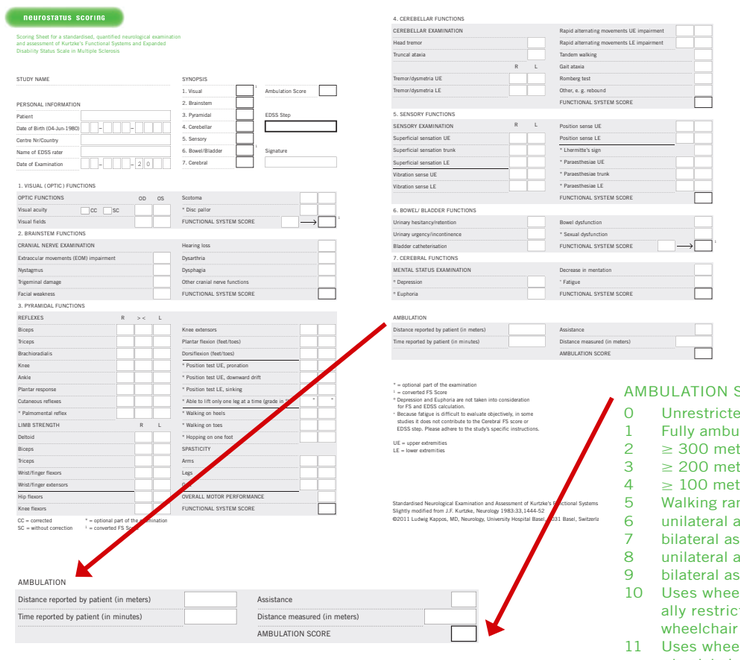


DISTANCE AND TIME REPORTED BY PATIENT

Maximal unassisted walking distance reported by patient (in meters) without rest or assistance and time required to walk max. distance according to patient (in minutes)

ASSISTANCE

0 Without help or assistance (allowing the use of an ankle foot orthotic device, without any other type of assistive device)
1 Unilateral assistance: one stick/crutch/brace
2 Bilateral assistance: two sticks/crutches/braces or assistance by another person
3 Wheelchair

DISTANCE

Measure the distance the patient is able to walk im meters.
Unassisted: observe the patient walking unassisted for a minimum distance of 500 meters and measure the time needed, if possible.
Assisted: observe the patient walking with the assistive device or help by another person for a minimum distance of 130 meters, if possible.

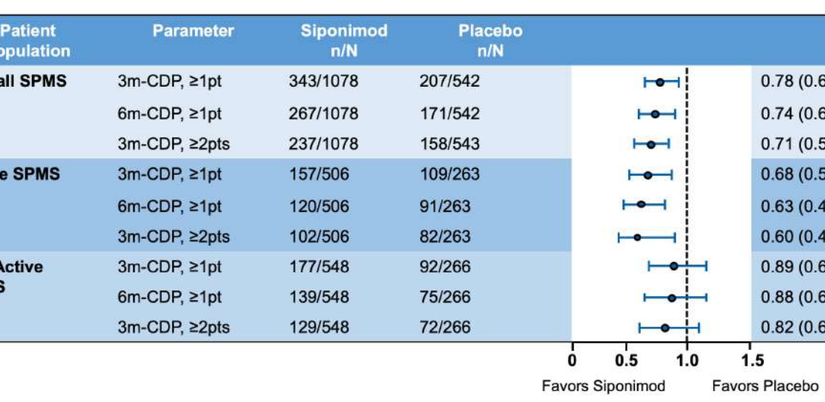
AMBULATION SCORE

0 Unrestricted
1 Fully ambulatory
2 ≥ 300 meters, but < 500 meters, without help or assistance (EDSS 4.5 or 5.0)
3 ≥ 200 meters, but < 300 meters, without help or assistance (EDSS 5.0)
4 ≥ 100 meters, but < 200 meters, without help or assistance (EDSS 5.5)
5 Walking range < 100 meters without assistance (EDSS 6.0)
6 unilateral assistance, ≥ 50 meters (EDSS 6.0)
7 bilateral assistance, ≥ 120 meters (EDSS 6.0)
8 unilateral assistance, < 50 meters (EDSS 6.5)
9 bilateral assistance, ≥ 5 meters, but < 120 meters (EDSS 6.5)
10 Uses wheelchair without help; unable to walk 5 meters even with aid, essentially restricted to wheelchair; wheels self and transfers alone; up and about in wheelchair some 12 hours a day (EDSS 7.0)
11 Uses wheelchair with help; unable to take more than a few steps; restricted to wheelchair; may need some help in transferring and in wheeling self (EDSS 7.5)
12 essentially restricted to bed or chair or perambulated in wheelchair, but out of bed most of day; retains many self-care functions; generally has effective use of

Results 2

Effect of siponimod on time to confirmed disease progression as measured using the AS in patients with SPMS

Patient population	Parameter	Siponimod n/N	Placebo n/N	HR	P value	Risk reduction
Overall SPMS	3m-CDP, ≥1pt	343/1078	207/542	0.78 (0.66-0.93)	0.0046	22-29%
	6m-CDP, ≥1pt	267/1078	171/542	0.74 (0.61-0.90)	0.0023	
	3m-CDP, ≥2pts	237/1078	158/543	0.71 (0.58-0.86)	0.0007	
Active SPMS	3m-CDP, ≥1pt	157/506	109/263	0.68 (0.53-0.87)	0.0021	32-40%
	6m-CDP, ≥1pt	120/506	91/263	0.63 (0.48-0.82)	0.0007	
	3m-CDP, ≥2pts	102/506	82/263	0.60 (0.45-0.80)	0.0005	
non Active SPMS	3m-CDP, ≥1pt	177/548	92/266	0.89 (0.69-1.15)	0.37	11-18%
	6m-CDP, ≥1pt	139/548	75/266	0.88 (0.66-1.16)	0.35	
	3m-CDP, ≥2pts	129/548	72/266	0.82 (0.61-1.09)	0.17	

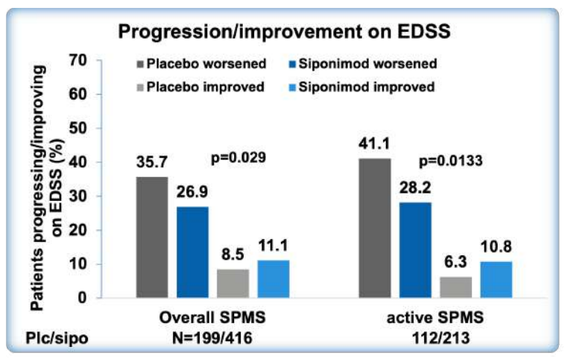


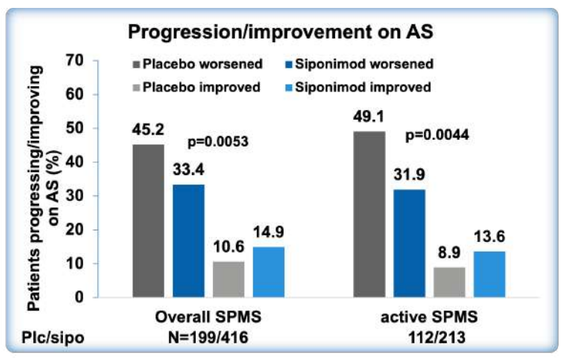
HR, hazardous ratiok; M, month; ns, non-significant; OP, overall population

Siponimod significantly reduced the risk of confirmed progression on the AS in overall and in the active SPMS population; the reduction was more apparent with more stringent parameters

Results 3

Effect of siponimod on proportion of patients with 6-m confirmed progression/improvement on EDSS and AS at 24 months





M, month; N, number of subjects; ns, non-significant; Plc, placebo; Sipo, Siponimod

- Significantly fewer patients worsened, and more patients improved on siponimod compared to patients on placebo on both the EDSS and the AS in overall SPMS and in the active SPMS population
- In patients with non-active SPMS, trends favoring siponimod vs placebo were observed for both the EDSS and the AS with fewer patients worsening on siponimod (Neurostatus-EDSS 24.6% vs 29.4% and AS 34.4% vs 40%, p=ns)

Conclusions

- These findings corroborate the efficacy of siponimod on disability progression in patients with SPMS
- Siponimod had a more pronounced effect on both Neurostatus-eEDSS and AS scores in overall and active SPMS sub-group and with the more stringent endpoint definitions
  - In non-active SPMS patients, favorable non-significant trends were observed
- Significantly less patients worsened, and more patients improved on the EDSS and AS with siponimod vs placebo
- The ambulation score of the Neurostatus-eEDSS might provide complementary information on disability progression, especially in patients with higher EDSS scores (requiring walking aids)
- The Neurostatus-eEDSS is a standardized method to reduce inconsistencies and background noise of the neurological assessment and to reliably detect progression