Long-term Efficacy and Safety of Siponimod in Patients with SPMS: EXPAND Extension Analysis up to 5 Years

Ludwig Kappos[1], Gavin Giovannoni[2], Ralf Gold[3], Robert J. Fox[4], Patrick Vermersch[5], Ralph H.B. Benedict[6], Amit Bar-Or[7], Nicolas Rouyrre[8], Daniela Piani-Meier[8], Shannon Ritter[9], Ajay Kilaru[8], Frank Dahlke[8], Goeril Karlsson[8], Bruce A.C. Cree[10]

Session S40.003

[1]Neurologic Clinic and Policlinic, Departments of Medicine, Clinical Research, Biomedicine and Biomedical Engineering, University Hospital and University of Basel, Basel, Switzerland; [2]Blizard Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, United Kingdom; [3]Department of Neurology, St Josef-Hospital/Ruhr-University Bochum, Bochum, Germany; [4]Mellen Center for Treatment and Research in Multiple Sclerosis, Neurological Institute, Cleveland Clinic, Cleveland, OH, USA; [5]Univ. Lille, INSERMU995, CHU Lille, FHU Imminent, F-59000 Lille, France; [6]Department of Neurology, University at Buffalo, Buffalo, NY, USA; [7]Center for Neuroinflammation and Experimental Therapeutics and Department of Neurology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; [8]Novartis Pharma AG, Basel, Switzerland; [9]Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; [10]Department of Neurology, UCSF Weill Institute for Neurosciences, University of California San Francisco, San Francisco, CA, USA

Disclosures

Ludwig Kappos' institution (University Hospital Basel) has received the following exclusively for research support: steering committee, advisory board and consultancy fees (Actelion, Addex, Bayer HealthCare, Biogen Idec, Biotica, Genzyme, Lilly, Merck, Mitsubishi, Novartis, Ono Pharma, Pfizer, Receptos, Sanofi, Santhera, Siemens, Teva, UCB and Xenoport); speaker fees (Bayer HealthCare, Biogen Idec, Merck, Novartis, Sanofi and Teva); support for educational activities (Bayer HealthCare, Biogen, CSL Behring, Genzyme, Merck, Novartis, Sanofi and Teva); license fees for Neurostatus products; and grants (Bayer HealthCare, Biogen Idec, European Union, Innoswiss, Merck, Novartis, Roche Research Foundation, Swiss MS Society and Swiss National Research Foundation).

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, Genzyme-Sanofi, 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).

Ralf Gold has received compensation for serving as a consultant or speaker from Bayer HealthCare, Biogen Idec, Merck Serono, Novartis and Teva Neuroscience, and he or the institution he works for has received research support from Bayer HealthCare, Biogen Idec, Merck Serono, Novartis and Teva Neuroscience; he has also received honoraria as a Journal Editor from SAGE and Thieme Verlag.

Robert J. Fox has received personal consulting fees from Actelion, Biogen, Celgene, EMD Serono, Genentech, Immunic, Novartis, and Teva. He has served on advisory committees for Actelion, Biogen, Immunic, and Novartis, and received clinical trial contract and research grant funding from Biogen and Novartis.

Patrick Vermersch has received honoraria and consulting fees from Biogen Idec, Genzyme-Sanofi, Bayer, Novartis, Merck Serono, GSK and Almirall, and research support from Biogen Idec, Genzyme-Sanofi, Bayer and Merck Serono.

Ralph H.B. Benedict has received fees from Acorda Therapeutics, Biogen, EMD Serono, Genentech-Roche, Mallinckrodt, National Multiple Sclerosis Society, Novartis Pharmaceuticals Corporation and Sanofi Genzyme.

Amit Bar-Or participated as a speaker in meetings sponsored by and received consulting fees and/or grant support from: Janssen/Actelion; Atara Biotherapeutics, Biogen Idec, Celgene/Receptos, Roche/Genentech, Medimmune, Merck/EMD Serono, Novartis, Sanofi-Genzyme.

Bruce A.C. Cree has received personal compensation for consulting from Akili, Alexion, Atara, Biogen, EMD Serono, Novartis, Sanofi and TG Therapeutics.

Nicolas Rouyrre, Daniela Piani Meier, Shannon Ritter, Ajay Kilaru, Frank Dahlke, and **Goeril Karlsson** are employees of Novartis.

Funding source: This study is supported by Novartis Pharma AG, Basel, Switzerland.

Acknowledgment: Medical writing support was provided by **Saimithra Thammera** and **Sreelatha Komatireddy** (employees of Novartis Healthcare Pvt. Ltd., Hyderabad, India). The final responsibility for the content lies with the authors.

Introduction

- Efficacy and safety of siponimod was evaluated in the EXPAND core study, the largest randomized, double-blind, parallel-group, placebo-controlled, event-driven Phase 3 trial in SPMS patients
    - An open-label extension is currently ongoing for up to a total of 7 years
- In the EXPAND core study, siponimod significantly reduced the relative risk of 3mCDP by 21% and 6mCDP by 26% compared with placebo and showed benefits in cognitive processing speed[1]
    - The safety profile of siponimod was in line with that of other S1P receptor modulators
- Long-term evaluation is important in the treatment of chronic disease progression in MS
    - Here we report the safety and efficacy results of the combined core and open-label extension parts of EXPAND study

CDP, confirmed disability progression; m, month; MS, multiple sclerosis; S1P, sphingosine 1-phosphate; SPMS, secondary progressive multiple sclerosis

1. Kappos L et al. *Lancet* 2018;391:1263-1273

Objective and Endpoints

Objective

- To assess the long-term safety and efficacy of siponimod in patients with SPMS from the core and extension parts of the EXPAND Phase 3 study

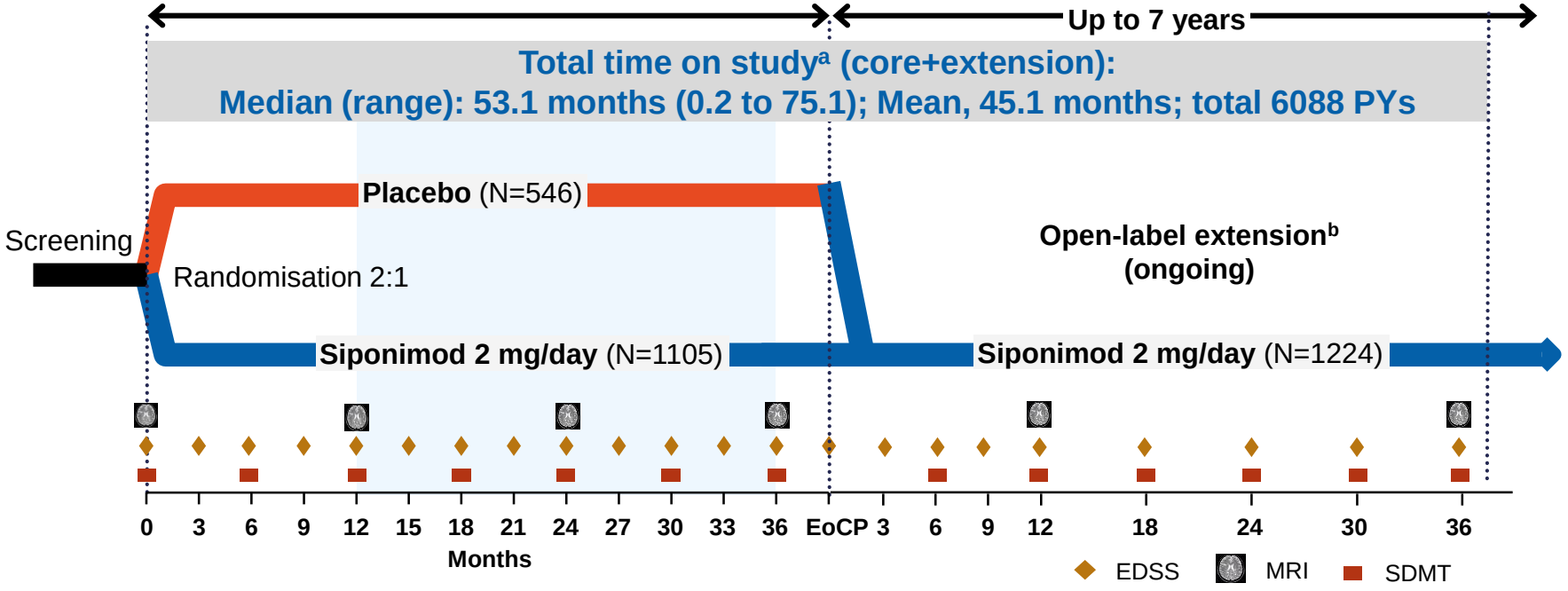
Endpoints

- Time-to-6mCDP based on EDSS score
- Time-to-6mCW[a] in cognitive processing speed (CPS) based on SDMT score
- ARR
- Safety (most common AEs, SAEs, AEs of special interest)

[a]Time-to-6m confirmed meaningful worsening of ≥4 points from baseline in SDMT score.

3m/6mCDP, 3-month or 6-month confirmed disability progression; 6mCW, 6-month confirmed worsening; AEs, adverse events; ARR, annualized relapse rate; CPS, cognitive processing speed; EDSS, Expanded Disability Status Scale; SAEs, serious adverse events; SDMT, Symbol Digit Modalities Test; SPMS, secondary progressive multiple sclerosis

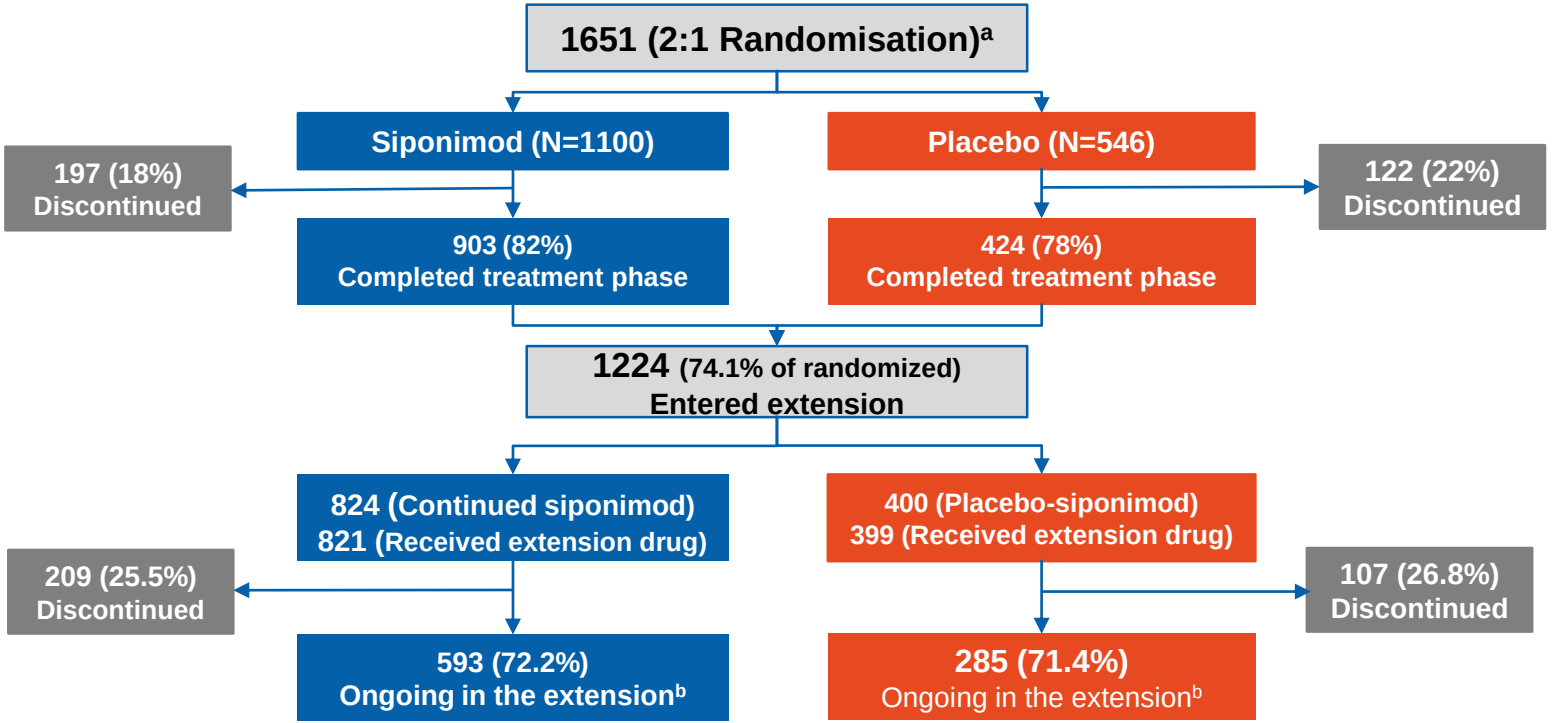
Study Design: EXPAND Core+Extension



[a]**Extension data cut-off: April 2019 (Month 36 visit of extension]; total study duration (core+extension): ≤5 years;** [b]Open-label starts when patient has an "event"

EDSS, Expanded Disability Status Scale; EoCP, end of core part; PYs, patient years; SDMT, Symbol Digit Modalities Test; SPMS, secondary progressive MS

Patient Disposition: Core+Extension



[a]Patients who received ≥1 dose of randomized treatment (siponimod 2 mg or placebo) in the core/extension parts were included in analysis; 5 patients randomized but not treated; [b]as of 06-Apr-2019

Baseline Characteristics at Randomization

Typical SPMS population

Parameter	Siponimod N=1105	Placebo N=546
Age, years	48.0 (7.8)	48.1 (7.9)
>41 years, n (%)	917 (83.0)	443 (81.1)
Duration of MS since the first symptom, years	17.1 (8.4)	16.2 (8.2)
Time since conversion to SPMS, years	3.9 (3.6)	3.6 (3.3)
Time since onset of the last relapse, years	5.15 (5.13)	4.52 (4.61)
No relapses in the last 2 years prior to screening, n (%)[a]	712 (64)	343 (63)
No relapses in the last year prior to screening, n (%)[a]	878 (79)	416 (76)
EDSS score	5.4 (1.1)	5.4 (1.0)
Median (min-max)	6.0 (2.0-7.0)	6.0 (2.5-7.0)
SDMT score	38.9 (13.99)	39.6 (13.34)
No Gd+ T1 lesions at baseline, n (%)[a]	833 (75)	415 (76)

All randomized set. Data represented as mean (SD), unless otherwise specified. [a]Number and percentage of patients with missing screening or baseline observations are not displayed

EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; SD, standard deviation; SPMS, secondary progressive multiple sclerosis

Duration of Exposure to Siponimod

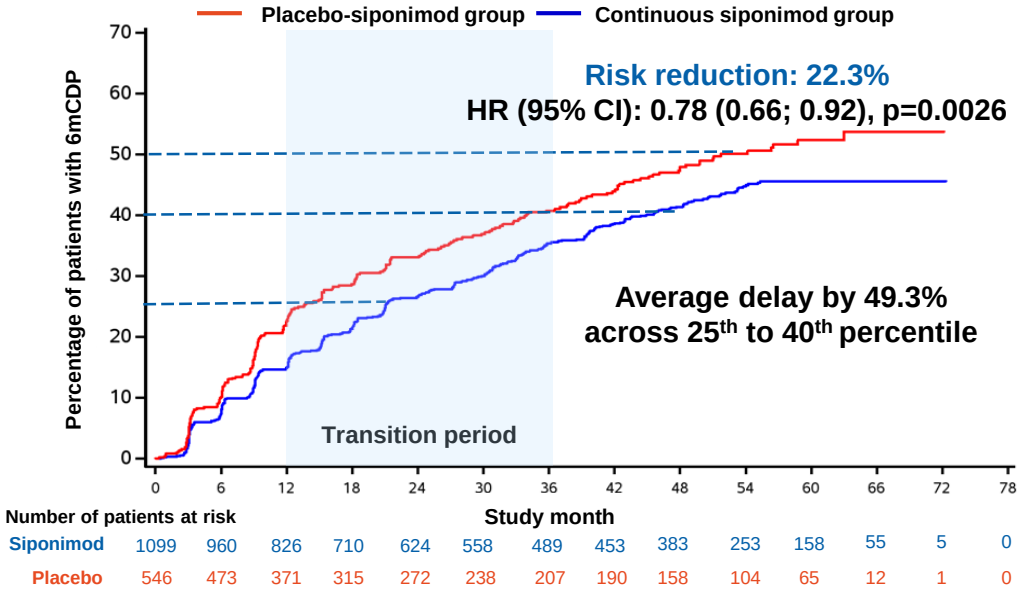
Cut-off: 06-Apr-2019

Duration of cumulative exposure to study drug	Continuous siponimod N=1099; n (%)	Placebo-siponimod N=418; n (%)	Overall siponimod 2 mg N=1517; n (%)
≥1 day	1099 (100)	418 (100)	1517 (100)
≥6 months	1005 (91.4)	394 (94.3)	1399 (92.2)
≥12 months	929 (84.5)	365 (87.3)	1294 (85.3)
≥18 months	865 (78.7)	336 (80.4)	1201 (79.2)
≥24 months	818 (74.4)	315 (75.4)	1133 (74.7)
≥3 years	728 (66.2)	226 (54.1)	954 (62.9)
≥4 years	615 (56.0)	19 (4.5)	634 (41.8)
≥5 years	278 (25.3)	2 (0.5)	280 (18.5)
Exposure in months, mean (SD)	**42.6 (21.8)**	**31.0 (12.5)**	**39.4 (20.4)**
Patient-time (patient-years)	**3903.6**	**1078.2**	**4981.7**

As of April 2019, the mean exposure to siponimod was 39.4 months, corresponding to 4981.7 patient-years

SD, standard deviation

Effect of Siponimod on 6-month Confirmed Disability Progression

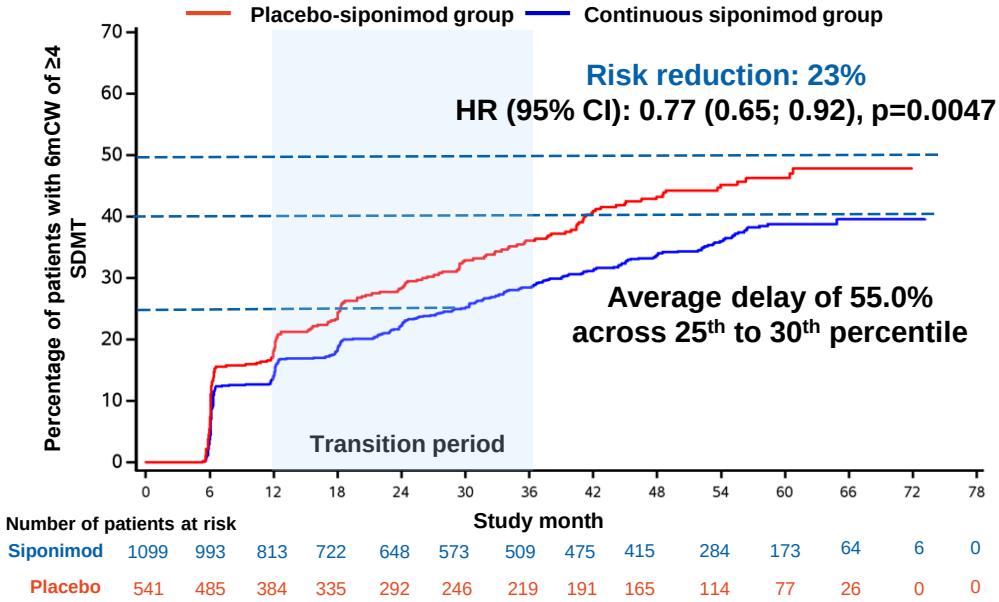


Percentile (months)	Placebo-siponimod (N=546)	Continuous siponimod (N=1099)	Delay (%)
25th	13.6	21.0	54%
30th	18.4	29.8	62%
40th	33.9	44.9	32%
Median	51.7	nr	

- **The risk of 6mCDP was reduced by 22.3% in the continuous siponimod group**
- **Time to 6mCDP was prolonged by 49%**

6mCDP, 6-month confirmed disability progression; CI, confidence interval; EDSS, Expanded Disability Status Scale; HR, hazard ratio; KM, Kaplan Meier

Effect of Siponimod on 6-month Confirmed Clinically Meaningful Worsening in Cognitive Processing Speed



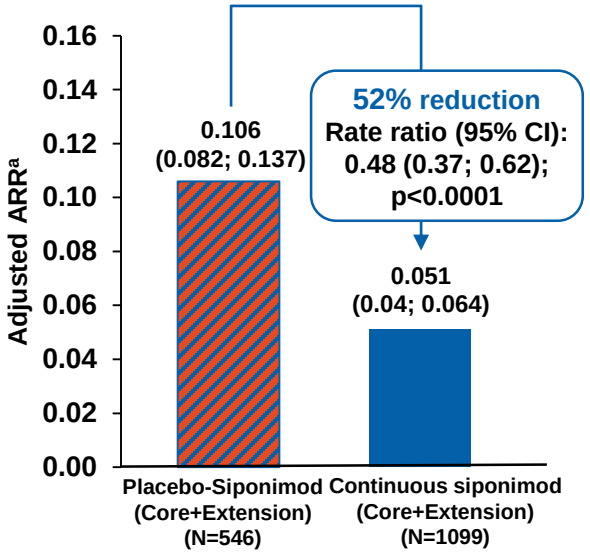
Percentile (months)	Placebo-siponimod (N=546)	Continuous siponimod (N=1099)	Delay (%)
25th	18.3	29.6	62%
30th	26.4	39.0	48%
40th	41.3	n.r.	

- The risk of 6mCW in Cognitive Processing Speed was reduced by 23% in the continuous siponimod group
- Time to 6mCW was prolonged by 55%

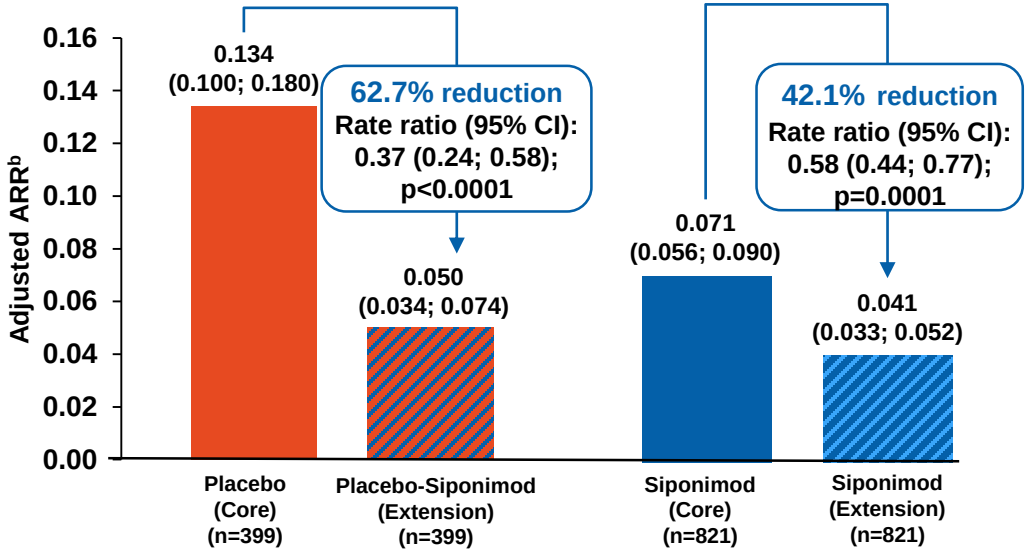
6mCW, 6-month confirmed worsening; CI, confidence interval; CPS, cognitive processing speed; HR, hazard ratio; KM, Kaplan Meier; n.r, not reached; SDMT, Symbol Digit Modalities Test

Siponimod Significantly Reduced ARR

Between group comparison (Continuous siponimod vs placebo-siponimod group)



Within group comparison (Within placebo and siponimod groups)

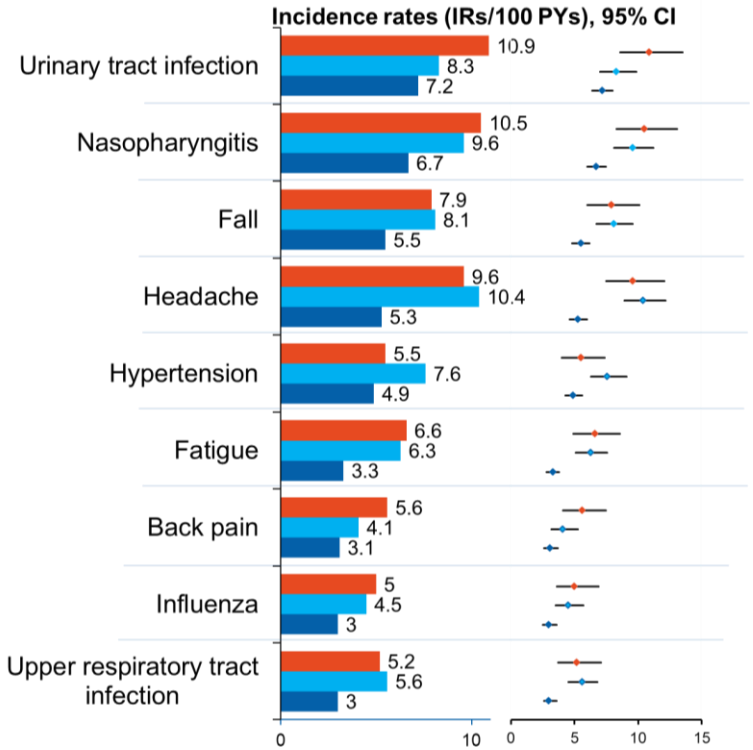


Overall ARR was significantly lower in the continuous siponimod versus the switch group
Relapse rate in the placebo group was lower after switching to siponimod

[a]Negative binomial regression model adjusted for the core part treatment group; [b]Poisson regression model adjusted for treatment period (core part, extension part); Both also adjusted for country, baseline EDSS, SPMS group (with/without superimposed relapses; baseline definition), and baseline number of T1 Gd+ lesions categories
ARR, annualized relapse rate; EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; SPMS, secondary progressive multiple sclerosis

Incidence of AEs per 100 Patient Years

IR ≥3 in Siponimod Group During Core+Extension



Placebo (Core) (N=546)

Siponimod (Core) (N=1099)

Siponimod (Core+Extension) (N=1517)

Patients with ≥1 AE

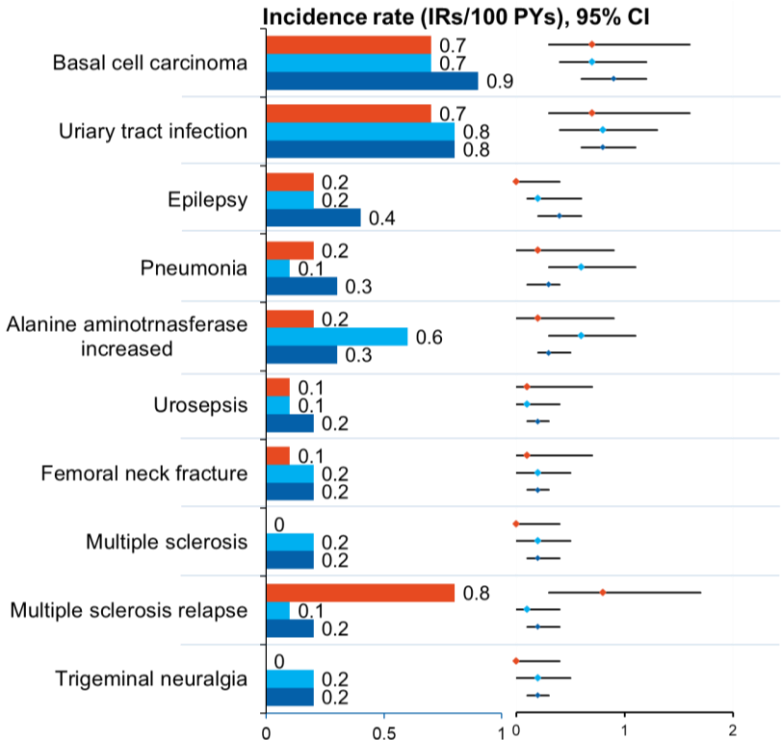
	n (IR)	Exposure (Patient Years)
Core study		
Siponimod (N=1099)	981 (249.2)	1674
Placebo (N=546)	446 (172.9)	809
Core+Extension		
Siponimod (N=1517)	1420 (184.2)	4982

IRs of the most common AEs reported in the core+extension parts were consistent with those of the core study

AEs, adverse events; **IR, incidence rate computed as number of patients with an AE divided by total exposure for the AE (i.e. cumulated exposure until first occurrence or until end of follow-up)**

Incidence of SAEs per 100 Patient Years

IR ≥0.2 in Siponimod Group During Core+Extension



Placebo (Core) (N=546)

Siponimod (Core) (N=1099)

Siponimod (Core+Extension) (N=1517)

Patients with ≥1 SAE

	n (IR)	Exposure (Patient Years)
Core study		
Siponimod (N=1099)	189 (12.1)	1674
Placebo (N=546)	74 (9.5)	809
Core+Extension		
Siponimod (N=1517)	463 (10.9)	4982

IRs of the most common SAEs reported in the core+extension parts were consistent with those of the core study

SAEs, serious adverse events; **IR, incidence rate computed as number patient with an SAE divided by total exposure for the SAE (i.e. cumulated exposure until first occurrence or until end of follow-up)**

AEs of Special Interest

AEs	Core (Double-Blind) Part		Core+Extension
	Siponimod 2 mg N=1099; n (IR)	Placebo N=546; n (IR)	Siponimod 2 mg N=1517; n (IR)
Infections and infestations[a]	545 (48.8)	270 (50.2)	958 (37.3)
VZV infections[b]	34 (2.0)	4 (0.5)	86 (1.8)
Herpes simplex virus infections[b]	25 (1.5)	11 (1.3)	44 (0.9)
Bradyarrhythmia during dose titration[b]	186 (12.6)	63 (8.3)	297 (7.0)
Hypertension[c*]	139 (8.9)	51 (6.6)	252 (5.8)
Liver function tests elevated[*]	146 (9.3)	22 (2.7)	253 (5.7)
Suicidality[c]	18 (1.0)	4 (0.5)	25 (0.5)
Lymphopenia[b*]	16 (0.9)	0 (0)	175 (3.7)**
Malignancies[c]	21 (1.2)	14 (1.7)	78 (1.6)
Basal cell carcinoma[d]	12 (0.7)	7 (0.8)	47 (0.9)

The incidence rates of AEs of special interest were similar in core and extension study

*Investigator-reported laboratory AEs; ***ALC were blinded in core phase but not in extension which increased lymphopenia in the extension study*

[a]System organ class; [b]Novartis MedDRA Query; [c]Standard MedDRA query (MedDRA version 19.0); [d]Preferred term; AEs, adverse events; **IR, incidence rate computed as number patient with an AE divided by total exposure for the AE (i.e. cumulated exposure until first occurrence or until end of follow-up**

Conclusions

- The treatment benefit of siponimod observed in the core study was sustained with long-term treatment for up to 5 years
  - Delay by approximately 50% in time to disability progression and to meaningful worsening in cognitive processing speed
- The long-term safety profile of siponimod for up to 5 years remained consistent with the core study
- Sustained differences favoring patients on continuous siponimod treatment versus patients who switched later from placebo to siponimod highlight the value of earlier treatment initiation