Siponimod versus placebo in secondary progressive multiple sclerosis (EXPAND): a double-blind, randomised, phase 3 study

*Ludwig Kappos, Amit Bar-Or, Bruce A C Cree, Robert J Fox, Gavin Giovannoni, Ralf Gold, Patrick Vermersch, Douglas L Arnold, Sophie Arnould, Tatiana Scherz, Christian Wolf, Erik Wallström, Frank Dahlke, for the EXPAND Clinical Investigators**

Summary

Background No treatment has consistently shown efficacy in slowing disability progression in patients with secondary progressive multiple sclerosis (SPMS). We assessed the effect of siponimod, a selective sphingosine 1-phosphate (S1P) receptor$_{1,5}$ modulator, on disability progression in patients with SPMS.

Methods This event-driven and exposure-driven, double-blind, phase 3 trial was done at 292 hospital clinics and specialised multiple sclerosis centres in 31 countries. Using interactive response technology to assign numbers linked to treatment arms, patients (age 18–60 years) with SPMS and an Expanded Disability Status Scale score of 3·0–6·5 were randomly assigned (2:1) to once daily oral siponimod 2 mg or placebo for up to 3 years or until the occurrence of a prespecified number of confirmed disability progression (CDP) events. The primary endpoint was time to 3-month CDP. Efficacy was assessed for the full analysis set (ie, all randomly assigned and treated patients); safety was assessed for the safety set. This trial is registered with ClinicalTrials.gov, number NCT01665144.

Findings 1651 patients were randomly assigned between Feb 5, 2013, and June 2, 2015 (1105 to the siponimod group, and 546 to the placebo group). One patient did not sign the consent form, and five patients did not receive study drug, all of whom were in the siponimod group. 1645 patients were included in the analyses (1099 in the siponimod group and 546 in the placebo). At baseline, the mean time since first multiple sclerosis symptoms was 16·8 years (SD 8·3), and the mean time since conversion to SPMS was 3·8 years (SD 3·5); 1055 (64%) patients had not relapsed in the previous 2 years, and 918 (56%) of 1651 needed walking assistance. 903 (82%) patients receiving siponimod and 424 (78%) patients receiving placebo completed the study. 288 (26%) of 1096 patients receiving siponimod and 173 (32%) of 545 patients receiving placebo had 3-month CDP (hazard ratio 0·79, 95% CI 0·65–0·95; relative risk reduction 21%; p=0·013). Adverse events occurred in 975 (89%) of 1099 patients receiving siponimod versus 445 (82%) of 546 patients receiving placebo; serious adverse events were reported for 197 (18%) patients in the siponimod group versus 83 (15%) patients in the placebo group. Lymphopenia, increased liver transaminase concentration, bradycardia and bradyarrhythmia at treatment initiation, macular oedema, hypertension, varicella zoster reactivation, and convulsions occurred more frequently with siponimod than with placebo. Initial dose titration mitigated cardiac first-dose effects. Frequencies of infections, malignancies, and fatalities did not differ between groups.

Interpretation Siponimod reduced the risk of disability progression with a safety profile similar to that of other S1P modulators and is likely to be a useful treatment for SPMS.

Funding Novartis Pharma AG.

Lancet 2018; 391: 1263–73

Published Online March 22, 2018 http://dx.doi.org/10.1016/S0140-6736(18)30475-6

See Comment page 1239

*Members listed in the appendix

Neurologic Clinic and Policlinic, Departments of Medicine, Clinical Research, Biomedicine, and Biomedical Engineering, University Hospital, University of Basel, Basel, Switzerland (Prof L Kappos MD); **Center for Neuroinflammation and Neurotherapeutics, and Multiple Sclerosis Division, Department of Neurology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA** (Prof A Bar-Or MD); **Neuroimmunology Unit, Montreal Neurological Institute and Hospital, McGill University, Montreal, QC, Canada** (Prof A Bar-Or); **UCSF Weill Institute for Neurosciences, Department of Neurology, University of California San Francisco, San Francisco, CA, USA** (Prof B A C Cree MD); **Mellen Centre for Multiple Sclerosis Treatment and Research, Neurological Institute, Cleveland Clinic, Cleveland, OH, USA** (R J Fox MD); **Blizard Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, UK** (Prof G Giovannoni MD); **Department of Neurology, St Josef-Hospital/Ruhr-University Bochum, Bochum, Germany** (Prof R Gold MD); **University of Lille, CHU Lille, LIRIC-INSERM U995, Lille, France** (Prof P Vermersch MD); **Montreal Neurological Institute, McGill University, Montreal, QC, Canada** (Prof D L Arnold MD); **NeuroRx Research, Montreal, QC, Canada** (Prof D L Arnold); **Novartis Pharma AG, Basel,**

Introduction

More than 50% of patients with relapsing-remitting multiple sclerosis (RRMS) transition to secondary progressive multiple sclerosis (SPMS) within 15–20 years.[1,2] Relapses are absent or infrequent in SPMS, yet disability continues to worsen gradually.[3,4] Most disease-modifying treatments for multiple sclerosis are indicated for relapsing forms of the disease, which include RRMS and SPMS with relapses. However, none of these therapies consistently showed efficacy in slowing disability progression in the subgroup of patients with SPMS.[5–9]

Siponimod selectively modulates sphingosine-1-phosphate (S1P) receptors S1P$_1$ and S1P$_5$.[10] Functional antagonism of S1P$_1$ reduces egress of lymphocytes from lymphoid tissues and prevents recirculation of peripheral lymphocytes to the CNS.[11] Siponimod readily crosses the blood–brain barrier,[12] and findings from preclinical studies suggest that it might prevent synaptic neurodegeneration[13] and promote remyelination in the CNS.[14] In a phase 2 dose-finding study in patients with RRMS, siponimod 2 mg/day reduced active brain lesion counts and annualised relapse rate (ARR) by approximately two-thirds.[15] Here, we report results from a

Switzerland (S Arnould MSc, T Scherz MD, E Wallström MD, F Dahlke MD)**; and Lycalis, Brussels, Belgium** (C Wolf MD)

Correspondence to: Prof Ludwig Kappos, Neurologic Clinic and Policlinic, Departments of Medicine, Clinical Research, Biomedicine, and Biomedical Engineering, University Hospital, University of Basel, CH-4031, Basel, Switzerland
ludwig.kappos@usb.ch

See Online for appendix

Research in context

Evidence before this study

A MEDLINE search from inception to Nov 9, 2017, with language restrictions, with the search terms ("secondary progressive multiple sclerosis"[Title] OR "secondary progressive MS"[Title] OR "SPMS"[Title]), identified 320 articles; search results were supplemented by a review of abstracts from recent major neurology conferences. Ten primary reports of randomised, masked, placebo-controlled clinical trials were identified as relevant. Five studies assessed interferon beta, whereas one each investigated the myelin-basic protein-derived synthetic peptide MBP8298, the antineoplastic agent mitoxantrone, the anti-α4-integrin monoclonal antibody natalizumab, intravenous immunoglobulins, and the immunomodulator linomide; this latter study was terminated prematurely. No active comparator studies were identified. The primary endpoint in six of the nine completed studies was disability progression confirmed by changes in Expanded Disability Status Scale (EDSS) score; this was a secondary endpoint in one study of interferon beta-1a, the primary endpoint of which was disability progression assessed using the Multiple Sclerosis Functional Composite scale. Two studies had composite primary endpoints: one study combined results of the EDSS, the timed 25-foot walk test, and the 9-hole peg test; the other study combined five clinical measures (change in EDSS, change in ambulation index, number of relapses requiring corticosteroids, time to first untreated relapse, and change in standardised neurological status). In the European interferon beta-1b study, patients receiving interferon beta-1b benefited from a significant reduction in time to confirmed disability progression (assessed by EDSS) compared with placebo, whereas patients in the subsequent US and Canadian interferon beta-1b study did not. Post-hoc analyses of the combined populations from these two trials showed that patients with active relapsing disease and above-average progressive disease before enrolment were most likely to benefit from treatment. In the study of intramuscular interferon beta-1a, patients receiving active treatment benefited from a reduction in disability worsening on the Multiple Sclerosis Functional Composite scale, but not on the EDSS relative to placebo. Mitoxantrone reduced disability progression and clinical exacerbations (as a composite endpoint) in a small study of fewer than 200 patients with worsening relapsing-remitting multiple sclerosis or secondary progressive multiple sclerosis (SPMS). Data supporting an effect on disability progression in the SPMS subgroup were not provided. None of the other trials showed a delay in disability progression.

Added value of this study

So far, no drug has consistently been shown to reduce disability progression in a representative SPMS population. EXPAND recruited a large population of patients with fewer signs of inflammatory disease activity and higher levels of disability at baseline than was the case in the European interferon beta-1b study, ensuring that outcomes were relevant to a representative SPMS population. For patients with SPMS, even numerically small changes in EDSS score can correspond to substantial changes in neurological function and daily activities. Accordingly, the delay in disability on EDSS (primary endpoint) and the benefits observed for several other clinical and MRI-related secondary outcomes are clinically relevant.

Implications of all available evidence

The siponimod EXPAND study is, to our knowledge, the first large trial of any disease-modifying therapy to show superiority over placebo in terms of disability progression in a representative population of patients with SPMS, including a large proportion of patients who had reached the non-relapsing stage of SPMS and had a high level of established disability.

phase 3, randomised, parallel-group, double-blind, placebo-controlled, event-driven, and exposure-driven trial (EXploring the efficacy and safety of siponimod in PAtients with secoNDary progressive multiple sclerosis [EXPAND]) that investigated the efficacy and safety of siponimod in patients with SPMS.

Methods

Study design and patients

This multicentre study was done at 292 hospital clinics and specialised multiple sclerosis centres in 31 countries (appendix p 7). The core part of the study was randomised, double blind, and placebo controlled. The core part was followed by an ongoing open-label extension part (appendix p 9), in which information is collected on long-term efficacy and safety for up to 10 years. Results reported here are from the core part of the study only.

We planned to do the primary analysis when a minimum of 374 3-month confirmed disability progression (CDP) events had been reported. During the study, more CDP events were observed than had been expected originally, thus possibly shortening the follow-up time. We therefore amended the protocol on Oct 6, 2015, to stop the core part of the study after occurrence of 374 CDP events and after at least 95% of patients had been randomly assigned to treatment for at least 12 months.

Patients were enrolled by study investigators. Key eligibility criteria were age 18–60 years, a diagnosis of SPMS,[3,4,16] documented moderate-to-advanced disability indicated by an Expanded Disability Status Scale (EDSS) score[17] of 3·0–6·5 at screening (range 0–10; higher scores indicate greater disability; 3·0=moderate disability in one functional system or minor disability in more than two functional systems; 6·0 or 6·5=unilateral or bilateral assistance needed to walk a minimum of 100 m or 20 m, respectively), a history of RRMS (2010 McDonald criteria),[18] documented EDSS progression in the 2 years

before the study, and no evidence of relapse in the 3 months before randomisation.

Key exclusion criteria included substantial immunological, cardiac, or pulmonary conditions, ongoing macular oedema, uncontrolled diabetes, CYP2C9*3/*3 genotype, and varicella zoster virus antibody negative status. Full eligibility criteria are listed in the appendix (pp 4–7).

The study protocol is available online.

For the **protocol** see https://dkf.unibas.ch/research/ludwig-kappos

Randomisation and masking

Eligible patients were randomly assigned (2:1) to receive once daily oral siponimod 2 mg or matching placebo by blocked randomisation with a block size of 6. Randomisation was stratified for each of the 31 countries (appendix p 7). From days 1–6, the dose of study drug was titrated from 0·25 mg to the 2 mg maintenance dose. Re-titration was needed if treatment was interrupted for 4 or more consecutive days. Study drug and placebo were identical in packaging, labelling, schedule of administration, appearance, taste, and odour.

To ensure that the treatment assignment was unbiased and concealed from patients and study staff, the randomisation list was produced by an interactive response technology provider (Parexel, Billerica, MA, USA) using a validated system automating the random assignment of patient numbers to randomisation numbers. Randomisation numbers were linked to the different treatment groups, which in turn were linked to medication numbers. A separate medication list was produced by Novartis drug supply management using a validated system that automated the random assignment of medication numbers to packs containing the study drugs. Patients and study staff remained masked to treatment assignment for the duration of the core part of the study.

Reductions of heart rate and lymphocyte counts are known pharmacological effects of siponimod that could potentially unmask study participants. To maintain masking, an independent doctor monitored patients during dose titration, and the counts for the total number of leucocytes, neutrophils, and lymphocytes were normally withheld by the central laboratory and only reported to the investigator in case of notable abnormalities (appendix p 6). All EDSS scores were obtained by trained, certified assessors who were not otherwise involved in patient management. The training and certification tool can be found online.

The trial adhered to the International Conference on Harmonization Guidelines for Good Clinical Practice and to the Declaration of Helsinki.[19] Institutional review boards or ethics committees approved the protocol at all sites. All patients included in the analysis gave written informed consent before commencing the study.

Procedures

A full neurological examination, including an assessment of walking range, Functional Systems and Expanded Disability Status Scale (EDSS) score, was obtained every 3 months by a trained and certified assessor. An electronic tablet-based tool (Neurostatus e-scoring, University Hospital Basel, Basel, Switzerland) was used to score neurological examinations, with real-time algorithm-based consistency checks and independent central expert review of inconsistencies.[20] MRI scans were scheduled at baseline, 12 months, 24 months, and 36 months and at the end of the controlled treatment phase (if different from annual visits). The data were analysed independently at a central reading site (NeuroRX Research, Montreal, QC, Canada), by staff unaware of trial group assignments.

Patients with 6-month CDP during double-blind treatment were reconsented to either continue double-blind treatment, switch to open-label siponimod, or stop study treatment while following an abbreviated schedule of assessments and either remain untreated or receive another disease-modifying therapy.

Outcomes

The primary endpoint was time to 3-month CDP. CDP was defined as a 1-point increase in EDSS if the baseline score was 3·0–5·0, or a 0·5-point increase if the baseline score was 5·5–6·5, confirmed at a scheduled visit at least 3 months later. The two key secondary endpoints were time to 3-month confirmed worsening of at least 20% from baseline in the timed 25-foot walk test (T25FW) and change from baseline in T2 lesion volume. Additional secondary endpoints were: time to 6-month CDP; ARR; time to first relapse; proportion of relapse-free patients; change in score on the patient-reported 12-item Multiple Sclerosis Walking Scale; number of new or enlarging T2 lesions; number of T1 gadolinium-enhancing lesions; and percentage change in brain volume from baseline. Time to 3-month CDP was also analysed in patient subgroups predefined by: the presence or absence of relapses in the 2 years before randomisation; rapid progression (an increase in EDSS score of at least 1·5 points in the 2 years before randomisation); and a Multiple Sclerosis Severity Score[21] of 4 or more at baseline.

Adverse events and laboratory abnormalities were reported descriptively. Adverse events were coded according to the Medical Dictionary for Regulatory Activities, version 19.0. To characterise cardiac safety during dose titration, patients underwent continuous mobile cardiac telemetry. For patients from countries where mobile cardiac telemetry technology was not approved as a medical device, holter electrocardiograms were recorded on 3 days (appendix p 8).

For the **assessor training and certification tool** see https://www.neurostatus.net/index.php?file=impressum

Statistical analysis

With 2:1 randomisation of siponimod to placebo, observation of at least 374 3-month CDP events gave the study 90% power to detect a 30% reduction in the risk of 3-month CDP, using a log-rank test with a two-sided significance level of 5%.

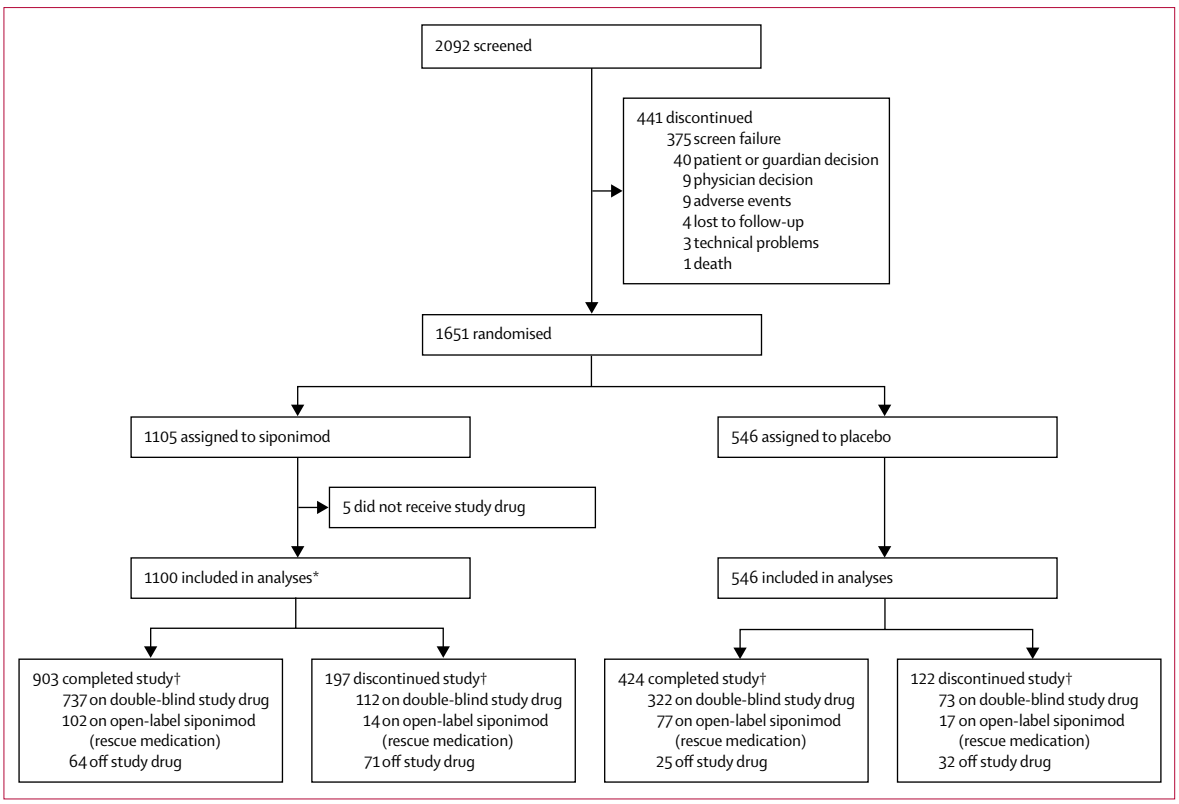

Figure 1: **Patient disposition**
*One patient randomly assigned to siponimod was excluded from all safety and efficacy analyses because no signed consent form was supplied before study entry.
†Double-blind, placebo-controlled core part of EXPAND.

The differences between siponimod and placebo in time to 3-month CDP and in time to 3-month confirmed worsening of at least 20% in the T25FW were tested using a Cox proportional hazards model and by the log-rank test. For the Cox proportional hazard model, patients with missing covariates were excluded from the analyses. Assumptions of the Cox proportional hazards model were tested. For the primary endpoint, treatment, country, baseline EDSS, and SPMS group (with or without superimposed relapses, baseline definition) were covariates in the Cox model. For the secondary endpoint of time to 3-month confirmed worsening of at least 20% from baseline in the timed T25FW, treatment, country, baseline EDSS, baseline T25FW, and SPMS group (with or without superimposed relapses, baseline definition) were covariates in the Cox model. Risk reduction was derived as (1–hazard ratio)×100.

T2 lesion volume and percentage change in brain volume were analysed using a mixed model for repeated measures, with visit as the categorical factor. For T2 lesion volume, the model was adjusted for treatment, country, age, baseline volume of T2 lesion, number of T1 gadolinium-enhanced lesions at baseline, and SPMS group (with or without relapses, baseline definition). Adjusted mean is defined as the change from baseline in T2 lesion volume. For percentage change in brain volume, the model was adjusted for treatment, country, age, normalised brain volume at baseline, number of T1 gadolinium-enhanced lesions at baseline, T2 lesion volume at baseline, and SPMS group (with or without relapses, baseline definition). Adjusted mean refers to percentage change in brain volume from baseline. Lesion numbers and ARR were estimated by negative binomial regression (appendix p 8).

The primary endpoint was tested at an adjusted α level of 0·0434 based on the O'Brien–Fleming correction (appendix p 8).[22] The two key secondary endpoints were tested in hierarchical order at a two-sided significance level of 0·05. Additional secondary endpoints were assessed at a nominal significance level of 0·05 without correction for multiplicity or hierarchical testing. Primary and secondary endpoints were analysed in the full analysis set, comprising all randomised and treated patients. Following the intention-to-treat principle, all available data were used, irrespective of premature discontinuation of blinded study medication.

Safety was assessed in the safety set, which included all patients who received at least one dose of study drug; patients were analysed according to the actual treatment received. Adverse events on the double-blind study drug continued for 30 days after the drug was stopped. Serious adverse events are reported for the

core part of the study, including open-label siponimod periods in the core part.

Results were reviewed by the sponsor and by the steering committee. An independent data monitoring committee reviewed safety data and provided guidance (appendix p 2).

This trial is registered with ClinicalTrials.gov, number NCT01665144.

Role of the funding source

The funder participated in the study design and conduct, data collection, management, analysis and interpretation, and the writing of the study report. All authors had full access to all the data in the study, and the corresponding author had final responsibility for the decision to submit for publication.

Results

From Feb 5, 2013, to June 2, 2015, 1651 patients were randomly assigned: 1105 to siponimod, and 546 to placebo (figure 1). In the siponimod group, five patients never received study drug, and one patient did not provide signed informed consent before starting study procedures; these patients were excluded from safety and efficacy analyses (figure 1). Baseline characteristics were similar between groups (table 1). Median time on study was 21 months (range 0·2–37·0). Median exposure to study drug was 18 months (range 0–37 months). 1327 (80%) of 1651 patients completed the study (903 [82%] on siponimod *vs* 424 [78%] on placebo), of whom 179 (11%) switched to open-label siponimod (102 [9%] *vs* 77 [14%]), and 89 (5%) stopped study medication (64 [6%] *vs* 25 [5%]) and followed an abbreviated assessment schedule.

In the time-to-event analysis, 288 (26%) of 1096 patients in the siponimod group and 173 (32%) of 545 in the placebo group had 3-month CDP (hazard ratio [HR] 0·79, 95% CI 0·65–0·95; risk reduction 21%; p=0·013; table 2, figure 2). The test of Cox model assumptions did not indicate a deviation from the proportional hazards assumption (p=0·37; appendix p 11).

No significant difference was observed in the time to 3-month confirmed worsening of at least 20% in T25FW for the overall population (HR 0·94, 95% CI 0·80–1·10; risk reduction 6%; p=0·44; table 2; appendix p 12) or for patients with a baseline EDSS score of 5·5 or lower (post-hoc analysis; p=0·25; appendix p 12). Post-hoc analysis of the percent change from baseline in T25FW revealed a high variability of this measure at month 12 and month 24, which was more pronounced in participants with higher baseline EDSS scores (data not shown).

The risk of 6-month CDP was reduced by siponimod (HR 0·74, 95% CI 0·60–0·92; risk reduction 26%; p=0·0058; table 2, figure 2). As shown in figure 2, point estimates of time to 3-month CDP in patient subgroups predefined by relapse activity, disease progression, and disease severity were consistent with the primary endpoint,

	Siponimod (n=1105)	Placebo (n=546)
Age (years)		
Mean (SD)	48·0 (7·8)	48·1 (7·9)
Median (range)	49·0 (22–61)	49·0 (21–61)
Age group		
18–40 years	188 (17%)	103 (19%)
>41 years	917 (83%)	443 (81%)
Sex		
Women	669 (61%)	323 (59%)
Men	436 (39%)	223 (41%)
Time since diagnosis of multiple sclerosis (years)		
Mean (SD)	12·9 (7·9)	12·1 (7·5)
Median (range)	12·0 (0·1–44·4)	11·2 (0·4–39·4)
Time since onset of multiple sclerosis symptoms (years)		
Mean (SD)	17·1 (8·4)	16·2 (8·2)
Median (range)	16·4 (1·4–45·0)	15·4 (1·3–43·0)
Time since conversion to SPMS (years)		
Mean (SD)	3·9 (3·6)	3·6 (3·3)
Median (range)	2·6 (0·1–24·2)	2·5 (0·1–21·7)
No previous use of disease-modifying therapy	245 (22%)	114 (21%)
No relapses in the year before screening	878 (79%)	416 (76%)
No relapses in the 2 years before screening*	712 (64%)	343 (63%)
Number of relapses in the year before screening		
Mean (SD)	0·2 (0·5)	0·3 (0·6)
Median (range)	0 (0–4)	0 (0–4)
Number of relapses in the 2 years before screening		
Mean (SD)	0·7 (1·2)	0·7 (1·2)
Median (range)	0 (0–12)	0 (0–8)
EDSS score		
Mean (SD)	5·4 (1·1)	5·4 (1·0)
Median (range)	6·0 (2·0–7·0)	6·0 (2·5–7·0)
EDSS categories		
<3·0	6 (1%)	2 (<1%)
3·0–4·5	312 (28%)	148 (27%)
5·0–5·5	165 (15%)	100 (18%)
6·0–6·5	620 (56%)	295 (54%)
>6·5	2 (<1%)	1 (<1%)
Gadolinium-enhancing lesions on T1-weighted images		
Yes	237 (21%)	114 (21%)
No	833 (75%)	415 (76%)
Not assessed	35 (3%)	17 (3%)
Total volume of lesions on T2-weighted images (mm^3)†		
Mean (SD)	15 632 (16 268)	14 694 (15 620)
Median (range)	10 286 (23–116 664)	9994 (0–103 560)
Normalised brain volume (cm^3)‡		
Mean (SD)	1422 (86)	1425 (88)
Median (range)	1421 (1136–1723)	1425 (1199–1691)

Data are number (%) or n/N (%), unless specified otherwise. Some percentages do not add up to 100 because of rounding. SPMS=secondary progressive multiple sclerosis. EDSS=Expanded Disability Status Scale. *For three patients in the siponimod and one patient in the placebo group, information on the number of relapses in the past 2 years was not available. †1074 patients were assessed in the siponimod, and 531 patients were assessed in the placebo group. ‡1071 patients were assessed in the siponimod group, and 531 patients were assessed in the placebo group.

Table 1: **Demographics and baseline characteristics in the randomised set**

	Siponimod (n=1099)	Placebo (n=546)	Between-group difference* (95% CI)	p value
Primary endpoint				
Confirmed disability progression at 3 months	288/1096 (26%)	173/545 (32%)	HR 0·79 (0·65 to 0·95)	0·013
Key secondary endpoints				
Worsening of ≥20% from baseline in T25FW confirmed at 3 months	432/1087 (40%)	225/543 (41%)	HR 0·94 (0·80 to 1·10)	0·44
Change from baseline in total volume of lesions on T2-weighted images (mm^3)†				
Month 12, adjusted mean	204·9 (72·6 to 337·3)	818·0 (646·8 to 989·3)	−613·1 (−800·2 to −426·0)	<0·0001‡
Month 12, total number	997	497	..	..
Month 24, adjusted mean	162·9 (17·9 to 307·9)	940·4 (749·7 to 1131·1)	−777·5 (−990·6 to −564·4)	<0·0001‡
Month 24, total number	614	299	..	..
Mean over months 12 and 24, adjusted mean	183·9 (53·8 to 314·0)	879·2 (711·6 to 1046·8)	−695·3 (−877·3 to −513·3)	<0·0001‡
Other secondary endpoints				
Clinical				
Disability progression confirmed at 6 months	218/1096 (20%)	139/545 (26%)	HR 0·74 (0·60 to 0·92)	0·0058‡
Annualised relapse rate (95% CI)	0·07 (0·06 to 0·09)	0·16 (0·12 to 0·21)	RR 0·45 (0·34 to 0·59)	<0·0001‡
Time to first confirmed relapse	113/1061 (11%)	100/528 (19%)	HR 0·54 (0·41 to 0·70)	<0·0001‡
Change in MSWS-12 score from baseline§				
Month 12, adjusted mean	1·53 (0·20 to 2·86)	3·36 (1·58 to 5·14)	−1·83 (−3·85 to 0·19)	0·076
Month 12, total number	917	448	..	..
Month 24, adjusted mean	4·16 (2·49 to 5·82)	5·38 (3·09 to 7·67)	−1·23 (−3·89 to 1·44)	0·37
Month 24, total number	401	194	..	..
Mean over all visits (up to an including month 30), adjusted mean	2·69 (1·46 to 3·92)	4·46 (2·82 to 6·10)	−1·77 (−3·59 to 0·05)	0·057
MRI related				
Percent brain volume change from baseline¶				
Month 12, adjusted mean	−0·28% (−0·34 to −0·23)	−0·46% (−0·52 to −0·39)	0·18% (0·10 to 0·25)	<0·0001‡
Month 12, total number	903	439	..	..
Month 24, adjusted mean	−0·71% (−0·78 to −0·64)	−0·84% (−0·93 to −0·75)	0·13% (0·02 to 0·24)	0·020‡
Month 24, total number	470	239	..	..
Mean over months 12 and 24, adjusted mean	−0·50% (−0·55 to −0·44)	−0·65% (−0·72 to −0·58)	0·15% (0·07 to 0·23)	0·0002‡
Cumulative number of gadolinium-enhancing lesions on T1-weighted MRI per scan from post-baseline scans up to and including month 24 (adjusted mean)‖	0·08 (0·07 to 0·10)	0·60 (0·47 to 0·76)	RR 0·14 (0·10 to 0·19)	<0·0001‡
Patients with no gadolinium-enhancing lesions on T1-weighted MRI on all post-baseline scans/patients with at least one scan post-baseline	917/1026 (89%)	341/510 (67%)	..	..
Mean number of new or enlarging lesions on T2-weighted images over all visits (adjusted mean)	0·70 (0·58 to 0·84)	3·60 (3·03 to 4·29)	RR 0·19 (0·16 to 0·24)	<0·0001‡
Patients with no new or enlarging lesions on T2-weighted images on all post-baseline scans/patients with at least one scan post-baseline	584/1026 (57%)	190/510 (37%)	..	..

Data are n/N (%) or adjusted mean (95% CI), unless otherwise specified. N=number of patients included in the analysis. Total number=number of patients with non-missing baseline and post-baseline values at a given visit. Hierarchical testing was confined to the primary and two key secondary endpoints. p values for secondary endpoints are not corrected for multiplicity. HR=hazard ratio. T25FW=timed 25-foot walk test. RR=rate ratio. MSWS-12=12-point Multiple Sclerosis Walking Scale. *Unless otherwise specified as HR or RR. †Data included in this analysis were available for 995 patients in the siponimod group and 495 patients in the placebo group (ie, patients with missing co-variates were excluded). ‡p values are nominally significant. §Data included in this analysis were available for 1022 patients in the siponimod group and 516 patients in the placebo group. ¶Data were available for 894 patients in the siponimod group and 436 patients in the placebo group. ‖Data included in this analysis were available for 996 patients in the siponimod group and 496 patients in the placebo group.

Table 2: **Primary and secondary endpoints**

favouring siponimod over placebo. Exploratory analyses of time to 3-month CDP in additional subgroups defined by occurrence of relapses or contrast-enhancing lesions before entry, and post-hoc sensitivity analyses including 3-month CDP sustained until the end of study were also consistent with the primary endpoint (appendix pp 11, 14). Furthermore, post-hoc analyses of time to 6-month CDP in pre-defined subgroups favoured siponimod across all endpoints (appendix p 13). The adjusted mean increase across all visits in the 12-item Multiple Sclerosis Walking Scale was 2·69 (95% CI 1·46–3·92) with siponimod versus 4·46 (2·82–6·10) with placebo (p=0·057; table 2). ARR was lower with siponimod than with placebo (rate ratio 0·45, 95% CI 0·34–0·59; risk reduction 55%, p<0·0001), as was time to confirmed first relapse (HR 0·54, 95% CI 0·41–0·70; risk reduction 46%; p<0·0001; table 2).

Increase in T2 lesion volume from baseline was lower with siponimod than with placebo (adjusted mean over months 12 and 24 183·9 mm^3 *vs* 879·2 mm^3; between-group difference –695·3 mm^3, 95% CI –877·3 to –513·3;

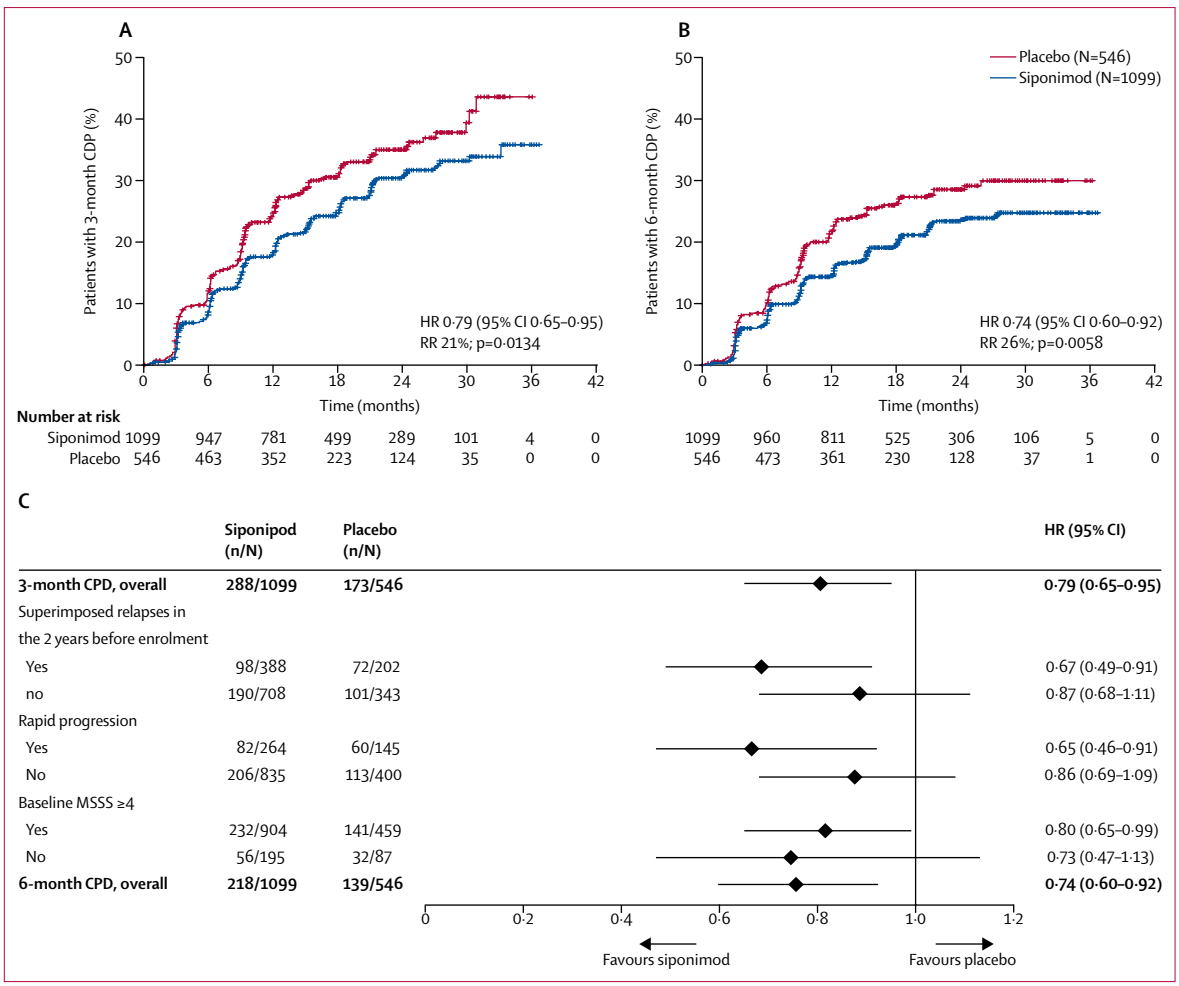

Figure 2: **Confirmed disability progression in the full analysis set**
(A) Time to 3-month CDP (primary endpoint). (B) Time to 6-month CDP (secondary endpoint). (C) Risk of 3-month CDP, overall and in predefined patient subgroups, and overall risk of 6-month CDP (secondary endpoints). N is the number of patients included in the subgroup. The study was not designed to test for a statistically significant difference between siponimod and placebo in these subgroups, so p values are not displayed. See appendix for exploratory analyses in further predefined subgroups for risk of 3-month CDP (p 11) and of 6-month confirmed disability progression (p 13). CDP=confirmed disability progression. HR=hazard ratio. RR=risk reduction. MSSS=Multiple Sclerosis Severity Score.

p<0·0001; table 2, figure 3A). Brain volume decreased at a lower rate with siponimod than with placebo (adjusted mean percentage brain volume change over months 12 and 24, –0·50% *vs* –0·65%; between-group difference 0·15%, 95% CI 0·07–0·23; p=0·0002; table 2, figure 3B). More patients receiving siponimod than placebo were free from gadolinium-enhancing lesions (89% *vs* 67%) and from new or enlarging T2 lesions (57% *vs* 37%; table 2).

1645 patients were included in the safety set: 1099 on siponimod and 546 on placebo (table 3). 975 patients (89%) receiving siponimod and 445 (82%) receiving placebo experienced at least one adverse event, and 197 (18%) patients on siponimod and 83 (15%) on placebo had at least one serious adverse event. 84 patients (8%) discontinued siponimod because of an adverse event compared with 28 (5%) patients on placebo.

Headache, nasopharyngitis, urinary tract infection, and falls were the most frequent adverse events, being reported in more than 10% of patients in both treatment groups (appendix p 16). Hypertension was reported in 115 patients (10%) on siponimod compared with 41 (8%) on placebo. Serious adverse events experienced by at least 0·5% of patients in either group were increased liver transaminase concentrations, basal cell carcinoma, concussion, depression, urinary tract infection, suicide attempt, gait disturbance, multiple sclerosis relapse, and paraparesis (table 3).

Four deaths occurred in each treatment group. Deaths in the siponimod group were due to metastatic gastrointestinal melanoma within 4 months of commencing siponimod; septic shock in a patient with terminal colon cancer; urosepsis more than 10 weeks after discontinuation of siponimod and after two doses of rituximab; and suicide. One additional patient withdrew consent from the study with metastatic lung carcinoma having been on siponimod for 11 months; this patient died

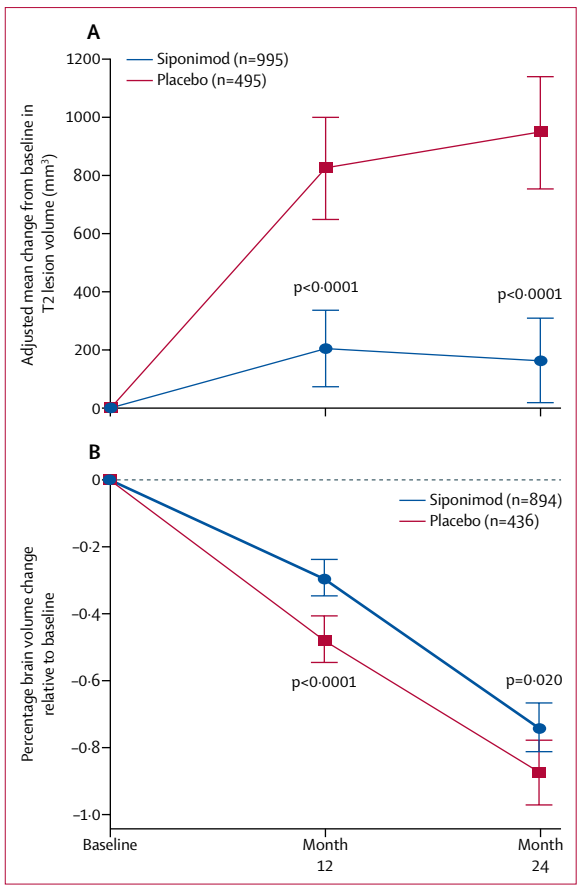

Figure 3: **MRI-related endpoints in the full analysis set**
(A) Absolute change in the total volume of brain lesions on T2-weighted MRI from baseline to month 24 (second key secondary endpoint). (B) Percentage change in brain volume from baseline to month 24 (secondary endpoint). Bars are 95% CIs. Volume of T2 lesions was assessed in 1494 patients (997 siponimod *vs* 497 placebo) at month 12 and in 913 patients (614 *vs* 299) at month 24. The percentage change in brain volume was assessed in 1342 patients (903 siponimod *vs* 439 placebo) at month 12 and in 709 patients (470 *vs* 239) at month 24.

(unspecified reason) about 5 months after discontinuing study medication. Deaths in the placebo group were due to haemorrhagic stroke, lung cancer, gastric cancer, and for an unknown reason.

Proportionally more patients receiving siponimod experienced adverse events previously associated with S1P-receptor modulation, such as bradycardia at treatment initiation (4% *vs* 3%), hypertension (12% *vs* 9%), lymphopenia (1% *vs* 0%), and macular oedema (2% *vs* <1%). Convulsions were also more common with siponimod (2%) than with placebo (<1%; table 3). Rates of malignancies, including basal cell carcinoma, were similar in the two treatment groups (appendix p 17).

The frequencies of adverse events and serious adverse events related to infections were similar in both treatment groups, except for herpes zoster reactivation, which occurred more frequently with siponimod (2%) than with placebo (1%; table 3); one case of herpes zoster meningitis was reported in the siponimod group.

1346 (82%) of 1651 patients underwent continuous mobile cardiac telemetry for up to 6 days. During double-blind treatment initiation, the maximum reduction in mean heart rate on day 1 was 5·3 bpm in the siponimod group (4 h post-dose) and 1·2 bpm in the placebo group (1 h post-dose; appendix p 15). On day 7, mean reductions were 3·1 bpm and 2·0 bpm, respectively (3 h post-dose; appendix p 15). For 68 patients (6%) receiving siponimod and 17 (3%) receiving placebo, bradycardia, decreased heart rate, or sinus bradycardia were reported as adverse events. Two of these events on day 7 in the siponimod group were symptomatic, one leading to treatment discontinuation. No cases of Mobitz type II or high-degree atrioventricular block were observed during double-blind treatment.

Discussion

In this large randomised controlled trial, siponimod significantly reduced 3-month CDP compared with placebo, with a safety profile similar to other drugs in the class. Overall, the results of EXPAND suggest that siponimod might be a useful treatment for patients with SPMS.

Our trial included a typical SPMS population, with characteristics compatible with natural history data and with other studies in SPMS.[1,6–8] By definition, SPMS includes patients, who after a relapsing-remitting phase, present with continuous progression of neurological deficits and might still experience relapses. In the most recent consensus on the classification of multiple sclerosis phenotypes,[5] both continuous progression and activity (defined as relapses or new, enlarging, or enhancing MRI lesions) were proposed as descriptors of progressive multiple sclerosis (a term that includes primary and SPMS).[5] Nearly two-thirds of the EXPAND study population had not relapsed in the 2 years before enrolment. At baseline, only about 20% of patients had focal inflammatory activity, as depicted by the presence of gadolinium-enhancing lesions, and more than 50% needed assistance for walking.

Across the trials in RRMS, SPMS, and primary progressive multiple sclerosis (PPMS), the patients in EXPAND belong to least active populations with the most advanced disability at baseline. As detailed in the appendix (p 18), in comparison with other SPMS studies, and the recent ORATORIO study in PPMS,[23] our study recruited patients with similar or longer mean and median times since onset of documented continuous progression. With 56% of patients having a baseline EDSS of 6·0 or more, our study, together with another SPMS study (ASCEND), in which natalizumab did not slow disability progression versus placebo,[6] included the highest proportion of severely disabled patients. With only 21% of patients showing gadolinium enhancement at baseline and only 19% of placebo patients relapsing during the study, EXPAND recruited a smaller proportion of patients with signs of inflammatory disease activity than comparable

SPMS trials and a similar population to those included in ORATORIO in PPMS.[23]

In this population with established disabilities, siponimod delayed further disability progression as measured by a 3-month confirmed change in EDSS score. Sensitivity analyses of the primary endpoint and the effects observed on 6-month CDP and other clinical and MRI-defined secondary outcomes—notably reduction in brain volume loss (an objective marker of permanent tissue damage)—were consistent with this result.

Progression and activity as the key constituents of progressive multiple sclerosis are thought to be driven by different pathogenic processes. Consequently, establishing whether siponimod exerts its effect on one or both of these processes is of interest. From a clinical point of view, an answer to this question would allow better preselection of patients for treatment. Although not powered for this purpose, by its size, this study permitted informative analyses of the primary outcome, 3-month CDP, in predefined subgroups. These subgroup analyses favoured siponimod over placebo across the entire bracket of previous disease duration, disability status, and age. Review of these subgroup analyses also suggests that the treatment effect became less pronounced with increasing age, disability, baseline disease duration, and diminishing signs of disease activity. Exploratory analysis of the secondary endpoint of 6-month CDP, a less sensitive but more robust outcome than 3-month CDP, in these predefined subgroups supports these findings. A possible interpretation (especially in view of the recent negative results of a study with the potent anti-inflammatory agent natalizumab[6]) is that siponimod exerts its effect on both aspects of the pathogenesis of secondary progressive disease, albeit not equally. Further, more sophisticated, analyses and longer term observations are underway and might help to further inform these considerations.

EXPAND did not show a significant effect on T25FW. The T25FW is an appropriate and well established measure of gait velocity with a high association with the EDSS; however, T25FW does not include the person's ability to vary gait to perform different tasks needed during walking.[24] The T25FW test is therefore variably sensitive to change in populations of patients with progressive multiple sclerosis because of a high SD.[25] Post-hoc analysis of the T25FW results in our study also suggested that the high variability of this measure in a population in which most are already dependent on walking aids might have reduced this measure's sensitivity for change.

Confirmed EDSS increases in an SPMS population are of clinical significance because they are more likely to be irreversible in SPMS than in RRMS.[26] An increase in a high EDSS score affects patients' day-to-day activities substantially. For patients who need walking aids (EDSS score of 6·0 or 6·5), disability progression by 0·5 points means dependence on bilateral instead of unilateral support, or becoming unable to walk more than a few steps even with support. Based on estimated risk reduction, between a fifth (3-month CDP) and a quarter (6-month CDP) of clinically relevant worsening of neurological ability is spared when treated with siponimod.

The study's design allowed some patients to transition to active, open-label treatment as rescue medication as early as 6 months after random allocation. This protocol-defined rescue option was more frequently chosen by patients in the placebo group than in the siponimod group (17% *vs* 11%), and will have reduced the power of the study to show effects on secondary outcomes since patients were

	Siponimod (n=1099)	Placebo (n=546)
Event		
Any adverse event	975 (89%)	445 (82%)
Non-serious adverse event leading to discontinuation of study drug	48 (4%)	15 (3%)
Death	4 (<1%)	4 (1%)
Any serious adverse event	197 (18%)	83 (15%)
Serious adverse event leading to discontinuation of study drug	36 (3%)	13 (2%)
Areas of interest with S1P-receptor modulators		
Liver-related investigations, signs and symptoms (SMQ broad)	135 (12%)	21 (4%)
Hypertension (SMQ narrow)	137 (12%)	50 (9%)
Hypertension (PT)	115 (10%)	41 (8%)
Thromboembolic events (NMQ)*	33 (3%)	15 (3%)
Infections and infestations (SOC)	539 (49%)	268 (49%)
Herpes viral infections (HLT)	53 (5%)	15 (3%)
Herpes zoster (PT)	25 (2%)	4 (1%)
Skin neoplasms, malignant and unspecified (SMQ narrow)	14 (1%)	8 (1%)
Lymphopenia (PT)	9 (1%)	0
Lymphocyte count decreased (PT)	4 (<1%)	0
Oedema peripheral (PT)	50 (5%)	13 (2%)
Macular oedema (PT)	18 (2%)	1 (<1%)
Convulsions (including all types of seizure; SMQ broad)	19 (2%)	2 (<1%)
Bradycardia (PT) during treatment initiation	48 (4%)	14 (3%)
Bradyarrhythmia (including conduction defects and disorders of sinus node function; SMQ broad) during treatment initiation	29 (3%)	2 (0·4%)
Sinus bradycardia (PT) during treatment initiation	14 (1%)	1 (<1%)
Serious adverse events occurring in ≥0·5% of patients in either group		
Alanine aminotransferase increased	10 (1%)	2 (<1%)
Aspartate aminotransferase increased	5 (<1%)	1 (<1%)
Basal cell carcinoma	11 (1%)	6 (1%)
Concussion	5 (<1%)	0
Depression	5 (<1%)	2 (<1%)
Urinary tract infection	13 (1%)	6 (1%)
Suicide attempt	4 (<1%)	3 (1%)
Gait disturbance	1 (<1%)	3 (1%)
Multiple sclerosis relapse	2 (<1%)	7 (1%)
Paraparesis	0	3 (1%)

Data are number of patients (%). S1P=sphingosine 1-phosphate. SMQ=standardised MedDRA query. PT=preferred term. NMQ=Novartis MedDRA query. SOC=system organ class. HLT=high-level term. *Include "Central nervous system haemorrhages and cerebrovascular conditions (SMQ broad)", "Embolic and thrombotic events, arterial (SMQ)", and "Ischaemic heart disease (SMQ broad)".

Table 3: **Adverse events in the safety set**

analysed as randomly assigned. With a median duration of 18 months, the placebo-controlled part of this study was shorter than in most trials in SPMS. Although the effect of siponimod on both 3-month and 6-month CDP is remarkable, the short study period under double-blind conditions did not allow assessment of the persistence of effects over a long period. Further limitations relate to the effect of pre-study disease-modifying therapy on assignment of the proper clinical activity status for subgroup analysis. However, our attempt to address this effect suggests that there was no difference in the frequencies of relapses during the 2 years before the study between the patients who received disease-modifying therapies and those who did not (appendix p 19).

The safety profile of siponimod in EXPAND was generally aligned with that of other drugs in the class. Adverse events more frequent in patients on siponimod than on placebo included elevated liver transaminase concentrations, bradycardia at treatment initiation, macular oedema, hypertension, varicella zoster virus reactivation, and convulsions, all of which have been described previously in the context of S1P-receptor modulation in multiple sclerosis.[27] Overall frequencies of infections were not increased, nor were frequencies of death and malignancies. The dose-titration scheme used in this study, which was based on experience in the phase 2 trial, largely mitigated heart rate and conduction effects previously observed without titration.[15]

Contributors

LK, AB-O, BACC, RJF, GG, RG, PV, and EW conceived and designed the study. All other authors assisted in study design. LK was the trial's steering committee chair; AB-O, BACC, RJF, GG, RG, and PV were members of the trial's steering committee. LK, CW, and FD wrote the first draft of the manuscript. DLA oversaw all MRI analyses. SA was the trial statistician, and designed and did the primary and subsequent statistical analyses. TS, CW, and EW did the concurrent medical review of data during the trial. All authors were involved in interpretation and critical review of the data, drafting or revising of the manuscript for important intellectual content, and approval of the final version.

Declaration of interests

LK reports that, in the last 3 years, his institution (University Hospital Basel) has received funding used exclusively for research support and educational activities from Actelion, Alkermes, Allergan, Almirall, Bayer, Biogen, Celgene, CSL Behring, df-mp, the European Union, Excemed, GeNeuro, Genzyme, Merck, Mitsubishi Pharma, Novartis, Pfizer, Receptos/Celgene, Roche, Roche Research Foundations, Sanofi-Aventis, Santhera, the Swiss Multiple Sclerosis Society, the Swiss National Research Foundation, Teva, UCB Pharma, and Vianex; and licence fees for Neurostatus products. AB-O has received personal compensation for consulting, serving on scientific advisory boards or speaking activities, or a combination thereof, from Bayer, Bayhill Therapeutics, Berlex, Biogen Idec, BioMS, Diogenix, Eli Lilly, F Hoffmann-La Roche, Genentech, GlaxoSmithKline, Guthy-Jackson/GGF, Merck Serono, Novartis, Ono Pharmacia, Sanofi-Aventis, Teva Neuroscience, and Wyeth. BACC reports personal fees for consulting from AbbVie, Biogen, EMD Serono, GeNeuro, Novartis, Sanofi Genzyme, and Shire. RJF reports personal fees from Actelion, Biogen, Genentech, Novartis, Teva, Mallinckrodt, and Xenoport; grants from Novartis; and other support from Biogen (clinical trial contracts). GG reports personal fees for consultancy from AbbVie (steering committee: daclizumab trials), GW Pharma, Five Prime, Synthon BV, Eisai, Elan, Genentech, GSK, and Pfizer; grants from UCB Pharma; grants and personal fees for consultancy from Novartis (steering committee: fingolimod and siponimod trials), Biogen (steering committee: BG12 and daclizumab trials), Canbex, Merck Serono, Teva (steering committee: laquinimod trials), Roche (steering committee: ocrelizumab trials), Bayer-Schering, Ironwood, and Genzyme/Sanofi; and honoraria for speaking at physicians' summits and several medical education meetings from agencies or sponsoring companies. GG is also the co-chief Editor of *Multiple Sclerosis and Related Disorders* (Elsevier). RG 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. PV reports grants, personal fees, and non-financial support from Novartis, Sanofi-Genzyme and Roche; personal fees and non-financial support from Biogen, Merck, and Teva; and personal fees from Servier, Celgene, and Actelion. DLA has received grants and personal fees from Biogen and Novartis; grants from Immunotec; and personal fees from Acorda Therapeutics, Adelphi Communications, Alkermes Genentech, Genzyme, Hoffman LaRoche, Immune Tolerance Network, MedDay, Pfizer, Receptos, Roche, and Sanofi-Aventis. DLA is also an employee and stock or stock option holder of NeuroRx. SA is an employee of Novartis Pharma AG. TS was an employee and shareholder of Novartis during the conduct of the study, and is now an employee of Actelion Pharmaceuticals (a Janssen Pharmaceutical company of Johnson & Johnson). CW reports personal fees from Novartis, Synthon, Mylan, Teva, Desitin, and ICON. EW was an employee and shareholder of Novartis, and is now an employee of Sanofi Genzyme. EW has a patent pending regarding siponimod, with no personal royalties. FD is an employee of Novartis Pharma AG.

Acknowledgments

The study investigators and Novartis are grateful to all of the patients in EXPAND for their participation in and commitment to the study. We thank Tobias Derfuss, Jens Kuhle, Davorka Tomic, and David Leppert for advice during the project. Davorka Tomic, Göril Karlsson, Nicolas Rouyrre, Harald Pohlmann, Tobias Derfuss, and Jens Kuhle provided input and help in the assessment, analysis, and interpretation of the data. This research was funded by Novartis Pharma AG (Basel, Switzerland). Ludwig Kappos, Christian Wolf, and Frank Dahlke wrote the first draft of this manuscript. Medical writing assistance was provided by Mark Rolfe and Kim Wager (Oxford PharmaGenesis, Oxford, UK), with input from all authors. Jane Francis (Oxford PharmaGenesis, Oxford, UK) copyedited and styled the manuscript as per the journal requirements. Their services were paid for by Novartis Pharma. Frauke Treppke (University Hospital Basel) provided secretarial assistance.

References

1 Tremlett H, Yinshan Z, Devonshire V. Natural history of secondary-progressive multiple sclerosis. *Mult Scler* 2008; **14:** 314–24.

2 Scalfari A, Neuhaus A, Daumer M, Muraro PA, Ebers GC. Onset of secondary progressive phase and long-term evolution of multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2014; **85:** 67–75.

3 Lublin FD, Reingold SC. Defining the clinical course of multiple sclerosis: results of an international survey. National Multiple Sclerosis Society (USA) Advisory Committee on Clinical Trials of New Agents in Multiple Sclerosis. *Neurology* 1996; **46:** 907–11.

4 Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. *Neurology* 2014; **83:** 278–86.

5 Shirani A, Okuda DT, Stuve O. Therapeutic advances and future prospects in progressive forms of multiple sclerosis. *Neurotherapeutics* 2016; **13:** 58–69.

6 Steiner D, Arnold D, Freedman MS, et al. Natalizumab versus placebo in patients with secondary progressive multiple sclerosis (SPMS): results from ASCEND, a multicenter, double-blind, placebo-controlled, randomized phase 3 clinical trial. *Neurology* 2016; **86** (16 supplement)**:** E22.

7 Panitch H, Miller A, Paty D, Weinshenker B. Interferon beta-1b in secondary progressive MS: results from a 3-year controlled study. *Neurology* 2004; **63:** 1788–95.

8 Placebo-controlled multicentre randomised trial of interferon beta-1b in treatment of secondary progressive multiple sclerosis. European Study Group on interferon beta-1b in secondary progressive MS. *Lancet* 1998; **352:** 1491–97.

9 Kappos L, Weinshenker B, Pozzilli C, et al. Interferon beta-1b in secondary progressive MS: a combined analysis of the two trials. *Neurology* 2004; **63:** 1779–87.

10 Gergely P, Nuesslein-Hildesheim B, Guerini D, et al. The selective sphingosine 1-phosphate receptor modulator BAF312 redirects lymphocyte distribution and has species-specific effects on heart rate. *Br J Pharmacol* 2012; **167:** 1035–47.

11 Brinkmann V. FTY720 (fingolimod) in multiple sclerosis: therapeutic effects in the immune and the central nervous system. *Br J Pharmacol* 2009; **158:** 1173–82.

12 Aslanis V, Faller T, Van de Kerkhof E, Schubart A, Wallström E, Beyerbach A. Siponimod (BAF312) (and/or its metabolites) penetrates into the CNS and distributes to white matter areas. *Mult Scler* 2012; **18** (4 suppl)**:** 279–508.

13 Gentile A, Musella A, Bullitta S, et al. Siponimod (BAF312) prevents synaptic neurodegeneration in experimental multiple sclerosis. *J Neuroinflammation* 2016; **13:** 207.

14 Jackson SJ, Giovannoni G, Baker D. Fingolimod modulates microglial activation to augment markers of remyelination. *J Neuroinflammation* 2011; **8:** 76.

15 Selmaj K, Li DK, Hartung HP, et al. Siponimod for patients with relapsing-remitting multiple sclerosis (BOLD): an adaptive, dose-ranging, randomised, phase 2 study. *Lancet Neurol* 2013; **12:** 756–67.

16 Rovaris M, Confavreux C, Furlan R, Kappos L, Comi G, Filippi M. Secondary progressive multiple sclerosis: current knowledge and future challenges. *Lancet Neurol* 2006; **5:** 343–54.

17 Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology* 1983; **33:** 1444–52.

18 Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Ann Neurol* 2011; **69:** 292–302.

19 World Medical Association. WMA Declaration of Helsinki—ethical principles for medical research involving human subjects. https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/ (accessed Oct 25, 2016).

20 D'Souza M, Yaldizli O, John R, et al. Neurostatus e-Scoring improves consistency of Expanded Disability Status Scale assessments: a proof of concept study. *Mult Scler* 2017; **23:** 597–603.

21 Roxburgh RH, Seaman SR, Masterman T, et al. Multiple sclerosis severity score: using disability and disease duration to rate disease severity. *Neurology* 2005; **64:** 1144–51.

22 O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. *Biometrics* 1979; **35:** 549–56.

23 Montalban X, Hauser SL, Kappos L, et al. Ocrelizumab versus placebo in primary progressive multiple sclerosis. *N Engl J Med* 2017; **376:** 209–20.

24 Bennett SE, Bromley LE, Fisher NM, Tomita MR, Niewczyk P. Validity and reliability of four clinical gait measures in patients with multiple sclerosis. *Int J MS Care* 2017; **19:** 247–52.

25 Tanigawa M, Stein J, Park J, Kosa P, Cortese I, Bielekova B. Finger and foot tapping as alternative outcomes of upper and lower extremity function in multiple sclerosis. *Mult Scler J Exp Transl Clin* 2017; **3:** 2055217316688930.

26 Ebers GC, Heigenhauser L, Daumer M, Lederer C, Noseworthy JH. Disability as an outcome in MS clinical trials. *Neurology* 2008; **71:** 624–31.

27 Kappos L, Radue EW, O'Connor P, et al. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. *N Engl J Med* 2010; **362:** 387–401.