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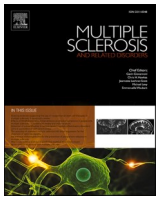

Effects of baseline age and disease duration on the efficacy and safety of siponimod in patients with active SPMS: *Post hoc* analyses from the EXPAND study

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ABSTRACT

Background: Older age and longer disease duration (DD) may impact the effectiveness of disease-modifying therapies in patients with multiple sclerosis (MS). Siponimod is a sphingosine 1-phosphate receptor modulator approved for the treatment of active secondary progressive MS (SPMS) in many countries. The pivotal phase 3 EXPAND study examined siponimod versus placebo in a broad SPMS population with both active and non-active disease. In this population, siponimod demonstrated significant efficacy, including a reduction in the risk of 3-month confirmed disability progression (3mCDP) and 6-month confirmed disability progression (6mCDP). Benefits of siponimod were also observed across age and DD subgroups in the overall EXPAND population. Herein we sought to assess the clinical impact of siponimod across age and disease duration subgroups, specifically in participants with active SPMS.

Methods: This study is a *post hoc* analysis of a subgroup of EXPAND participants with active SPMS ($\geq$ 1 relapse in the 2 years before the study and/or $\geq$ 1 T1 gadolinium-enhancing magnetic resonance imaging lesion at baseline) receiving oral siponimod (2 mg/day) or placebo during EXPAND. Data were analyzed for participant subgroups stratified by age at baseline (primary cut-off: $<$ 45 year $\geq$ 45 years; and secondary cut-off: $<$ 50 years or $\geq$ 50 years) and by DD at baseline ($<$ 16 years or $\geq$ 16 years). Efficacy endpoints were 3mCDP and 6mCDP. Safety assessments included adverse events (AEs), serious AEs, and AEs leading to treatment discontinuation.

Results: Data from 779 participants with active SPMS were analyzed. All age and DD subgroups had 31–38% (3mCDP) and 27–43% (6mCDP) risk reductions with siponimod versus placebo. Compared with placebo, siponimod significantly reduced the risk of 3mCDP in participants aged $\geq$ 45 years (hazard ratio [HR]: 0.68; 95% confidence interval [CI]: 0.48–0.97), $<$ 50 years (HR: 0.69; 95% CI: 0.49–0.98), $\geq$ 50 years (HR: 0.62; 95% CI: 0.40–0.96), and in participants with $<$ 16 years DD (HR: 0.68; 95% CI: 0.47–0.98). The risk of 6mCDP was significantly reduced with siponimod versus placebo for participants aged $<$ 45 years (HR: 0.60; 95% CI: 0.38–0.96), $\geq$ 45 years (HR: 0.67; 95% CI: 0.45–0.99), $<$ 50 years (HR: 0.62; 95% CI: 0.43–0.90), and in participants with $<$ 16 years DD (HR: 0.57; 95% CI: 0.38–0.87). Increasing age or longer MS duration did not appear to increase the risk of AEs, with an observed safety profile that remained consistent with the overall active SPMS and overall SPMS populations in EXPAND.

Abbreviations: 3mCDP, 3-month confirmed disability progression; 6mCDP, 6-month confirmed disability progression; AE, Adverse event; CDP, Confirmed disability progression; DMT, Disease-modifying therapy; EDSS, Expanded Disability Status Scale; HR, Hazard ratio; MS, Multiple sclerosis; OLE, Open-label extension; RRMS, Relapsing-remitting multiple sclerosis; S1P, Sphingosine 1-phosphate; SPMS, Secondary progressive multiple sclerosis.

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Conclusions: In participants with active SPMS, treatment with siponimod demonstrated a statistically significant reduction in the risk of 3mCDP and 6mCDP compared with placebo. Although not every outcome reached statistical significance in the subgroup analyses (possibly a consequence of small sample sizes), benefits of siponimod were seen across a spectrum of ages and DD. Siponimod was generally well tolerated by participants with active SPMS, regardless of baseline age and DD, and AE profiles were broadly similar to those observed in the overall EXPAND population.

1. Introduction

Secondary progressive multiple sclerosis (SPMS) is characterized by gradual neurological deterioration following an initial relapsing-remitting multiple sclerosis (RRMS) disease course (Cree et al., 2021). Increasing disease duration is associated with greater disability accumulation in relapsing- and progressive-onset disease (Scalfari et al., 2011). Increasing age is also associated with disability accumulation, irrespective of multiple sclerosis (MS) disease duration (Scalfari et al., 2011). Recent evidence also suggests that age is important in MS because it is associated with disease worsening for all phenotypes, which appears partly independent of new focal inflammatory activity (Dahlke et al., 2021). Furthermore, neuronal plasticity and the functional adaptive reserve of the brain decrease with greater age and disease duration (Ksiazek-Winiarek et al., 2015). Greater adaptive reserve may allow younger patients or those with a shorter disease duration to experience greater benefits from treatments such as siponimod on cognitive processing speed (Benedict et al., 2021). Increasing age and disease duration may also independently impact the effectiveness of disease-modifying therapies (DMTs); increasing age is associated with disability accumulation, irrespective of MS disease duration (Cerqueira et al., 2018; Scalfari et al., 2011). A regression analysis of data from 38 clinical trials involving > 28,000 participants across the MS disease continuum demonstrated a strong correlation between decreasing efficacy of DMTs and advancing age (R^2 = 0.6757; overall F-test, P = 6.39e−09). The model suggested that therapeutic efficacy of such treatments may be minimal after 53 years of age (Weideman et al., 2017). However, a separate meta-analysis, based on group-level data from > 28,000 participants with RRMS from 26 clinical trials, found no significant association between age and the effects of DMTs on disease activity (Zhang et al., 2020).

Despite these latter findings, patients with SPMS, who are older and have longer disease duration than those at earlier disease stages, are a potentially challenging population to treat, because older age and longer disease duration may lead to greater disability and reduced DMT efficacy. Lower efficacy in older populations and those with longer disease duration have been observed in clinical studies (Gold et al., 2022; Kapoor et al., 2018; Panitch et al., 2004; Secondary Progressive Efficacy Clinical Trial of Recombinant Interferon-Beta-1a in MS (SPECTRIMS) Study Group, 2001).

Siponimod is a selective sphingosine 1-phosphate (S1P) receptor modulator, with increased selectivity for $S1P_1$ and $S1P_5$ receptors (European Medicines Agency, 2020), approved in the USA for the treatment of adults with relapsing forms of MS, including clinically isolated syndrome, RRMS, and active SPMS (Food and Drug Administration, 2019). Siponimod is also approved in the EU for the treatment of SPMS with active disease evidenced by relapses or imaging features of inflammatory activity (European Medicines Agency, 2020), and for the treatment of SPMS without the requirement for recent disease activity in some countries (Novartis Pharmaceuticals Australia Pty Limited, 2019). In the phase 3 EXPAND study, which evaluated the efficacy and safety of siponimod in 1651 participants with SPMS, siponimod significantly reduced the risk of 3- and 6-month confirmed disability progression (3mCDP/6mCDP) compared with placebo (Kappos et al., 2018). The primary analysis also revealed consistent benefits of siponimod across age and MS duration subgroups in the overall EXPAND population, which included patients with active or non-active SPMS (Kappos et al., 2018). Finally, the safety profile of siponimod in EXPAND was similar to that reported for other S1P receptor modulators (Kappos et al., 2018). An open-label extension (OLE) of EXPAND evaluating the long-term safety, tolerability, and efficacy of siponimod is ongoing (Cree et al., 2022; Giovannoni G, 2020).

Previous analyses of a subpopulation with active SPMS in EXPAND demonstrated a reduced risk of disability progression and benefits on imaging outcomes with siponimod compared with placebo among these participants (Arnold et al., 2022), consistent with the overall SPMS population (Gold et al., 2022). Additional subgroup analyses of the overall EXPAND population (including participants with active and non-active SPMS) indicated a trend toward younger participants having greater benefits on 3mCDP and 6mCDP risk reductions with siponimod versus placebo, compared with older individuals (Kappos et al., 2018). This is consistent with previous observations suggesting that MS disease activity decreases with age, making it potentially harder to demonstrate a treatment effect in this population (Dahlke et al., 2021). These considerations are important because, in clinical practice, the mean age of patients using siponimod appears to be higher than in EXPAND. In a recent retrospective real-world US study of patients initiating siponimod, mean age was 53 years and patients had moderate-to-severe disability (IQVIA claims database) (Shah et al., 2020). In another retrospective cohort study using the IBM® and MarketScan® Research Databases, the mean age of patients initiating siponimod was 52 years (Deshpande et al., 2021).

The *post hoc* analyses presented here aimed to investigate the effects of age and disease duration on the efficacy and safety of siponimod in the EXPAND population, with a focus on those with active SPMS. The active SPMS subpopulation was chosen because it represents the population for which siponimod is approved in the majority of countries (Novartis Pharmaceuticals Australia Pty Limited, 2019). The primary age subgroups of < 45 years or ≥ 45 years were used to reflect the median age of EXPAND participants with active SPMS (46 and 48 years for the siponimod and placebo groups, respectively). An additional cut-off (< 50 years or ≥ 50 years) was also examined to investigate outcomes in a population more closely aligned with the reported real-world age of patients receiving siponimod (average age: 52–53 years) (Deshpande et al., 2021; Shah et al., 2020). A disease duration at baseline cut-off of < 16 years or ≥ 16 years was used to reflect the median disease duration of 15–16 years in participants with SPMS in EXPAND (Kappos et al., 2018).

2. Methods

2.1. Study design and participants

EXPAND (NCT01665144) was a phase 3, randomized, double-blind, placebo-controlled, parallel-group, event- and exposure-driven study that evaluated the efficacy and safety of oral siponimod in participants with SPMS. Briefly, adults aged 18–60 years with an SPMS diagnosis, an Expanded Disability Status Scale (EDSS) score of 3.0–6.5 at screening, a history of RRMS, documented EDSS progression in the 2 years before the study, and no evidence of relapses in the 3 months before randomization were eligible. Participants were randomized (2:1) to oral siponimod (2 mg once daily) or matching placebo and were followed for up to 3 years (median duration [range]: 21 months [< 1 month to 37 months]) and treated for up to 3 years (median duration [range]: 18 months [1

day to 37 months]), or until a prespecified number of confirmed disability progression (CDP) events had occurred in the study. Full details of the EXPAND study design were reported previously (Kappos et al., 2018).

2.2. Post hoc analyses

All *post hoc* analyses were conducted in the full analysis sets, unless otherwise stated, using data from participants with active and non-active SPMS who were enrolled in EXPAND (Kappos et al., 2018). The full active SPMS and non-active SPMS analysis sets included all participants with active or non-active SPMS, respectively, who were randomized and received ≥ 1 dose of study drug. In these analyses, active SPMS was defined by the occurrence of ≥ 1 relapse in the 2 years before screening and/or ≥ 1 T1 gadolinium-enhancing lesion at study baseline (Gold et al., 2022). Data were analyzed for participant subgroups stratified by age at baseline (primary age cut-off: </≥ 45 years; secondary age cut-off: </≥ 50 years), and by disease duration at baseline (</≥ 16 years). Efficacy endpoints were also analyzed for subgroups defined by both age and disease duration, including (1) age < 45 years and disease duration < 16 years, (2) age ≥ 45 years and disease duration < 16 years, (3) age < 45 years and disease duration ≥ 16 years, and (4) age ≥ 45 years and disease duration ≥ 16 years, as well as equivalent subgroups for the </≥ 50-year cut-off).

The efficacy endpoints analyzed in the subgroup analyses were time to 3mCDP and 6mCDP. CDP was defined as a 1-point increase in EDSS score if the baseline score was 3.0–5.0, or a 0.5-point increase if the baseline score was 5.5–6.5. Increases in EDSS score were confirmed at scheduled visits ≥ 3 months (3mCDP) or ≥ 6 months (6mCDP) after the previous EDSS assessment.

Safety assessments included adverse events (AEs), serious AEs, and AEs leading to treatment discontinuation. AEs were coded according to the Medical Dictionary for Regulatory Activities, version 19.0.

2.3. Statistical analyses

Baseline demographics between treatment groups for each subgroup were compared using chi-square test for categorical variables and Wilcoxon rank-sum test for continuous variables. The differences between siponimod and placebo with respect to time to 3mCDP or 6mCDP were analyzed in each subgroup using a Cox proportional hazards model that excluded participants with missing covariates; treatment and baseline EDSS score were included as explanatory variables. Risk reduction was derived as (1 − hazard ratio) × 100. All *post hoc* analyses were assessed at a nominal significance level of 0.05 without correction for multiplicity or hierarchical testing and were used for hypothesis generation only. AEs were reported descriptively, with statistical significance between treatment groups calculated using Fisher's exact test.

2.4. Standard protocol approval, registration, and participant consent

EXPAND is registered with ClinicalTrials.gov (NCT01665144). The trial was approved by the institutional review board or ethics committee at each participating institution. All participants provided informed consent before participation (Kappos et al., 2018).

3. Results

3.1. Participants

In EXPAND, 1651 participants were randomly assigned to study treatment (siponimod, $n = 1105$; placebo, $n = 546$). Of these, 779 met the definition of active SPMS (siponimod, $n = 516$; placebo, $n = 263$) and 827 met the definition of non-active SPMS (siponimod, $n = 557$; placebo, $n = 270$) and were included in these reported *post hoc* analyses. Active SPMS participant numbers, demographics, and baseline characteristics following stratification by the primary age cut-off (</≥ 45 years) and disease duration (</≥ 16 years) are summarized in Table 1; these were generally similar for siponimod and placebo within each subgroup. The only baseline characteristic that was statistically significantly different ($P < 0.05$) between treatment groups was median time (years) since diagnosis of MS in the </≥ 45 years subgroups (age < 45 years: siponimod, 7.7; placebo, 8.5; age ≥ 45 years: siponimod, 13.2; placebo, 10.9). Baseline participant demographics and disease characteristics for the secondary age subgroups (</≥ 50 years) and the EXPAND population of participants with non-active SPMS are provided in **Table S1** and **Table S2**, respectively.

To examine the potential overlap between age and disease duration, the number of participants who fell into both a given age and disease subgroup were calculated. In the active SPMS population ($n = 779$), 159 (30.8%) and 67 (25.5%) participants were < 45 years of age and had a disease duration of < 16 years in the siponimod and placebo groups, respectively, whereas 177 (34.3%) participants receiving siponimod and 95 (36.1%) receiving placebo were ≥ 45 years of age and had a disease duration of ≥ 16 years. In the non-active SPMS population ($n = 827$), 83 (14.9%) and 48 (17.8%) participants were < 45 years of age and had a disease duration of < 16 years in the siponimod and placebo groups, respectively, whereas 281 (50.4%) participants receiving siponimod and 107 (39.6%) receiving placebo were ≥ 45 years of age and had a disease duration of ≥ 16 years.

3.2. Efficacy

3.2.1. 45-year cut-off

Treatment with siponimod was associated with numerical reductions in the risk of 3mCDP and 6mCDP compared with placebo overall and across the primary age subgroups. Similar reductions in risk of 3mCDP with siponimod were detected in participants aged < 45 years (32%) and ≥ 45 years (32%); however, risk reduction with siponimod versus placebo failed to reach statistical significance in the < 45-years subgroup (Fig. 1A). For 6mCDP, siponimod was associated with a statistically significant risk reduction in both age subgroups; however, the risk reduction among participants aged < 45 years was greater than that for participants aged ≥ 45 years (40% vs 33%, respectively) (Fig. 1B).

3.2.2. Disease duration

Both disease duration subgroups had a risk reduction of 3mCDP of 32% with siponimod; this risk reduction increased to 43% for 6mCDP in the < 16 years subgroup, compared with only 27% for participants with longer disease duration in the ≥ 16 years subgroup. For both 3mCDP and 6mCDP, risk reduction with siponimod only reached statistical significance in participants with < 16 years disease duration (Fig. 1).

3.2.3. 50-year cut-off

When stratified by age < 50 or ≥ 50 years, 3mCDP risk reduction was slightly greater for participants aged ≥ 50 years (38%) than those aged < 50 years (31%) (**Fig. S1A**). In contrast, risk reductions of 6mCDP with siponimod were similar for the < 50 years subgroup (38%) and ≥ 50 years subgroup (37%). However, reduction of 6mCDP risk with siponimod only reached statistical significance in the younger age subgroup (**Fig. S1B**).

3.2.4. Subgroups defined by both age and disease duration

The direction of effect of siponimod was consistent across all subgroups; risk of 3mCDP and 6mCDP were reduced in patients receiving siponimod for each combined age and disease duration subgroup (**Tables S3** and **S4**). Using the 45-year cut-off, the greatest risk reduction for both 3mCDP and 6mCDP was seen in the age ≥ 45 years and disease duration < 16 years (47% and 50%, respectively) and age < 45 years and disease duration ≥ 16 years (59% and 43%, respectively) subgroups (**Table S3**). When using the 50-year cut-off, the subgroups of age ≥ 50 years and disease duration < 16 years and age < 50 years and disease

Table 1
Participant demographics and baseline characteristics in the overall active SPMS EXPAND study population and stratified by baseline age (</≥ 45 years) and disease duration.

	Overall active SPMS population		Age < 45 years		Age ≥ 45 years		MS duration < 16 years		MS duration ≥ 16 years	
	Siponimod ($n = 516$)	Placebo ($n = 263$)	Siponimod ($n = 213$)	Placebo ($n = 93$)	Siponimod ($n = 303$)	Placebo ($n = 170$)	Siponimod ($n = 285$)	Placebo ($n = 142$)	Siponimod ($n = 231$)	Placebo ($n = 121$)
Age (years)										
Mean (SD)	46.2 (8.1)	47.2 (8.5)	38.4 (5.0)	37.7 (5.2)	51.8 (4.5)	52.4 (4.6)	43.7 (8.6)	44.7 (8.9)	49.4 (6.3)	50.2 (7.0)
Median (range)	46.0 (23–61)	48.0 (21–60)	40.0 (23–44)	38.0 (21–44)	51.0 (45–61)	52.0 (45–60)	43.0 (23–61)	45.5 (21–60)	50.0 (33–61)	51.0 (34–60)
Sex										
Female	331 (64)	166 (63)	134 (63)	52 (56)	197 (65)	114 (67)	175 (61)	85 (60)	156 (68)	81 (67)
Male	185 (36)	97 (37)	79 (37)	41 (44)	106 (35)	56 (33)	110 (39)	57 (40)	75 (33)	40 (33)
Time since diagnosis of MS (years)										
Mean (SD)	11.7 (7.4)	11.1 (6.7)	8.7 (5.4)	10.0 (5.7)	13.8 (7.9)	11.7 (7.1)	7.5 (4.1)	7.4 (4.0)	16.8 (7.4)	15.5 (6.6)
Median (range)	10.7 (0–37)	10.3 (0–33)	7.7 (0–24)*	8.5 (1–24)*	13.2 (0–37)*	10.9 (0–33)*	7.3 (0–16)	7.4 (0–16)	17.3 (1–37)	16.3 (1–33)
Time since onset of MS symptoms (years)										
Mean (SD)	15.6 (7.9)	15.5 (8.2)	12.1 (5.9)	12.2 (5.6)	18.0 (8.2)	17.4 (8.8)	9.8 (3.9)	9.3 (3.7)	22.7 (5.3)	22.9 (5.4)
Median (range)	14.8 (1–42)	14.7 (1–41)	11.5 (2–26)	11.3 (2–24)	17.8 (1–42)	17.3 (1–41)	10.2 (1–16)	9.2 (1–16)	21.9 (16–42)	22.0 (16–41)
Time since conversion to SPMS (years)										
Mean (SD)	3.2 (3.3)†	3.1 (3.2)	2.8 (3.1)‡	2.7 (2.4)	3.6 (3.4)	3.3 (3.5)	2.3 (2.1)§	2.0 (1.7)	4.4 (4.1)	4.4 (4.0)
Median (range)	2.1 (0–24)†	1.9 (0–22)	1.6 (0–20)‡	1.8 (0–13)	2.3 (0–24)	2.0 (0–22)	1.6 (0–15)§	1.6 (0–10)	2.8 (0–24)	2.8 (1–22)
No relapses in the year before screening	291 (57)†	134 (51)	117 (55)	49 (53)	174 (57)‖	85 (50)	156 (55)	69 (49)	135 (59)¶	65 (54)
No relapses in the 2 years before screening	127 (25)†	61 (23)	41 (19)	18 (19)	86 (29)‖	43 (25)	62 (22)	32 (23)	65 (28)¶	29 (24)
Number of relapses in the year before screening										
Mean (SD)	0.5 (0.7)†	0.6 (0.7)	0.5 (0.7)	0.5 (0.6)	0.5 (0.7)‖	0.6 (0.8)	0.6 (0.7)	0.6 (0.7)	0.5 (0.7)¶	0.5 (0.7)
Median (range)	0 (0–4)†	0 (0–4)	0 (0–4)	0 (0–2)	0 (0–4)‖	0.5 (0–4)	0 (0–4)	1 (0–4)	0 (0–4)¶	0 (0–4)
Number of relapses in the 2 years before screening										
Mean (SD)	1.4 (1.4)†	1.4 (1.3)	1.5 (1.4)	1.4 (1.1)	1.3 (1.5)‖	1.4 (1.4)	1.5 (1.4)	1.6 (1.5)	1.3 (1.4)¶	1.2 (1.1)
Median (range)	1 (0–12)†	1 (0–8)	1 (0–12)	1 (0–5)	1 (0–12)‖	1 (0–8)	1 (0–12)	1 (0–8)	1 (0–12)¶	1 (0–6)
EDSS score										
Mean (SD)	5.5 (1.1)	5.4 (1.0)	5.4 (1.1)	5.4 (1.0)	5.5 (1.1)	5.4 (1.1)	5.4 (1.1)	5.3 (1.1)	5.6 (1.0)	5.5 (1.0)
Median (range)	6.0 (2–7)	6.0 (3–7)	6.0 (3–7)	6.0 (3–7)	6.0 (2–7)	6.0 (3–7)	6.0 (2–7)	6.0 (3–7)	6.0 (3–7)	6.0 (3–7)

Data are number (%) unless specified otherwise. Some percentages do not add up to 100 because of rounding. For 1 participant with an unknown disease duration, a disease duration of ≥ 16 years was assumed.
EDSS, Expanded Disability Status Scale; MS, multiple sclerosis; SD, standard deviation; SPMS, secondary progressive multiple sclerosis.

* $P < 0.05$ for siponimod versus placebo, calculated using Wilcoxon rank-sum test.
† $N = 515$.
‡ $N = 212$.
§ $N = 284$.
‖ $N = 302$.
¶ $N = 230$.

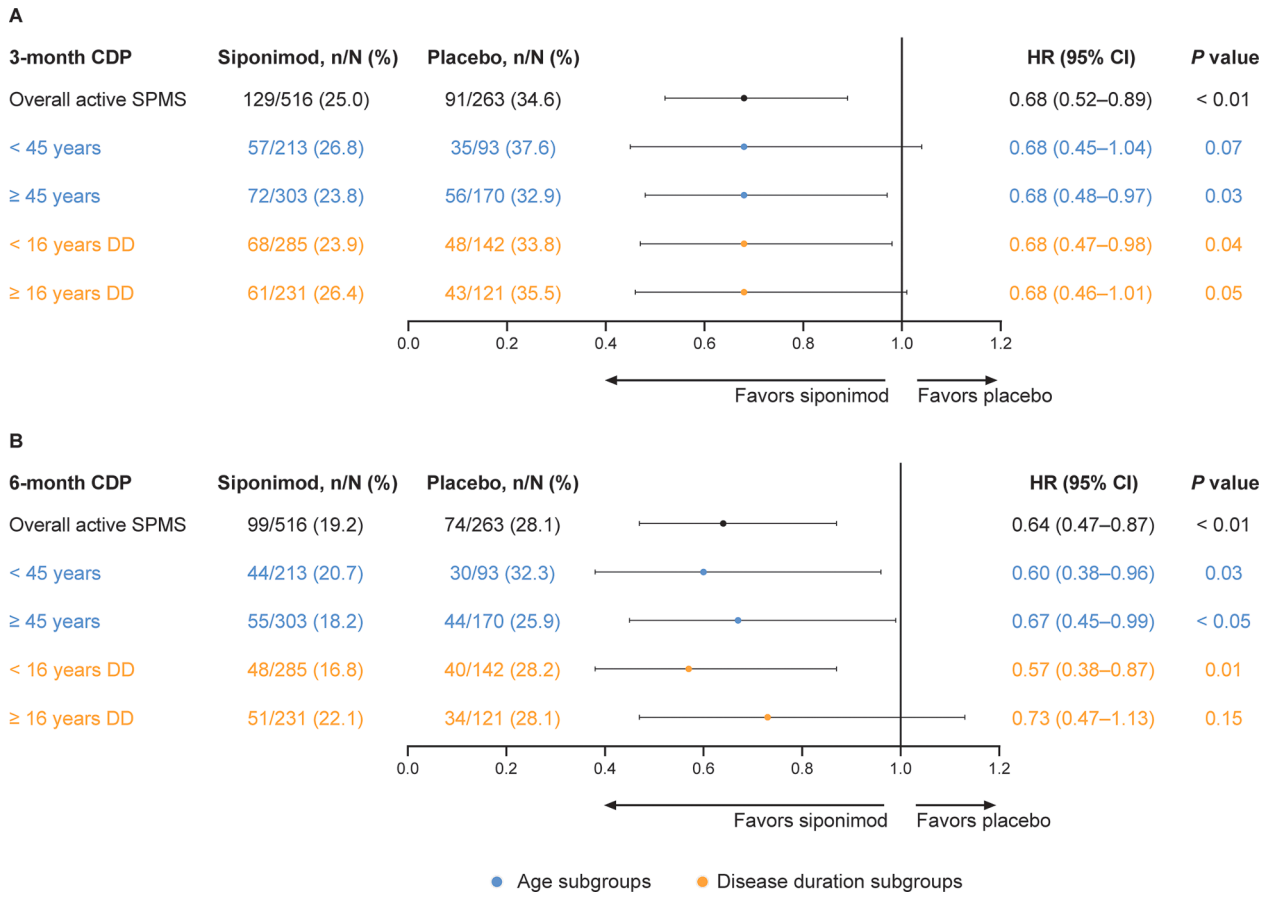

Fig. 1. CDP in the overall active SPMS EXPAND study population and stratified by baseline age (</≥ 45 years) and disease duration, for (A) 3-month CDP, and (B) 6-month CDP.
For 1 participant with an unknown DD, a DD of ≥ 16 years was assumed.
CDP, confirmed disability progression; CI, confidence interval; DD, disease duration; HR, hazard ratio; SPMS, secondary progressive multiple sclerosis.

duration ≥ 16 years demonstrated the greatest risk reduction for 3mCDP (52% and 40%, respectively; **Table S4**). The greatest risk reduction in 6mCDP was seen in the subgroups of age < 50 years and disease duration < 16 years (42%) and age ≥ 50 years and disease duration < 16 years (53%).

3.2.5. *Non-active SPMS population*

Compared with participants with active SPMS, participants with non-active SPMS had less pronounced reductions in risk of 3mCDP and 6mCDP with siponimod versus placebo across all subgroups; no comparisons reached statistical significance (**Fig. S2**).

3.3. *Safety*

3.3.1. *45-year cut-off*

Overall, patients in the siponimod treatment groups reported more AEs versus placebo, regardless of age (Table 2). In participants with active SPMS in the primary age subgroups, the proportions of participants reporting any AEs were significantly higher with siponimod than with placebo in the older age subgroup (≥ 45 years) (Table 2). Although proportions of participants reporting serious AEs were numerically higher in the placebo treatment groups and the older age subgroup, these differences were not significant (Table 2). The proportions of participants with AEs leading to discontinuation were similar across treatment groups; however, there was a slight trend toward a higher occurrence in the older age subgroups (Table 2). Proportionally more participants receiving siponimod than placebo had AEs known to be associated with S1P receptor modulation (Table 2), including hypertension and bradycardia. Hypertension occurred more regularly in those ≥ 45 years of age, whereas bradycardia was reported at a higher rate in those < 45 years of age (Table 2).

3.3.2. *Disease duration*

The proportions of participants reporting any AEs were significantly higher with siponimod than with placebo in the lower disease duration subgroup (< 16 years) (Table 2). Any AEs, serious AEs, and AEs leading to treatment discontinuation occurred more often in participants with a disease duration of ≥ 16 years than in the < 16 years subgroup (Table 2).

3.3.3. *50-year cut-off*

In the secondary age subgroups, similar trends were observed for the proportion of participants reporting AEs; the proportions of participants reporting any AEs were significantly higher with siponimod than with placebo in the older age subgroup (≥ 50 years) (**Table S5**). Proportions of participants with hypertension were higher in the ≥ 50 years subgroup compared with the < 50 years subgroup (**Table S5**); in contrast, the proportion of participants with bradycardia were consistently higher in the < 50 years subgroup compared with the ≥ 50 years subgroup (**Table S5**).

3.3.4. *Non-active SPMS population*

In participants with non-active SPMS, AEs were reported in the siponimod groups at higher rates in the ≥ 45 years subgroup, ≥ 50 years subgroup and ≥ 16 years disease duration subgroup than the comparator age and disease duration subgroups (**Table S6**).

Table 2
Summary of AEs and AEs associated with S1P receptor modulation in the overall active SPMS EXPAND population and stratified by baseline age (</≥ 45 years) and disease duration.

Event	Overall active SPMS population		Age < 45 years		Age ≥ 45 years		MS duration < 16 years		MS duration ≥ 16 years	
	Siponimod (n = 516)	Placebo (n = 263)	Siponimod (n = 213)	Placebo (n = 93)	Siponimod (n = 303)	Placebo (n = 170)	Siponimod (n = 285)	Placebo (n = 142)	Siponimod (n = 231)	Placebo (n = 121)
Any AEs	448 (86.8)*	206 (78.3)*	176 (82.6)	77 (82.8)	272 (89.8)*	129 (75.9)*	242 (84.9)*	107 (75.4)*	206 (89.2)	99 (81.8)
Serious AEs	82 (15.9)	47 (17.9)	27 (12.7)	14 (15.1)	55 (18.2)	33 (19.4)	43 (15.1)	20 (14.1)	39 (16.9)	27 (22.3)
AEs leading to study drug discontinuation	30 (5.8)	16 (6.1)	7 (3.3)	4 (4.3)	23 (7.6)	12 (7.1)	15 (5.3)	7 (4.9)	15 (6.5)	9 (7.4)
AEs associated with S1P receptor modulation										
Bradycardia†	31 (6.0)	8 (3.0)	19 (8.9)	4 (4.3)	12 (4.0)	4 (2.4)	21 (7.4)	5 (3.5)	10 (4.3)	3 (2.5)
Hypertension	54 (10.5)	19 (7.2)	14 (6.6)	4 (4.3)	40 (13.2)	15 (8.8)	28 (9.8)	8 (5.6)	26 (11.3)	11 (9.1)
Lymphopenia	4 (0.8)	0	4 (1.9)	0	0	0	3 (1.1)	0	1 (0.4)	0
Macular edema	7 (1.4)	1 (0.4)	2 (0.9)	0	5 (1.7)	1 (0.6)	1 (0.4)	0	6 (2.6)	1 (0.8)
Herpes zoster	9 (1.7)	1 (0.4)	4 (1.9)	0	5 (1.7)	1 (0.6)	7 (2.5)	1 (0.7)	2 (0.9)	0

Data are number of participants (%). For 1 participant with an unknown disease duration, a disease duration of ≥ 16 years was assumed.
AE, adverse event; MS, multiple sclerosis; S1P, sphingosine 1-phosphate; SPMS, secondary progressive multiple sclerosis.
* $P < 0.05$ for siponimod versus placebo, obtained from Fisher's exact test.
† Preferred Term, within 14 days after treatment initiation.

4. Discussion

In this *post hoc* analysis of the subgroup of participants with active SPMS from EXPAND, siponimod showed benefit across all age and MS duration subgroups compared with placebo, with significance reached in those aged < 45 years (6mCDP), ≥ 45 years (3mCDP and 6mCDP), < 50 years (3mCDP and 6mCDP), and ≥ 50 years (3mCDP), as well as those with disease duration of < 16 years (3mCDP and 6mCDP). Less pronounced improvements were observed in participants with non-active SPMS.

CDP risk with siponimod between the primary age subgroups (</≥ 45 years) was similar, but showed a numerically greater reduction in risk of 6mCDP with younger versus older participants; compared with placebo, the only reduction that did not reached statistical significance was for 3mCDP in the < 45 years subgroup (Fig. 1). Risk of 6mCDP in the secondary age subgroups (</≥ 50 years) was similar to those reported for the primary subgroup, with a trend toward an increased risk reduction in the younger subgroup; however, this trend was reversed in those in the 3mCDP </≥ 50 years categories, where younger age was instead associated with a lower risk reduction (**Fig. S1**). This apparent contradiction could be attributed to variability associated with small sample sizes and the increased stringency in achieving 6mCDP as an outcome. The EXPAND primary efficacy endpoint was time to 3mCDP; however, the greater reduction in risk of 6mCDP versus 3mCDP shown here and in previous EXPAND analyses (Gold et al., 2022; Kappos et al., 2018) suggests sustained clinical benefit of siponimod. Moreover, 6mCDP is providing insights into long-term siponimod efficacy in the EXPAND OLE (Cree et al., 2022).

Participants with disease duration of < 16 years had significant reductions in CDP risk with siponimod, unlike their counterparts with ≥ 16 years duration. However, both subgroups had identical hazard ratio values for 3mCDP, possibly reflecting the small sample sizes (and thus wide 95% CIs). A lower number of participants in the ≥ 16 years disease duration subgroup and a tendency for participants with more advanced disease to progress more slowly (thereby limiting the number of events seen during the relatively short duration of EXPAND) may partially account for the lack of statistical significance. Nonetheless, a more notable difference between disease duration groups was observed for 6mCDP, suggesting a greater reduction in CDP risk for participants with shorter disease duration versus those with longer disease duration.

Previous studies suggested that increasing age and longer disease duration may alter the efficacy of DMTs in MS, resulting in less pronounced treatment benefits (Cerqueira et al., 2018; Kappos et al., 2018; Weideman et al., 2017). The risk reductions across the age and disease duration subgroups of participants with active SPMS reported here are consistent with the overall active SPMS population in EXPAND (31% and 37% for 3mCDP and 6mCDP, respectively) (Gold et al., 2022), as well as to those in the overall EXPAND SPMS population (21% and 26% risk reduction of 3mCDP and 6mCDP, respectively), which included participants with active and non-active SPMS (Kappos et al., 2018). Contrary to earlier reports (Cerqueira et al., 2018; Weideman et al., 2017), the data reported here indicate that siponimod confers similar benefits across the age range and possibly disease duration. The combined effect of these 2 factors was also investigated in subgroups of both age and disease duration, and the direction of the siponimod effect was consistent across all subgroups; however, due to limited sample size, further analysis is required.

Siponimod efficacy versus placebo was less pronounced with non-active SPMS compared with active SPMS. This is consistent with the EXPAND OLE, which reported greater delays in 6mCDP in the active SPMS subgroup versus the overall SPMS study population (Cree et al., 2022). However, objective and more sensitive magnetic resonance imaging measures related to neurodegeneration and tissue integrity have shown consistently significant beneficial results in both the active and non-active disease subgroups in EXPAND (Arnold et al., 2022; Gold et al., 2022); therefore, the CDP measure used here may not fully capture

the underlying disease in patients with non-active SPMS.

Increasing age or longer MS duration did not appear to increase the risk of AEs in most S1P modulation safety areas of interest. The only notable difference between subgroups was a higher incidence of hypertension with increasing age (in both, siponimod-, and placebo-treated participants). This is consistent with observations of age-related hypertension in patients with MS (Marrie et al., 2016). Meanwhile, bradycardia was reported at a higher rate in those < 45 years of age.

The subgroup analyses reported here are limited by the number of participants included in the analyses, whereas EXPAND was designed to analyze the primary endpoint of 3mCDP in the overall SPMS population. Therefore, this study was under-powered to demonstrate efficacy in several subgroups. Combined with variability associated with small sample sizes, this limited the interpretation of potential differences between age and disease duration subgroups. Positive effects of siponimod were observed in most subgroups and findings from the EXPAND OLE suggested that a longer follow-up period than the duration of the core study (median 21 months) may be required to see the full effect of siponimod on CDP (Cree et al., 2022). Furthermore, EXPAND only enrolled participants up to 60 years of age, and the findings presented here are limited to this age group at the initiation of treatment with siponimod. Finally, the *post hoc* nature of this study is hypothesis generating and precludes definitive interpretation, and the statistical analyses should be interpreted cautiously because of the lack of multiplicity adjustment.

5. Conclusion

In conclusion, the *post hoc* analyses from EXPAND reported here appear to demonstrate that siponimod reduces 3mCDP and 6mCDP risk in participants with active SPMS across age and MS duration subgroups. The siponimod safety profile in these subgroups remained consistent with the overall EXPAND population. Collectively, these data suggest that disease activity may be a better predictor of clinical outcome than age, because patients with active SPMS across a wide age spectrum displayed clinical benefit with siponimod.

CRediT authorship contribution statement

Le H Hua: Conceptualization, Methodology, Investigation, Formal analysis, Data curation, Writing – review & editing. **Amit Bar-Or:** Conceptualization, Methodology, Investigation, Formal analysis, Data curation, Writing – review & editing. **Stanley L Cohan:** Conceptualization, Methodology, Investigation, Formal analysis, Data curation, Writing – review & editing. **Fred D Lublin:** Conceptualization, Methodology, Investigation, Formal analysis, Data curation, Writing – review & editing. **Patricia K Coyle:** Conceptualization, Methodology, Investigation, Formal analysis, Data curation, Writing – review & editing. **Bruce AC Cree:** Conceptualization, Methodology, Investigation, Formal analysis, Data curation, Writing – review & editing. **Xiangyi Meng:** Conceptualization, Methodology, Investigation, Formal analysis, Data curation, Writing – review & editing. **Wendy Su:** Conceptualization, Methodology, Investigation, Formal analysis, Data curation, Writing – review & editing. **Gina Mavrikis Cox:** Conceptualization, Methodology, Investigation, Formal analysis, Data curation, Writing – review & editing. **Robert J Fox:** Conceptualization, Methodology, Investigation, Formal analysis, Data curation, Writing – review & editing.

Declaration of Competing Interest

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Supplementary materials

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