Core Submission Dossier PTJA08

Siponimod (Mayzent®)
for the treatment of adult patients with secondary progressive multiple sclerosis (SPMS) with active disease

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Abbreviations

AE	Adverse event
ARR	Annualised relapse rate
ATC	Anatomical therapeutic chemical
CDP	Confirmed disability progression
CE	Contrast estimate
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CNS	Central nervous system
CONSORT	Consolidated standards of reporting trials
DMT	Disease modifying therapy
DSM	Diagnostic and Statistical Manual of Mental Disorders
EDSS	Expanded disability status scale
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EXPAND	EXploring the efficacy and safety of siponimod in PAtients with secoNDary progressive multiple sclerosis
FDA	Food and Drugs Administration
Gd+	Gadolinium enhancing
HR	Hazard ratio
HTA	Health technology assessment
ICD	International classification of disease
IFNB	Interferon beta
IM	Intramuscular
IPD	Individual patient data
ITC	Indirect treatment comparison
ITT	Intention to treat
IV	Intravenous
MAIC	Matching-adjusted indirect comparison
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
MSFC	Multiple sclerosis functional composite
MSWS-12	Multiple Sclerosis Walking Scale
n/a	Not applicable
NMA	Network meta-analysis
NR	Not reported
OR	Odds ratio
PBO	Placebo
PBVC	Percentage brain volume change
PO	Oral
PPMS	Primary progressive multiple sclerosis
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
q2d	Once every other day
q4w	Once every 4 weeks
qd	Once daily
qw	Once weekly
RCT	Randomised controlled trial
RMS	Relapsing multiple sclerosis
RRMS	Relapsing remitting multiple sclerosis
S1P	Sphingosine 1 phosphate

SAE	Serious adverse event
SC	Subcutaneous
SD	Standard deviation
SDMT	Symbol digit modalities test
SE	Standard error
SF-36	Short Form Health Survey 36
SLR	Systematic literature review
SmPC	Summary of product characteristics
SPMS	Secondary progressive multiple sclerosis
STC	Simulated treatment comparison
STROBE	Strengthening the reporting of observational studies in epidemiology
T25FW	Timed 25-foot walk test
tiw	Three times weekly
VnR	Nordic Article Number
9HPT	9-hole peg test

Contents

Submission Summary

Health problem and current clinical practice

- Multiple sclerosis (MS) is a chronic condition in which damage to the central nervous system (CNS) leads to an increasing loss of physical and cognitive function.[1]
- MS is a highly heterogeneous disease, but three broad clinical phenotypes of disease have been identified, classified by the pattern and frequency of relapses and the rate of progression of the disease: relapsing remitting MS (RRMS); secondary progressive MS (SPMS); and primary progressive MS (PPMS).[2] Over time, the majority of patients with RRMS develop SPMS.[3, 4]
- Whereas the defining characteristic of RRMS is relapses, SPMS patients experience a steady, irreversible progression of disability, with or without acute exacerbations.[2] Progressive forms of MS can be categorized as having active inflammation (so-called "active") or not having active inflammation (so-called "non-active") based upon the presence or absence of clinical relapses, and/or magnetic resonance imaging (MRI) signs of activity.[2] However, there are challenges associated with the diagnosis of SPMS and further problems with such sub-classification.
- Due to challenges associated with the diagnosis of SPMS and a lack of specific diagnostic codes in MS that can be used to differentially classify patients with RRMS, SPMS and PPMS, estimates of the numbers of individuals with SPMS vary widely across countries; In France, Germany, Italy, Spain, and the UK, SPMS prevalence ranges from 11 to 58 people per 100 000 of the general population.[5-13] Superimposed relapses are characteristic of the earlier stages of SPMS, and cross-sectionally, approximately half of SPMS patients are estimated to continue to experience superimposed relapses.[14]
- Patients with SPMS experience a significant clinical and humanistic burden, with symptoms including loss of mobility, cognitive impairment, and pain.[15] Symptoms are often worse than for patients with RRMS,[15] and SPMS patients experience a corresponding reduction in health-related quality of life.[16]
- Despite a high burden of disease, no treatments are approved for the full spectrum of SPMS or SPMS with active disease evidenced by relapses or imaging features of inflammatory activity; potential treatments are restricted to SPMS with relapses (interferon β) or are limited in their use due to toxicity (mitoxantrone).[17-19] Some disease modifying therapies (DMTs) are licensed for use in relapsing MS (RMS), which would include SPMS patients with superimposed relapses. DMTs approved for RMS have shown effects on disability by reducing relapses and thus reducing incomplete recovery from relapses, however no DMT has shown effects on disability in the active subgroup of SPMS; contrastingly, siponimod has shown efficacy on CDP in a typical, more advanced, SPMS population, with stronger efficacy in the active SPMS population. Siponimod addresses a clear need for a therapy that slows disability progression in patients with active SPMS with a manageable safety profile.
- Due to the lack of treatment options for SPMS and because DMTs are frequently not reimbursed following confirmation of SPMS, clinicians frequently maintain the RRMS diagnosis and treatment with R(R)MS DMTs throughout the transition phase to SPMS despite their lack of evidence in slowing disability progression; only once evidence of SPMS is irrefutable treatment with R(R)MS DMTs is reconsidered, although it is often continued for lack of better options.[20] As a result, R(R)MS DMTs are used in practice in all SPMS populations: the level of DMT usage in SPMS in Member States is 56%, including both relapsing (85%) and non-relapsing patients (39%);[20] if patients unable to walk (EDSS of 7 or greater) were excluded, these percentages would further increase.

Siponimod

- Siponimod is a sphingosine-1-phosphate (S1P) receptor modulator.[21] For most patients, siponimod is taken as a once-daily oral tablet at a dose of 2 mg following an initial dose titration phase. A 1 mg maintenance dose is available for patients with specific genotypes (CYP2C9*2*3 or *1*3) who metabolise siponimod more slowly, and therefore require a reduced dose to achieve similar exposure.
- Siponimod is a selective and potent agonist for the S1P1 and S1P5 receptors. This contrasts with fingolimod, which at pharmacological doses, is additionally selective for the S1P3 and S1P4 receptors, has a longer half-life and is administered as a prodrug.[22, 23]
- Siponimod should not be used in patients with a CYP2C9*3*3 genotype; use of siponimod in these patients results in substantially elevated siponimod plasma levels and a resultant risk of cardiac events.[21] Other than genotyping for CYP2C9, the equipment and supplies required to use siponimod are anticipated to be largely similar to those currently required for other DMTs.
- Siponimod received positive opinion from the Committee for Medicinal Products for Human Use (CHMP) on 14th November 2019 for the treatment of adult patients with secondary progressive multiple sclerosis (SPMS) with active disease evidenced by relapses or imaging features of inflammatory activity. This submission considers siponimod for the treatment of SPMS patients with active disease, as indicated in the summary of product characteristics (SmPC).
- Based upon the expected siponimod license and current clinical usage of DMTs within the EU/EEA Member States, Novartis anticipate that siponimod will displace interferon β, ocrelizumab, fingolimod and natalizumab in the treatment of SPMS patients. As 56% of SPMS patients are currently on DMTs, it is anticipated that such displacement will occur across all SPMS populations. In the relapsing population, DMT usage is 85%.

Clinical evidence for siponimod

- Evidence for the efficacy and safety of siponimod in patients with SPMS comes from EXPAND, a multicentre, double-blind, placebo-controlled randomised controlled trial (RCT), which is the largest phase 3 trial in SPMS patients to date (n=1,651).[24]
- EXPAND included a typical population with SPMS who had reached a high level of established disability and included those with and without inflammatory activity. Over 50% of patients had EDSS ≥6 (required at least one walking aid). Outcomes from this study are therefore relevant to the overall population with SPMS.[24]
- In the intention-to-treat (ITT) population (including patients with both active and inactive SPMS), EXPAND met its primary endpoint, with siponimod reducing the risk of 3-month confirmed disability progression (CDP), determined using a time-to-event analysis, by 21% versus placebo (p = 0.013; Hazard ratio [HR] 0.79, 95% confidence interval [CI] 0.65–0.95).[24] Siponimod also reduced the risk of 6-month CDP, which is considered the more robust disability measure, by 26% versus placebo (p = 0.0058; HR 0.74, 95% CI 0.60–0.92).[24] A consistency of effect on CDP outcomes was observed across all pre-specified subgroups considered for the primary endpoint; for 3-month CDP, the favourable outcomes were seen for patients with (HR, 0.67) and without (HR, 0.87) superimposed relapses in the 2 years prior to the study.
- Siponimod's treatment effects on CDP is strongly corroborated by the positive findings on associated MRI endpoints, which are objective, fully blinded, reliably quantifiable and generally accepted as supportive evidence. Effects on both brain volume loss and T2 lesion volume are correlated with disability progression[25] and the robust study results on T2 lesion volume independently support the primary endpoint.

- In patients with active disease, *post hoc* analyses to support the label showed that:
  - Siponimod significantly delayed the time to 3-month and 6-month confirmed disability progression (CDP), displaying a 30.7%% (HR 0.69, 95% CI 0.53–0.91) and 36.5% (HR 0.63, 95% CI 0.47–0.86) risk reduction compared with placebo for these endpoints.
  - A 46.1% annualised relapse rate reduction for confirmed relapses was observed for siponimod versus placebo (ARR ratio 0.539, p=0.0004).
  - For the key secondary endpoint of time to 3-month confirmed worsening in timed 25-foot walk (T25FW), there was an observed risk reduction of 14.3% in favour of the siponimod group, although this result was not significant (p=0.1879). Research published after EXPAND was designed has suggested that T25FW may have suboptimal sensitivity for change in patients with pronounced ambulatory disability (such as those in the EXPAND trial, with median EDSS of 6.0 at baseline, i.e. over 50% of patents requiring at least one walking aid).[24]
  - The change in patient-reported impact of disease on walking ability (MSWS-12) assessed as a secondary endpoint, was significantly improved with siponimod therapy (p=0.0494). However, baseline MSWS-12 scores near the maximal possible score, reflecting the high disability of the study population, only allowed modest further increase (ceiling effect), narrowing the ability to show a treatment effect.
  - Statistically significant results in favour of siponimod were also observed for MRI outcomes, including change in T2 lesion volume from baseline, the number of new or enlarging T2 lesions and the number of T1 gadolinium-enhancing lesions at 12 and 24 months.
- EXPAND is the first study to demonstrate the positive effect of an intervention on cognitive processing speed (CPS) in SPMS patients, as measured using symbol digit modalities test (SDMT). In the ITT population, siponimod treatment resulted in less deterioration in processing speed compared with placebo; a nominally statistically significant difference in adjusted means over all time-points assessed was observed for siponimod (1.384, p=0.007, unadjusted for multiplicity). In a *post hoc* exploratory analysis, siponimod also significantly reduced the overall clinically significant risk of SDMT score worsening (decline ≥ 4 points) by 21% (p = 0.0157); a 4-point change is considered to be clinically meaningful as it impacts vocational status.[26, 27]. Significant differences in change from baseline in CPS were observed between placebo and siponimod in both relapsing and non-relapsing SPMS patients, although this was greater in relapsing SPMS patients (siponimod, +0.926; placebo, -1.647; difference = +2.57; p=0.0151) than the non-relapsing SPMS patients (siponimod, +1.703 points; placebo, -0.74 points; difference = +2.44, p=0.0099).[28]
- Beyond the core part of the EXPAND trial (up to 3 years), a time-to-wheelchair analysis further supports the clinical relevance of the effect of siponimod on delaying disability progression in patients with SPMS: compared with placebo, siponimod treatment has been shown to result in a 31.0% and 37.6% risk reduction in the risk of progressing to EDSS ≥7 in the overall population and in patients with EDSS 6.5 at baseline.[29] Whilst this was in the ITT population, given the more favourable hazard ratios in the active SPMS sub-population, it is anticipated that this result would be a conservative estimate of the relative effectiveness of siponimod in the active SPMS population with lower EDSS.
- Siponimod was generally well tolerated in the double-blind core study, and there were no safety signals in patients with SPMS that were unexpected for the S1P receptor modulator class.[24] The overall frequencies of infections, malignancies and fatalities did not differ between the siponimod and placebo groups. Side effects that occurred at a higher frequency with siponimod versus placebo were generally consistent with the known safety

profiles of other S1P receptor modulators. Siponimod is currently being further evaluated in an open label long-term follow up study.

Comparative evidence for siponimod

- No direct evidence for the clinical effectiveness of siponimod versus active comparators exists, therefore an indirect treatment comparison is necessary. Novartis anticipate that siponimod will displace the following comparators: interferon β preparations, ocrelizumab, natalizumab, and fingolimod.
- For relevant comparators in this appraisal, trial data in SPMS patients are only available for interferon β-1b, interferon β-1a and natalizumab; 6-month CDP data, which are considered most relevant for HTA appraisals in MS, are only available for two studies other than EXPAND. Furthermore, there is no comparator data pubilshed for the active SPMS sub-population. Results are available for interferon β in the "relapsing" sub population, but no baseline characteristics are reported; therefore, an exploratory unadjusted Bucher indirect comparison was therefore conducted in this population but results of such an unadjusted comaprison are limited by heterogeneity between studies.
- Only one comparator study, of interferon β-1b, showed any statistically significant effect on the primary endpoint of disability progression compared to placebo. However, this study enrolled a very different study population of younger patients with shorter disease duration and more inflammatory disease activity. This result could not be replicated in another study with interferon β-1b nor with any other interferon-β studied in SPMS.
- Due to significant heterogeneity between the EXPAND and the comparator trials when considering patient populations (inclusion/exclusion criteria and baseline characteristics) and trial outcomes (dissimilar placebo-arm outcomes), the assumptions of similarity and homogeneity required for a network meta-analysis (NMA) approach were not met. Whilst the results of an NMA would be unreliable and biased due to significant clinical heterogeneity and dissimilarity, as well as an imbalance of effect modifiers between EXPAND and each of the comparator trials, the availability of patient-level data for the EXPAND trial allowed individual comparisons to each of the other SPMS trials identified, using a matching-adjusted indirect comparison (MAIC) approach. Notably, MAICs were not feasible in any subgroups, such as the active SPMS subgroup, due to the lack of comparator subgroup data.
- In the pairwise MAICs, siponimod demonstrated numerical superiority for all CDP outcomes, although such comparisons were not possible for all comparators of interest; siponimod was determined to be statistically significantly more effective for the outcome of time to 6-month CDP, which is seen as the more relevant measure of CDP, compared with Betaferon® (Interferon β-1b). For ARR, with the exception of natalizumab, siponimod was demonstrated to be at least numerically superior to all comparators.
- In the active SPMS sub-population, the only available data is derived from the European Study; baseline data from the European study reveal that the population is very dissimilar to both the full EXPAND population as well as the active sub-population. Therefore, a MAIC and NMA were deemed not to befeasible in this population, however an exploratory Bucher ITC was conducted against interferon β-1a and interferon β-1b within the relapsing SPMS population for 3-month CDP outcomes. Siponimod demonstrated numerical superiority for 3-month CDP outcomes, however substantial limitations of the Bucher ITC approach undermine the clinical validity of this approach. However, the results of the matching and adjusting process show that the base case comparison to interferon β-1b is selective for a more active subset of the EXPAND trial: average age and baseline EDSS are lowered, the proportion of patients experiencing relapses in the two years prior to the trial is increased, as is the average number of relapses per patients in the two years prior

to the trial. Therefore, although the extrapolation of the MAIC results from the ITT population to the active SPMS subgroup has inherent limitations, it remains preferable to an unadjusted naïve comparison of subgroup data between two trials which are known to differ in many respects.

Conclusions

- Siponimod will be the first treatment with proven efficacy in reducing disability progression and cognitive decline in an SPMS population with active disease.
- EXPAND provides high quality evidence for the efficacy of siponimod, and the appropriate use of the MAIC approach demonstrates the improved efficacy of siponimod relative to comparators.
- Patients with active SPMS currently have no effective treatment options available for the treatment of inflammation and progression/disability and suffer high burden of disease; siponimod offers a significant therapeutic advance that can slow disease progression in active SPMS.

1 Description and technical characteristics of the technology

Summary of the characteristics of the technology

- Siponimod (BAF312) is a sphingosine-1-phosphate (S1P) receptor modulator with specificity for S1P1 and S1P5 receptors expressed on lymphocytes and cells in the central nervous system (CNS). Through its binding to S1P1 and S1P5 receptors, siponimod has peripheral anti-inflammatory effects, and potentially direct effects in the CNS.
- Siponimod is indicated for the treatment of adult patients with secondary progressive multiple sclerosis (SPMS) with active disease evidenced by relapses or imaging features of inflammatory activity.
- For most patients, siponimod is taken as a once-daily oral tablet at a dose of 2 mg following an initial dose titration phase. In patients with a CYP2C9*2*3 or *1*3 genotype, the recommended maintenance dose is 1 mg taken once daily; these patients metabolise siponimod more slowly, and therefore require a reduced dose to achieve similar exposure.
- Siponimod is the first treatment with proven efficacy in reducing disability progression and cognitive decline in patients with SPMS, addressing a substantial unmet need.
- Siponimod received a positive CHMP opinion for its use in “adult patients with secondary progressive multiple sclerosis (SPMS) with active disease evidenced by relapses or imaging features of inflammatory activity” on 14th November 2019.
- Siponimod has previously been approved by the FDA for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.

1.1 Characteristics of the technology

1. In Table 1 provide an overview of the technology.

Table 1: Features of the technology

Non-proprietary name	Siponimod
Proprietary name	Mayzent
Marketing authorisation holder	Novartis Europharm Limited
Class	Sphingosine-1-phosphate (S1P) receptor modulator
Active substance(s)	Siponimod (hemifumarate)
Pharmaceutical formulation(s)	0.25 mg or 2 mg tablets
ATC code	L04AA42
Mechanism of action	Siponimod is a sphingosine-1-phosphate (S1P) receptor modulator with specificity for S1P1 and S1P5 receptors expressed on lymphocytes and cells in the central nervous system (CNS). This contrasts with fingolimod, which at pharmacological doses, is additionally selective for the S1P3 and S1P4 receptors, has a longer half-life and is administered as a prodrug.[22, 23] Through its binding to S1P1 and S1P5 receptors, siponimod has peripheral anti-inflammatory effects, and potentially direct effects in the CNS. The peripheral anti-inflammatory effects of siponimod are

	mediated through its binding to S1P1 receptors on lymphocytes, preventing their egress from lymph nodes. In addition, preclinical observations suggest direct and strong neuroprotective effects for siponimod, most likely S1P1-dependent on astrocytes and S1P5-dependent on oligodendrocytes, such as: • Enhanced myelination, as shown in models of cultured human oligodendrocytes[30] • Reduced demyelination, as shown in models of toxin-induced demyelination[31, 32] • Strong pro-myelinating properties, most likely S1P5-mediated, as recently described in a xenopus tadpole model of toxin-induced demyelination.[33]

Source: Siponimod draft SmPC.[21]

2. In Table 2, summarise the information about administration and dosing of the technology.

Table 2: Administration and dosing of the technology

Method of administration	Oral use. Siponimod film-coated tablets should be swallowed whole with water, with or without food.
Doses	Siponimod is available in 0.25 mg and 2 mg film coated tablets. Dose titration starts with 0.25 mg once daily on days 1 and 2, followed by once daily doses of 0.5 mg (two tablets of 0.25 mg) on day 3, 0.75 mg (three tablets of 0.25 mg) on day 4, and 1.25 mg (five tablets of 0.25 mg) on day 5, to reach the maintenance dose of siponimod starting on day 6. The maintenance dose of siponimod is 2 mg once daily, although a 1 mg maintenance dose is recommended for certain CYP genotypes (see below).
Dosing frequency	Once daily.
Average length of a course of treatment	It is anticipated that siponimod is taken continuously.
Anticipated average interval between courses of treatments	It is anticipated that siponimod is taken continuously.
Anticipated number of repeat courses of treatments	It is anticipated that siponimod is taken continuously.
Dose adjustments	In patients with a CYP2C9*3*3 genotype, siponimod should not be used. In patients with a CYP2C9*2*3 or *1*3 genotype, the recommended maintenance dose is 1 mg taken once daily. Treatment titration is the same as specified above. Patients with these genotypes have a reduced ability to metabolise siponimod, and therefore substantially elevated siponimod plasma levels are observed. This may be associated with a risk of cardiac events, and is mitigated with the dose titration and lower maintenance dose. No dose adjustment is required for elderly patients, or patients with hepatic or renal impairment.

Source: Siponimod draft SmPC.[21]

3. State the context and level of care for the technology (for example, primary healthcare, secondary healthcare, tertiary healthcare, outside health institutions or as part of public health or other).

The context and level of care for siponimod is anticipated to vary between countries. For example, in Ireland, siponimod will be prescribed in the hospital setting but dispensed in the community setting.

4. State the claimed benefits of the technology, including whether the technology should be considered innovative.

While there are several effective disease modifying therapies (DMTs) available for patients with relapsing (remitting) MS (R(R)MS), none of the available DMTs have been shown to effectively or *consistently* delay progression of disability in a typical SPMS patient population, or the active sub-population. Contrastingly, siponimod effectively demonstrated a reduction in disability progression in a typical population of patients with SPMS with stronger results in the active SPMS subgroup.

The efficacy of siponimod in SPMS was investigated in a multicentre, double-blind, placebo-controlled Phase 3 study, EXPAND, which enrolled 1,651 patients, 779 of which were included in the *post hoc* active SPMS subgroup analysis (defined as ongoing relapses and/or MRI activity in patients with SPMS); the study population had a high level of disability (median EDSS score of 6.0 at baseline) with a low level of clinical relapse and MRI inflammatory activity and was representative of a typical SPMS population. Compared to patients enrolled in typical R(R)MS studies, such as those of fingolimod, dimethyl fumarate and alemtuzumab,[34-36] the EXPAND patients were older by more than 10 years, had longer disease duration and much higher EDSS scores (Table 16). They also showed substantially less inflammatory disease activity before and during the study.

EXPAND met its primary endpoint, with siponimod reducing the risk of 3-month confirmed disease progression (CDP), determined using a time-to-event analysis, by 21% versus placebo ($p = 0.013$; HR 0.79, 95% CI 0.65–0.95) in the ITT population (SPMS).[24] Siponimod also reduced the risk of 6-month CDP, which is considered a more robust outcome, by 26% versus placebo ($p = 0.0058$; HR 0.74, 95% CI 0.60–0.92).[37] In the ITT population, annualised relapse rate (ARR) was decreased by 55% ($p < 0.0001$) and time to first confirmed relapse analysis showed a risk reduction of 46% ($p < 0.0001$) in patients receiving siponimod versus those receiving placebo.[24] Siponimod slowed the rate of brain volume loss by 23% versus placebo over 12 and 24 months ($p = 0.0002$). Siponimod treatment results in less deterioration in cognitive processing speed (CPS), as measured using symbol digit modalities test (SDMT), compared with placebo; a nominally statistically significant difference in adjusted means over all time-points assessed was observed for siponimod (1.384, p=0.007, unadjusted for multiplicity). In a *post hoc* exploratory analysis, siponimod also significantly reduced the risk of SDMT score worsening (decline ≥ 4 points) by 21% ($p = 0.0157$) and this was sustained until the end of the study; a 4-point change is considered to be the minimum clinically important difference.[26, 27] Not all trial endpoints demonstrated a statistically significant benefit in favour of siponimod; however, whilst non-significant, numerically favourable outcomes were observed for the timed 25-foot walk test (T25FW) and Multiple Sclerosis Walking Scale (MSWS-12).

The results of the EXPAND trial also demonstrate the clinical efficacy of siponimod in reducing the risk of disability progression in patients with active SPMS: Siponimod significantly delayed

the time to 3-month and 6-month confirmed disability progression (CDP), with risk reductions of 30.7%% (HR 0.69, 95% CI 0.53–0.91) and 36.5% (HR 0.63, 95% CI 0.47–0.86), respectively. A 46.1% annualised relapse rate reduction for confirmed relapses was observed for siponimod versus placebo (ARR ratio 0.539, p=0.0004). Statistically significant results in favour of siponimod were also observed for MRI outcomes, including change in T2 lesion volume from baseline, the number of new or enlarging T2 lesions and the number of T1 gadolinium-enhancing lesions at 12 and 24 months.

Furthermore, analysis of the EXPAND ITT population demonstrated that siponimod was generally well tolerated in the double-blind core study with no unexpected safety signals in patients with SPMS. The overall frequencies of infections, malignancies and fatalities did not differ between the siponimod and placebo groups. Siponimod is currently being further evaluated in an open label long-term follow up study.

Siponimod will be the first treatment with proven efficacy in reducing disability progression and cognitive decline in patients with SPMS, including patients with active and non active SPMS. The clinical benefits of siponimod are combined with its convenient oral administration, which may result in higher levels of treatment compliance by patients. For patients with active SPMS who experience a high disease burden, but for whom there are currently no effective treatment options, siponimod offers a significant therapeutic advancement that can slow the progression of disease.

1.2 Regulatory status of the technology

1. Complete Table 3 with the marketing authorisation status of the technology.

Please refer to Table 3 for details of the marketing authorisation status of siponimod in Europe and USA.

2. State any other indications not included in the assessment for which the technology has marketing authorisation.

Siponimod does not have European marketing authorisation for any indication.

3. State any contraindications or groups for whom the technology is not recommended.

Siponimod is contraindicated in patients with a hypersensitivity to the active substance or the list of excipients listed in the Summary of Product Characteristics (SmPC).[21] Siponimod should not be used in patients with a CYP2C9*3*3.[21]

4. List the other countries in which the technology has marketing authorisation.

Siponimod has marketing authorisation in the US.[38, 39]

Table 3: Regulatory status of the technology

Country	Organisation issuing approval	Verbatim wording of the (proposed) indication(s)	(Expected) Date of approval	Type of approval (full, conditional, exceptional)	Launched (yes/no). If no include proposed date of launch	Marketing authorisation number (if available)
Country of application						
Member States of the European Union (EU) and the European Economic Area (EEA)	EMA	Mayzent is indicated for the treatment of adult patients with secondary progressive multiple sclerosis (SPMS) with active disease evidenced by relapses or imaging features of inflammatory activity.	January/February 2020	Full	No. Proposed launch date January/February 2020.	Not available
Switzerland	Swissmedic	Mayzent is indicated for the treatment of adult patients with secondary progressive multiple sclerosis (SPMS).	February 2020	Full	No. Proposed launch date September 2020.	Not available
Other countries						
USA	FDA	Mayzent is a sphingosine 1-phosphate receptor modulator indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.[39]	26/03/2019	Full	Yes	–
Canada	Health Canada	MAYZENT™ (siponimod) is indicated for the treatment of patients with secondary progressive multiple sclerosis (SPMS).	December 2019	Full	No. Proposed launch date March 2020.	Not available
Australia	Therapeutic Drugs Administration (TGA)	Mayzent is indicated for the treatment of adult patients with secondary progressive multiple sclerosis (SPMS).	October 2019	Full	No. Proposed launch date June 2020.	Not available

Japan	Pharmaceuticals and Medical Devices Agency (PMDA)	Prevention of relapse and delay of progression of physical disability in secondary progressive multiple sclerosis.	March 2020	Full, Orphan	No. Proposed launch date May 2020.	Not available
China	The National Medical Products Administration (NMPA)	Siponimod is indicated for treatment of patients with secondary progressive multiple sclerosis (SPMS).	June 2020	Full, Priority	No	Not available

2 Health problem and current clinical practice

Summary of issues relating to the health problem and current clinical practice

- Multiple sclerosis (MS) is the most common autoimmune demyelinating disorder of the central nervous system (CNS), affecting more than 2.3 million individuals worldwide. The pathogenesis of MS is complex and not completely understood. Depending on the course of neurological disability, it can be classified into three main disease phenotypes: relapsing–remitting, secondary progressive and primary progressive MS.
- RRMS and SPMS form a continuum, with no clearly defined 'transition point' between the two phenotypes. SPMS is associated with significant, irreversible disability, interfering with day-to-day functioning; reduced ambulatory capacity is the hallmark clinical feature such that aids for walking are needed and eventually wheelchairs are required to get about. Patients with SPMS may or may not have signs of the focal inflammatory disease activity characteristic of RRMS, including relapses and/or magnetic resonance imaging (MRI) activity. Typically, focal inflammatory disease activity declines over time but inflammatory lesion activity in the CNS behind an intact blood brain barrier is present until the latest stages of the disease.[40]
- There is a wide variation in the prevalence of SPMS across and within countries. Across France, Germany, Italy, Spain, and the UK, the prevalence of SPMS ranges from 11–58 people per 100 000 of the general population. In the absence of data regarding the epidemiology of active SPMS, the proportions of patients with SPMS who have super imposed relapses ranges from 39.5–52.7%.[14, 41] Importantly, these studies do not take MRI into account; using MRI as an additional way to establish active disease will likely increase the prevalence of active SPMS.
- Most treatments used in SPMS have been demonstrated to be effective in reducing relapses but have not demonstrated effectiveness in slowing disability progression in SPMS, including in active SPMS. This includes highly effective anti-inflammatory treatments such as natalizumab which failed to demonstrate efficacy in a phase 3 study in SPMS on disability progression.[42] This represents a clear unmet need in a population that has a high burden of disease compared with patients with RRMS, for whom several treatment options are available.
- Siponimod is anticipated to address this unmet need, representing a treatment option that is effective at reducing the risk of progression in the active SPMS population. Siponimod is also effective in reducing relapses, which remain a feature of the disease, particularly in active SPMS. Siponimod may also have a positive effect on cognition in SPMS patients.

2.1 Overview of the disease or health condition

1. Define the disease or health condition in the scope of this assessment.

Siponimod is anticipated to be indicated for the treatment of adults with secondary progressive multiple sclerosis (SPMS).

Disease course

Multiple sclerosis (MS) is the most common autoimmune demyelinating disorder of the central nervous system (CNS), affecting more than 2.3 million individuals worldwide.[43]

Approximately 85% of patients present with a relapsing-remitting course with neurological stability between relapses (relapsing-remitting MS (RRMS)). With time, an increasing number of these patients (>50% within 15 to 20 years) experience a decreasing frequency of relapses and in parallel a steady disability worsening, called “progression”. Natural history studies have shown that once an Expanded Disability Status Scale (EDSS) score of 4 (limited walking ability but able to walk at least 500 meters without aid or rest) is reached, further progression develops independent of relapses, i.e., at a similar rate irrespective of individual relapse frequency.[44, 45] This stage is called secondary progressive phase of MS (SPMS).[2, 4, 44-50] The transition from RRMS to SPMS is determined retrospectively based on evidence that disability progression is occurring independently of relapses, though relapses and focal inflammatory activity may still continue to be present. There is a wide variation in the reported time of conversion from RRMS to SPMS: 10 years after the onset of RRMS, approximately 23.5–40% of patients progress to SPMS; this increases to 52.7% by 20 years,[47, 51, 52] and 65.7% by 25 years.[47] In long-term studies, 75.4% of patients with RRMS have converted to SPMS at 30 years, 78% at 40 years, and 86% at 50 years.[47, 53, 54] The median time to conversion to SPMS is reported to be between 9–21.4 years.[4, 52, 55]

SPMS is associated with significant, irreversible disability, interfering with day-to-day functioning. Reduced ambulatory capacity is the hallmark clinical feature such that aids for walking are needed and eventually wheelchairs are required to get about. A majority of SPMS patients also experience cognitive impairment, in particular slowed cognitive processing speed (CPS) which is the most commonly affected cognitive domain in MS and affects about 75% of SPMS patients.[56, 57] Deterioration in CPS has been found to be the most predictive marker of unemployment.[58] In addition, these patients experience bulbar dysfunction, visual impairment, impaired arm function, fatigue, pain and depression, coupled with often severe sphincter control issues. All of which leads to a markedly reduced quality of life as well as reduced employment opportunities, frequently with a major impact on other family members. Compared to RRMS, SPMS is associated with lower overall quality of life scores, higher absenteeism and unemployment rates and higher healthcare costs.[13, 59-62]

RRMS, SPMS with relapses, and SPMS without relapses form a continuum in the phenotypic development of MS over time. Accordingly, neuroanatomic (histopathology, MRI imaging), immunologic and genetic features of MS are shared among these disease stages with only quantitative differences for inflammatory and neurodegenerative pathology.[63-66] This applies as well for primary progressive MS (PPMS), the form of MS with progression from onset on, but without acute exacerbations.[67, 68] These findings have led to a recent revision of the traditional categorization into RRMS, SPMS and PPMS to a strictly descriptive one, based on the course of MS with relapsing and progressive MS being the two main categories, the latter being subdivided as 'active' or 'not active' based on presence or absence of acute disease activity (relapses or lesion formation in MRI).[2, 49]

Identification of SPMS itself is challenging as there are no clear clinical, imaging, immunologic, or pathologic criteria to determine a “transition point” when RRMS has progressed to SPMS.[2] One reason for this is the challenge of separating out temporary deterioration caused by relapses from chronic deterioration caused by progression, although progression due to incomplete recovery from relapses is a major reason for deterioration in earlier phases of disease. SPMS is therefore always recognised retrospectively, considering the gradual increase in disability, which is independent of relapses.[69] This uncertainty in diagnosis often delays SPMS diagnosis for years.[49] In addition to the challenges of diagnosis, physicians are often hesitant to diagnose

SPMS due to the psychological burden associated with the diagnosis and the lack of effective treatment options.[70]

The distinction of relapsing or non-relapsing SPMS is determined also retrospectively, based on presence or absence of recent relapse or MRI lesion activity (e.g., over at least the previous 1 year.[2] However, clinical studies, including the Phase 3 study with siponimod, have shown that the presence or absence of previous relapse activity is not predictive of future relapse activity: patients with relapses in the past 1 to 2 years may be relapse-free for the next 1 or 2 years. Conversely, patients without relapses for several years may experience relapses later in disease. In fact, subclinical inflammatory activity may be present intermittently in most patients with SPMS; its detection is a function of how frequently MRI assessments are done. Furthermore, in practice, many SPMS patients are acknowledged to still be receiving DMTs, which are known to be efficacious in reducing inflammatory activity: the level of DMT usage in SPMS in Member States is 56%, including both relapsing (85%) and non-relapsing patients (39%);[20] if patients unable to walk (EDSS of 7 or greater) were excluded, these percentages would further increase. Importantly, DMTs may be considered to act as a significant diagnostic confounder for SPMS sub-group classification.

Unlike in RRMS, where relapses lead typically to incomplete recovery/remnant disability, they do not appear to be the major driver of disability in progressive MS. This suggests that the disease course in SPMS is driven by two partly independent pathomechanisms, recurrent acute focal inflammation and progressive neurodegeneration. These results in demyelination, axonal damage and loss of repair capacity in the CNS and manifest as progressive neurological deterioration. This has implications for the ability to conduct studies in progressive MS targeting patients exclusively without relapses/inflammatory activity. Furthermore, in SPMS patients who have been relapse-free for many years, age-related central nervous system (CNS) changes become an important additional confounding variable together with more advanced CNS pathology which likely reduce the potential for demonstrating any treatment effects in a substantial proportion of enrolled patients.

2. Present an estimate of prevalence and/or incidence for the disease or health condition including recent trends.

Population-based epidemiological studies that reported both the prevalence of MS and the proportion of patients with SPMS within this group allowed calculation of the prevalence of SPMS in selected countries. In the absence of specific data, the prevalence of active SPMS specifically can be determined using estimates of the proportion of SPMS patients that experience superimposed relapses. Using MRI as an additional way to establish active disease will likely increase the prevalence of active SPMS.

The proportion of patients with SPMS relative to the total population of patients with MS in France, Germany, Italy, Spain, and the UK are presented in Table 4. There was a wide variation across selected countries in the proportion of patients with MS who were diagnosed with SPMS, ranging from 16% to 39%. When multiple studies were available for the same country, variations in the proportion of patients with MS who had SPMS were also observed within countries: Germany, 7.5–34.0%; Italy, 21.6–36.2; Spain, 8.7–23.9%; UK, 37.2–41.5%.

The calculated prevalence of SPMS in France, Germany, Italy, Spain, and the UK is summarised in Table 4. Estimates across selected countries ranged from 11 people per 100 000 of the general population in Spain to 58 people per 100 000 of the general population in the UK. When

multiple studies were available for the same country, variations in the prevalence of SPMS within countries were also observed: Germany, 13.1–50.6/100 000; Italy, 19.4-33.0/100 000; Spain, 2.8–16.7/100 000; UK, 40.9–74.6/100 000.

Further studies are required to measure the prevalence of SPMS across Europe and to ascertain whether variations in the proportion of patients with SPMS and prevalence of SPMS are due to real differences or reflect differences in study methodology, healthcare system and patient management that may delay the transition to SPMS, or differences in diagnostic classification. A potential reason for the variation in prevalence of SPMS across and within countries may be a result of not having specific diagnostic codes in MS that can be used to differentially classify patients with RRMS, SPMS or PPMS. Only Germany and Switzerland have specific ICD codes for different types of MS. This has resulted in an increasing trend of patients being mapped to specific types of MS in Germany.[71] Other countries only have one ICD code for MS, which includes RRMS, SPMS and PPMS; this makes it challenging to determine the prevalence of a particular type of MS. Furthermore, countries within the region vary with regards to access to healthcare and treatment strategies; in countries with more “aggressive” treatment approach, where they are able to start MS treatment earlier and thereby potentially postpone the transition to SPMS, prevalence may be lower. Additional reasons for the observed variation include the challenges of retrospective clinical diagnosis and a lack of an agreement on the definition of SPMS, as previously described.[72]

Table 4: Calculated prevalence of SPMS in selected countries

Country	MS prevalence, per 100 000	Source	Proportion of patients with SPMS	Source	Calculated prevalence of SPMS per 100 000
France	94.7		26.9%		25.5
France	94.7	Fromont et al., 2010[73]	26.9%	Confavreux and Vukusic, 2006[41]	25.5
Germany	157.7		21.9%		33.3
Germany	149	Atlas of MS database, 2013[8a]	24.3%	Akkad et al., 2009[74]	36.1
Germany	149	Atlas of MS database, 2013[8a]	34.0%	Akkad et al., 2009[74]	50.7
Germany	175	Hoer et al., 2014[71]	7.5%	Hoer et al., 2014[71]	13.1
Italy	89.4		26.6%		23.8
Italy	85	Solaro et al., 2005[75]	28.2%	Solaro et al., 2005[75]	24.0
Italy	90	Atlas of MS database, 2013[8a]	21.6%	Berto et al., 2011[76]	19.4
Italy	96.0	Gajofatto et al., 2013[77]	21.9%	Gajofatto et al., 2013[77]	21.0
Italy	85	Iuliano et al., 2014[78]	25.3%	Iuliano et al., 2014[78]	21.5
Italy	91.0	Bellantonio et al., 2013[79]	36.2%	Bellantonio et al., 2013[79]	32.9
Spain	62.9		16.4%		11.0

Country	MS prevalence, per 100 000	Source	Proportion of patients with SPMS	Source	Calculated prevalence of SPMS per 100 000
Spain	43.4	Benito-Leon et al., 1998[5]	10.6%	Benito-Leon et al., 1998[5]	4.6
Spain	32	Modrego Pardo et al., 1997[6]	8.7%	Modrego Pardo et al., 1997[6]	2.8
Spain	78.6	Otero et al., 2010[7]	21.2%	Otero et al., 2010[7]	16.7
Spain	59	Atlas of MS database, 2013[8]	16.2%	Antiguedad et al., 2009[80]	9.6
Spain	65	Bartulos Iglesias et al., 2015[9]	19.0%	Bartulos Iglesias et al., 2015[9]	12.4
Spain	90.2	Izquierdo et al., 2015[10]	15.4%	Izquierdo et al., 2015[10]	13.9
Spain	71.9	Candeliere-Merlicco et al., 2016[11]	23.9%	Candeliere-Merlicco et al., 2016[11]	17.2
UK	145		39.4%		57.8
UK	110	Atlas of MS database, 2013[8a]	37.2%	Orme et al., 2007[13]	40.9
UK	180	Simpson et al., 2015[12]	41.5%	Simpson et al., 2015[12]	74.6

[a]Data for the country MS prevalence were based on 2008 estimates. Where these studies did not describe the prevalence of MS, other sources of MS prevalence data were used. Where more than one source is available for each country, overall estimates (shaded) are calculated as unweighted averages of the individual estimates.

MS, multiple sclerosis; SPMS, secondary progressive multiple sclerosis.

Epidemiology of SPMS with or without relapses

Novartis is not aware of data regarding the epidemiology of active SPMS, and only two population-based studies have investigated the proportion of patients with SPMS who had or did not have superimposed relapses (Table 5). These studies provide estimates from large patient populations, where the proportions of patients with SPMS who had superimposed relapses ranged from 39.5–52.7%. Importantly, these studies do not take MRI into account; using MRI as an additional way to establish active disease will likely increase the prevalence of active SPMS.

Table 5: Proportion of patients with SPMS who had superimposed relapses in population based studies

Reference	Country, study type	Definition of SPMS	Number of patients with SPMS	Proportion of patients with SPMS who had superimposed relapses
Confavreux and Vukusic, 2006[41]	France, prospective	Lublin and Reingold, 1996[49a]	496	39.5%
Khil et al., 2009[14]	Germany, registry study	Definition not specified; patient classification as	2954 (2939 with relapse data)	52.7%

Reference	Country, study type	Definition of SPMS	Number of patients with SPMS	Proportion of patients with SPMS who had superimposed relapses
		recorded in the registry data		

[a]SPMS is defined as "an initial RR disease course followed by disease progression with or without occasional relapses, minor remissions and plateaux."

SPMS, secondary progressive multiple sclerosis.

3. Describe the symptoms and burden of the disease or health condition for patients.

Patients with SPMS experience wide-ranging symptoms and a high symptomatic burden throughout their disease course. Reduced ambulatory capacity is the hallmark clinical feature such that aids for walking are needed and eventually wheelchairs are required to get about. In addition, these patients experience cognitive impairment, bulbar dysfunction, visual impairment, impaired arm function, fatigue, pain and depression, coupled with often severe sphincter control issues. All of which leads to a markedly reduced quality of life as well as reduced employment opportunities, frequently with a major impact on other family members. These can also be accompanied by bowel, bladder, sexual dysfunction, speech and auditory impairment, and oedema related symptoms. A number of studies have demonstrated that patients with SPMS experience greater symptom severity than those with RRMS, across the spectrum of symptoms experienced.[15, 81]

Patients with SPMS may experience cognitive impairment which appears to be worse than in patients with RRMS.[82] Cognitive impairment may manifest in a number of different ways: a large European cross-sectional, questionnaire-based study evaluated the proportion of patients experiencing moderate difficulty concentrating. This was significantly higher in patients with SPMS (n=142, 19.01%) than RRMS (n=881, 5.79%; $p = 0.0002$).[81] CPS is increasingly recognized as the most relevant cognitive domain affected in MS, and potentially most apparent in SPMS patients. Slowed CPS occurs in approximately half of MS patients[83] and approximately 75% of SPMS patients have a deficit in this domain.[56, 57] CPS is the most prevalent cognitive deficit in MS[84] and possibly the underlying, explanatory cognitive deficit in MS.[85]

Disability progression in MS leads to a loss of mobility, reducing a patient's ability to perform daily tasks and often leading to loss of autonomy. This is a significant burden in SPMS and is associated with a greater loss of mobility compared with RRMS; in all higher EDSS ranges, (above EDSS 4.5), it is likely that most patients will have SPMS. A cross-sectional study to evaluate patient-reported physical functioning in the US demonstrated that patients with SPMS were reported to have significantly worse physical component scores (32.6 vs 40.4; $p < 0.001$) and scores in the physical domains of the 36-item Short-Form Health Survey (SF-36) version 2, including physical functioning (28.4 vs 40.1; $p < 0.001$), role limitations due to physical health (33.1 vs 40.4; $p < 0.001$) and general health (36.0 vs 40.8; $p < 0.001$) compared with patients with RRMS.[15] Moreover, in a Hungarian study, 44% of patients with SPMS (n = 48) were reported to be wheelchair-bound versus 7% of those with RRMS (n = 137).[86]

Fatigue is a commonly reported symptom in patients with SPMS or RRMS and can severely impact on patient's daily lives by reducing their mental and physical ability to perform daily tasks and participate in activities. A recent German study used a survey to assess the prevalence of

sleep disturbances and fatigue in 2052 patients with MS, of whom 17% (n = 356) had SPMS and 77% had RRMS (n = 1578).[87] In this analysis, sleep disturbances, and symptoms of fatigue were reported by approximately half of patients with SPMS (sleep disturbances, 54%; fatigue symptoms, 49%) and RRMS (sleep disturbances, 54–60%; fatigue symptoms, 45–50%). Severity of fatigue is reported to be higher in patients with SPMS than those with RRMS; in a large European cross-sectional, questionnaire-based study, moderate fatigue was reported by a significantly higher proportion of patients with SPMS than those with RRMS (24.7% vs 15.0%; $p = 0.0001$).[81]

Pain is a common symptom in patients with SPMS or RRMS, which can cause distress, fear, anger and frustration, reported to be experienced in 49.5% of patients with SPMS.[15] Patients with SPMS may experience more severe pain than those with RRMS; it has been shown that a significantly higher proportion of patients with SPMS than those with RRMS reported experiencing moderate pain without apparent cause (14.1% vs 3.1%; $p < 0.0001$).[81]

In addition to physical symptoms, patients with SPMS experience symptoms related to depression and an altered mood. In a UK MS registry-based study, 56.9% of SPMS patients experienced depression, with moderate and severe depression reported in 29.5% and 5.0% of SPMS patients, respectively.[16] Similar results were also observed in an Italian study.[88]

The symptom burden contributes to a large humanistic burden of SPMS, and patients experience a reduced health-related quality of life (HRQoL) accordingly. Two large, UK-based cross-sectional studies have evaluated the HRQoL of SPMS and RRMS patients using the EQ-5D. A significant correlation was found between SPMS and reduced HRQoL (regression coefficient: –0.080; $p < 0.001$),[89] and it was demonstrated that SPMS patients had significantly worse utility scores compared with patients with RRMS (regression coefficient: –0.045; $p = 0.005$).[13]

Both relapse-associated worsening and progression independent of relapse activity are associated with increased societal economic costs compared to patients without disease activity; [90] the substantial clinical, humanistic and economic burden of SPMS therefore supports the requirement for an effective treatment to delay disease worsening of this disease.

Impact of siponimod on burden of disease

Siponimod has been demonstrated to reduce disability progression in patients with active SPMS, and displayed a 30.7% and 36.5% risk reduction compared with placebo for time to 3-month and 6-month CDP, respectively. [24] EXPAND studied a far more advanced ITT population (mean EDSS at baseline: 5.4; median EDSS at baseline: 6.0) compared with typical RRMS studies. In this higher EDSS range, an increase in EDSS is reflective of a clinically relevant change; for example, a change from 6.0 to 6.5 means that a patient deteriorates in mobility from being able to walk 100m with one walking aid to approximately 20m with two walking aids. By delaying disability progression in this active SPMS population, patients are able to maintain their current level of physical and cognitive abilities and their quality of life for longer.

Within the EXPAND ITT population, siponimod has been demonstrated to have a positive effect on cognitive processing speed: results from an exploratory analysis using the symbol digit modalities test (SDMT), indicated that, compared with placebo, siponimod treatment results in more stability and improvement in CPS.[28] Compared with placebo, SDMT results showed a nominally statistically significant difference in adjusted means over all time-points assessed was observed for siponimod (1.384, p=0.007, unadjusted for multiplicity) over a mean follow-up time of 18 months in the core study. In a *post hoc* analysis, siponimod also significantly reduced the

risk of SDMT score worsening (decline ≥ 4 points) by 21% (p = 0.0157); a 4-point change is considered to be clinically meaningful as it impacts vocational status.[26, 27] Analysis of SDMT scores based on relapse history in the two years prior to randomisation demonstrates the beneficial effect of siponimod independent of relapses; significant differences in change from baseline were observed between placebo and siponimod in both relapsing and non-relapsing SPMS patients, although was greater in relapsing SPMS patients (siponimod, +0.926; placebo, -1.647; difference = +2.57; p=0.0151) than the non-relapsing SPMS patients (siponimod, +1.703 points; placebo, -0.74 points; difference = +2.44, p=0.0099).[28]

The reduction in symptom burden may also impact upon the societal burden of disease, as reduced disease progression will delay the requirement for greater care needs.

2.2 Target population

1. Describe the target population and the proposed position of the target population in the patient pathway of care.

In line with the anticipated marketing authorisation and positive CHMP opinion of siponimod, the target population for siponimod is “adult patients with secondary progressive multiple sclerosis (SPMS) with active disease”. SPMS typically develops following an RRMS disease course; in the patient pathway of care, this population therefore develops from the population eligible for R(R)MS DMT treatment.

Despite the fact that there are no widely accepted criteria to diagnose SPMS, there is consensus that a typical SPMS population would include patients who have progression of disease independent of relapses with or without occasional superimposed relapses. Active SPMS is evidenced by relapses or imaging features of inflammatory activity.

This population forms a sub-population of the EXPAND study, which demonstrated that siponimod is both effective and well-tolerated in the active SPMS population. In addition, this population faces a substantial unmet need, with no other currently available DMT shown to effectively or consistently delay progression of disability in these patients.

2. Estimate the size of the target population. Include a description of how the size of the target population was obtained and whether it is likely to increase or reduce over time.

No European-wide estimates of SPMS incidence have been published. However, the size of the total SPMS population can be crudely estimated based on the epidemiological estimates presented earlier, where the calculated prevalence of SPMS ranged from 11 people per 100 000 of the general population in Spain to 58 people per 100 000 of the general population in the UK. These estimates can be used to derive estimates for the active SPMS population.

Estimates for the size of the adult population (18 years and over) in each EU & EEA Member State were obtained from Eurostat.[91] As there is known to be a North–South gradient in the prevalence of MS,[92] the number of patients with SPMS in those countries denoted as ‘South’ was calculated using the Spanish prevalence, and those denoted as ‘North’ used the UK prevalence (refer to Table 6 for details) – it is acknowledged that such assumptions are necessarily somewhat arbitrary. The total SPMS population was subsequently calculated from the sum of the estimated SPMS populations in each country, giving an estimate of 181,108 patients.

In the absence of data concerning the epidemiology of active SPMS specifically, two population-based studies provide estimates for the prevalence of SPMS with superimposed relapses, demonstrating that this ranges between 39.5–52.7% (Table 5). Due to the large population considered (n=2,939 with relapse data), the more recent 2009 German registry study was selected to inform the calculations for the size of the SPMS population with superimposed relapses.[14] Therefore, assuming 52.7% of patients with SPMS have superimposed relapses,[14] the size of the active SPMS population is estimated to be 95,444 patients, although this does not account for the non-relapsing but MRI-active SPMS population. Using the alternative lower estimate for population prevalence (39.5%),[41] the size of the relapsing SPMS population is calculated to be 71,538 patients. These studies do not take MRI into account; using MRI as an additional way to establish active disease will likely increase the prevalence of active SPMS. Furthermore, in clinical practice, many SPMS patients are still receiving DMTs, which are known to be efficacious in reducing inflammatory activity: for such patients the rate of relapses may be reduced, further underestimating the target population size. With levels of DMT usage in SPMS in Member States being 56%, the magnitude of this issue is considerable.[20]

Novartis is not aware of any evidence that is able to address the question of whether the prevalence of SPMS is likely to increase or reduce over time.

Table 6: Countries assigned as 'North' or 'South' for the target population calculation

North	South
Austria	Bulgaria
Belgium	Croatia
Czechia	Cyprus
Denmark	Greece
Estonia	Italy
Finland	Malta
France	Portugal
Germany	Romania
Hungary	Slovenia
Iceland	Spain
Ireland	
Latvia	
Lithuania	
Luxembourg	
Netherlands	
Norway	
Poland	
Slovakia	
Sweden	
United Kingdom	

2.3 Clinical management of the disease or health condition

1. Describe the clinical pathway of care for different stages and /or subtypes of the disease being considered in the assessment.

Currently, 11 disease-modifying therapies (DMTs) are available (country/regional differences exist) for the treatment of MS (interferon beta-1a and interferon beta-1b, glatiramer acetate, fingolimod, natalizumab, teriflunomide, dimethyl fumarate, alemtuzumab, ocrelizumab, cladribine, and mitoxantrone). Treatments that are approved for use in patients with SPMS in the EU/EEA Member States, and their licensed indications, are summarised in Table 7. Clinical treatment guidelines have also recommended treatment options for patients with SPMS, which may not be specifically approved for use in this population; these guidelines are summarised in Table 8.

Table 7: DMTs approved for use in patients with SPMS in the EU/EEA Member States and their licensed indication

DMT	Wording of licensed indication relevant to SPMS
IFNβ-1b (Extavia®/Betaferon ®)	The treatment of SPMS with active disease, evidenced by relapses.
IM IFNβ-1a (Avonex®)	The treatment of relapsing MS and should be discontinued in patients who develop progressive MS.
SC IFNβ-1a (Rebif®)	The treatment of relapsing MS. Efficacy has not been demonstrated in patients with SPMS without ongoing relapse activity.
Mitoxantrone (Novantrone®)	The treatment of highly active relapsing MS associated with rapidly evolving disability where no alternative therapeutic options exist.
Cladribine (Mavenclad®)	The treatment of highly active relapsing MS as defined by clinical or imaging features.
Ocrelizumab (Ocrevus®)	The treatment of relapsing forms of MS with active disease defined by clinical or imaging features

Source: Avonex® SmPC,[93] Betaferon® SmPC,[18] Extavia® SmPC,[17] Mavenclad® SmPC,[19] Novantrone® SmPC,[94] Ocrevus® SmPC,[95], Rebif® SmPC.[96]

Table 8: Relevant guidelines for the treatment of SPMS

Name of society/organisation issuing guidelines	Date of issue or last update	Country to which guideline applies	Summary of recommendations (Level of evidence/grade of recommendation for the indication under assessment)
ECTRIMS	2018	Europe	Consider treatment with interferon-1a or -1b, or mitoxantrone, for patients with active secondary-progressive MS taking into account, in discussion with the patient, the dubious efficacy, as well as the safety and tolerability profile of these drug. Consider treatment with ocrelizumab or cladribine for patients with active SPMS.[97]
Association of British Neurologists	2015	UK	Patients with SPMS with relapses may benefit from treatment with DMTs if their relapses are the main cause of disability progression. No treatments are recommended for patients with SPMS without relapses.[98]
German Society of Neurologists	2014	Germany	These guidelines recommended IFNβ and mitoxantrone for patients with

			SPMS.[99] Guidelines were valid until 2017.
Spanish Neurology Society	2013	Spain	For SPMS with exacerbations, IFNβ or glatiramer acetate is recommended. For SPMS without exacerbations, they do not recommend any medication owing to the fact no effective treatment is available.[100]

DMT, disease modifying therapy; ECTRIMS, European Committee for Treatment and Research in Multiple Sclerosis; IFN, interferon; SPMS, secondary progressive multiple sclerosis.

Most DMTs are approved for RRMS or relapsing forms of MS (relapsing multiple sclerosis (RMS), defined as RRMS and SPMS with relapses). Products for both indications were approved mainly based on treatment effect on relapses, MRI lesion activity, and less so for the delay in disability worsening, mainly driven by reducing incomplete recovery/remnant disability after relapses. These effects were demonstrated primarily in RRMS patients, who formed the vast majority in these studies. None of the agents approved for RMS has demonstrated a specific efficacy on slowing disability progression in the subgroup of SPMS patients with relapses. In fact, no dedicated SPMS studies with approved MS therapies have demonstrated efficacy on disability progression in the overall SPMS population, including a recent Phase 3 study with natalizumab (one of the most effective drugs for inflammatory disease) conducted in a typical SPMS population with population characteristics similar to that of the siponimod SPMS study.[42] Ocrelizumab is the only MS therapy that has demonstrated an effect on disability progression in a progressive MS population to date. It was recently approved in the EU for patients with early PPMS with inflammatory activity based on evidence from a Phase 3 study in PPMS that showed a 24% risk reduction in 3-month CDP vs placebo (p=0.03) in the overall study population.[101]

Betaferon® (also marketed as Extavia®), recombinant interferon (IFN) β-1b, is the only treatment specifically approved in “patients with SPMS”, but only for those who have active disease (evidenced by relapses).[17, 18] In the European trial of Betaferon® in SPMS, interferon beta-1b delayed the time to confirmed disability progression as measured by the EDSS. This treatment effect, independent of baseline EDSS score and previous relapses, led to the approval of interferon β-1b for patients with SPMS in Europe and Canada.[102] However, other phase III trials of interferon β preparations (the North American trial of interferon β-1b (Betaferon®), the Secondary Progressive Efficacy Clinical Trial of Recombinant Interferon β-1a in Multiple Sclerosis (SPECTRIMS) trial of interferon β-1a (Rebif®),[103] and the International Multiple Sclerosis Secondary Progressive Avonex Controlled Trial (IMPACT) of interferon β-1a (Avonex®)[104] could not confirm the treatment effect on disability. It is widely believed that these different treatment effects on disability progression as measured by the EDSS reflect differences in the study populations: Patients in the European SPMS trial were all treatment-naïve, younger and had more relapses in the 2 years before study enrolment compared to those in the negative trials which has likely contributed to the different outcome.[102] According to the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) / European Academy of Neurology (EAN) guidelines on the pharmacological treatment of MS, treatment with interferon beta-1a (subcutaneously) or interferon beta-1b should be considered in patients with active secondary progressive MS taking into account, in discussion with the patient, the uncertain efficacy, as well as the safety and tolerability profile of these drugs.[97] Furthermore, a Cochrane review has concluded that interferon β is not an effective treatment in SPMS.[105]

Ocrelizumab is a recombinant human anti-CD20 monoclonal antibody was recently approved by the EMA for relapsing MS in patients with active disease although its efficacy and safety have not been assessed specifically in patients with SPMS.[95] Evidence from large randomized trials of

patients with relapsing MS have shown that ocrelizumab was more effective than interferon β-1a for reducing relapses and, in the pooled analysis, disability progression. Ocrelizumab was also the first drug approved in the EU for the treatment of adult patients with early PPMS in terms of disease duration and level of disability, and with imaging features characteristic of inflammatory activity.[101] Market research has indicated some use of ocrelizumab for the treatment of SPMS in EU clinical practice.[20]

Fingolimod is a sphingosine analogue that modulates the S1P receptor and thereby alters lymphocyte migration, resulting in sequestration of lymphocytes in lymph nodes. This mechanism of action is similar to that of siponimod. There is evidence from several RCTs that fingolimod is effective in reducing the relapse rate in patients with RRMS. In a phase 3 trial in patients with PPMS (INFORMS trial), fingolimod compared with placebo failed to slow disease progression.[49, 106] No studies have assessed the efficacy of fingolimod in SPMS, although market research indicates usage of fingolimod for SPMS in EU clinical practice.[20]

Natalizumab is a recombinant monoclonal antibody directed against the alpha-4 sub-unit of integrin molecules, thereby blocking integrin association with vascular receptors and limiting adhesion and transmigration of leukocytes. Natalizumab is a highly effective drug for the treatment of RRMS, although use is restricted to JC-virus negative patients. However, in a recent phase III placebo-controlled trial in patients with SPMS for at least 2 years and disability progression unrelated to relapses in the previous year (ASCEND; n=889), natalizumab did not significantly reduce disability progression as assessed by the primary multicomponent endpoint (EDSS and T25FW) and secondary endpoints, including EDSS alone.[42]

Mitoxantrone is an anthracycline analogue that is used as a chemotherapeutic agent for some cancers. The largest trial of mitoxantrone in MS was a single multicentre, double-blind trial of 194 patients with worsening RRMS or SPMS (worsening defined as 1·0 or more EDSS points during the 18 months before enrolment).[107] Treatment with mitoxantrone was associated with significant clinical benefits compared with placebo on multivariate analysis, reducing progression of disability and clinical exacerbations. According to the ECTRIMS/EAN guidelines, treatment with mitoxantrone should be considered in patients with active SPMS taking into account, in discussion with the patient, the efficacy and specifically the safety and tolerability profile of this agent.[97] However, the risks of cardiotoxicity and potential for the development of leukaemia with mitoxantrone greatly limit its utility to patients with “highly active relapsing multiple sclerosis associated with rapidly evolving disability where no alternative therapeutic options exist”.[94, 108] Mitoxantrone is therefore not widely used in the treatment of SPMS.

Cladribine is a nucleoside analogue of deoxyadenosine that selectively depletes dividing and non-dividing T and B cells implicated in the pathogenesis of MS. Cladribine was recently approved by the EMA for highly active relapsing MS.[19] Controlled trials of cladribine have not shown consistent benefit specifically for patients with progressive forms of MS, although some data from two small trials in what was described in the trials as “chronic progressive” MS (n=159 and n=51) suggest some benefit on MRI parameters but no significant treatment effects were found, in terms of disability progression (determined through analysis of EDSS over time, and a time to failure analysis).[109, 110] The very small trial populations and a lack of relevant outcomes considered (3- and 6-month CDP determined using EDSS, ARR) are major limitations.[109, 110]

Rituximab is a recombinant human anti-CD20 monoclonal antibody that binds to a different epitope of CD20 to that of ocrelizumab. Rituximab has been studied in small RCTs of RRMS and PPMS patients,[111, 112] however is not a licensed treatment for MS. Treatment with rituximab in patients with PPMS was not associated with delayed time to confirmed disease progression in

the OLYMPUS trial,[111] and the phase 2 study of rituximab in RRMS considered limited endpoints in a population of 104 patients.[112]

Teriflunomide, dimethyl fumarate and alemtuzumab have not been studied in pivotal trials, nor approved, in the SPMS population.

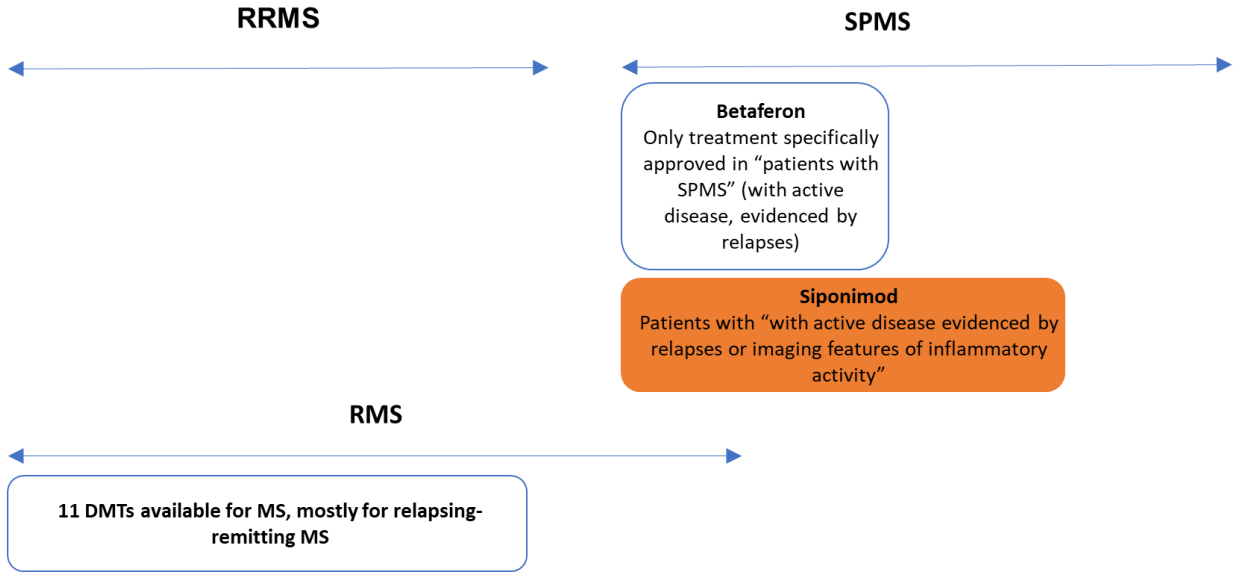
Thus, current therapeutic options for active SPMS patients are limited to drugs approved for RMS (or as for IFNB-1b in relapsing SPMS), for which there is no evidence of efficacy in slowing disability progression in the overall SPMS population. There is therefore an unmet medical need for a therapy with meaningful efficacy on disability progression and a well-characterized and manageable safety profile for patients with active SPMS. Due to the lack of alternative treatment options and the challenge in distinguishing relapsing disease, as previously described, most patients continue on treatments that they received during the RRMS phase of their disease.

Anticipated position and use of siponimod within clinical pathway of care

Should siponimod be adopted for use, it would become an alternative treatment for patients with active SPMS, (Figure 1). The introduction of siponimod is anticipated to cause a shift from R(R)MS DMTs that, though ineffective for disability progression in SPMS, were continued due to a lack of effective options, to the new, effective, option of siponimod.

All DMTs, including siponimod, are used in addition to Best Supportive Care (BSC), the package of symptomatic and supportive care provided to all MS patients, but which does not affect the occurrence of relapses or disability progression. While significant numbers of patients with SPMS are known to receive BSC alone, with no DMT, this is understood to reflect patients who have either an EDSS of 7 or greater (where trial data for DMT use is largely unavailable), or patients for whom DMTs are clinically inappropriate for other reasons and those patients who choose not to take DMTs. Novartis understand that the use of BSC increases with higher EDSS score and is therefore highly relevant for the SPMS population. The introduction of siponimod will not affect the use of BSC, which will continue to be provided to all patients with MS, and is also not expected to displace patients currently receiving no DMT.

Figure 1: Treatment pathway for MS following the introduction of siponimod



DMT, disease modifying therapy; MS, multiple sclerosis; RMS, relapsing multiple sclerosis; RRMS, relapsing remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis.

2.4 Comparators in the assessment

1. On the basis of the alternatives presented, identify the technologies to be used as comparator(s) for the assessment.

Due to the lack of treatment options for SPMS and because DMTs are frequently not reimbursed following confirmation of SPMS, clinicians frequently maintain the R(R)MS diagnosis and treatment with R(R)MS DMTs throughout the transition phase to SPMS; only once evidence of SPMS is irrefutable is treatment with R(R)MS DMTs reconsidered, although it is often continued for lack of better options.[20]

Table 9 presents a summary of the type of evidence available for each comparator specified in the EUnetHTA project plan. Whilst evidence indicates that a number of these DMTs are utilised in the treatment of SPMS across Europe, only interferon β and natalizumab have sufficient clinical evidence in SPMS to assess their relative effectiveness versus siponimod. Furthermore, in the active SPMS sub-population, the only data are derived from the European SPMS Study; [113, 114] however, baseline data reveal that the study population is very dissimilar to both the full EXPAND population as well as the active sub-population. These limitations preclude a valid indirect comparison in the active SPMS population, and the comparators in the submission were therefore determined based on the availability of data within the whole SPMS population.

No relevant studies in SPMS populations are available for ocrelizumab, rituximab, cladribine and fingolimod, preventing any comparison being made.

A discussion of the heterogeneity between EXPAND and the relevant comparator studies is presented in Section 5.2.3.

Table 9: Summary of available evidence for comparators specified in the EUnetHTA Project Plan

	Evidence of use[20]	Clinical evidence in SPMS
Interferon β	Yes	Yes
Ocrelizumab	Yes	No
Fingolimod	Yes	No
Natalizumab	Yes	Yes
Mitoxantrone	No	No
Cladribine	No	No
Rituximab	Yes	No

Interferon β 1-b (Betaferon®/Extavia®) is approved for “patients with secondary progressive multiple sclerosis with active disease, evidenced by relapses”,[17, 18] interferon β 1-a preparations (Avonex® and Rebif®) are approved for use in “patients with relapsing MS”,[93, 96] and there is evidence of widespread usage of interferon β products in the SPMS population. Furthermore, the

efficacy of interferon β in SPMS has been investigated in a number of clinical trials, permitting comparison with siponimod. Interferon β is therefore included as a comparator in this submission. A feasibility assessment (Section 5.3.3) determined that, whilst heterogeneity between the interferon beta SPMS studies and EXPAND precluded a network meta-analysis, a matching-adjusted indirect comparison (MAIC) is possible. The relative effectiveness of siponimod compared with interferon beta preparations is therefore presented in this submission.

Natalizumab is approved for the treatment of "patients with highly active relapsing remitting multiple sclerosis".[115] One study reported on the efficacy of natalizumab in patients with SPMS,[42] and there is evidence for its usage in the treatment of SPMS. A feasibility assessment determined that, whilst heterogeneity between the natalizumab SPMS study ASCEND and EXPAND precluded a network meta-analysis, a matching-adjusted indirect comparison (MAIC) is possible (Section 5.3.3). The relative effectiveness of siponimod compared with natalizumab is therefore presented in this submission.

Ocrelizumab is indicated for the treatment of "adult patients with relapsing forms of multiple sclerosis (RMS)".[95] Ocrelizumab has therefore been included in the list of comparators as its indication partially overlaps with that of SPMS,[95] and Novartis understand that there is some use in EU clinical practice. No relevant studies of ocrelizumab in SPMS have been identified, therefore no indirect comparison against siponimod can be made.

Fingolimod is approved for the treatment of "highly active relapsing remitting multiple sclerosis".[116] Fingolimod has been included in the list of comparators as market research indicates use for SPMS in EU clinical practice. Fingolimod has not been investigated in SPMS, therefore no indirect comparison against siponimod can be made.

Cladribine is indicated for the treatment of "highly active" relapsing MS.[19] Whilst cladribine has been investigated in trials for its use in RRMS and chronic progressive MS, no studies reporting relevant outcomes in SPMS patients were identified. Therefore, this submission is unable to present an indirect comparison of siponimod against cladribine.

Rituximab is not licensed for use in MS, and no relevant studies of rituximab in SPMS have been identified. Therefore, this submission does not present an indirect comparison of siponimod against rituximab.

Mitoxantrone has been shown to slow disability progression in a small phase 3 trial of patients with RMS, a subset of which had SPMS.[107] The SmPC specifies that the use of mitoxantrone is limited to patients with "highly active relapsing multiple sclerosis associated with rapidly evolving disability where no alternative therapeutic options exist", owing to the risk of adverse events, including cardiotoxicity and risk of cancer.[94, 108] Given that mitoxantrone is used as a 'last line therapy', siponimod would never be an alternative to mitoxantrone, Mitoxantrone has therefore been excluded from the list of comparators.

3 Current use of the technology

Summary of issues relating to current use of the technology

- Siponimod is not currently licensed in any European countries.

3.1 Current use of the technology

1. Describe the experience of using the technology, for example the health conditions and populations, and the purposes for which the technology is currently used. Include whether the current use of the technology differs from that described in the (expected) authorisation.

Not applicable.

2. Indicate the scale of current use of the technology, for example the number of people currently being treated with the technology, or the number of settings in which the technology is used.

Not applicable.

3.2 Reimbursement and assessment status of the technology

1. Complete Table 10 with the reimbursement status of the technology in Europe.

Not applicable.

Table 10: Overview of the reimbursement status of the technology in European countries

Country and issuing organisation	Status of recommendation (positive/negative/ongoing/not assessed)	If positive, level of reimbursement*
–	–	–
Include a reference to any publicly available guidance documents *For example full reimbursement or only partial reimbursement. If partial reimbursement give a percentage of reimbursement.		

4 Investments and tools required

Summary of issues relating to the investments and tools required to introduce the technology

- DMTs, the tools, equipment and personnel required do not vary by MS phenotype. Therefore, the equipment and supplies required to use siponimod are anticipated to be largely similar to those currently required.
- Before initiation of treatment with siponimod, patients must be genotyped for CYP2C9 to determine their CYP2C9 metaboliser status.

4.1 Requirements to use the technology

1. If any special conditions are attached to the regulatory authorisation more information should be provided, including reference to the appropriate sections of associated documents (for example, the EPAR and SPC). Include:

- conditions relating to settings for use, for example inpatient or outpatient, presence of resuscitation facilities
- restrictions on professionals who can use or may prescribe the technology
- conditions relating to clinical management, for example patient monitoring, diagnosis, management and concomitant treatments.

Treatment with siponimod should be initiated and supervised by a physician experienced in the management of multiple sclerosis.[21] As a precautionary measure, patients with the following cardiac conditions should be observed for a period of 6 hours after the first dose of siponimod for signs and symptoms of bradycardia:

- Sinus bradycardia (heart rate <55 bpm),
- First- or second-degree [Mobitz type I] atrioventricular block,
- History of myocardial infarction
- History of heart failure

In these patients, it is recommended that an electrocardiogram is obtained prior to dosing and at the end of the observation period. If post-dose bradyarrhythmia or conduction-related symptoms occur or if echocardiogram 6 hours post-dose shows new onset second-degree or higher AV block or QTc ≥500 milliseconds, appropriate management should be initiated and observation continued until the symptoms/findings have resolved.[21]

Before initiation of treatment with siponimod, patients must be genotyped for CYP2C9 to determine their CYP2C9 metaboliser status. Such genotyping is not required before use of other DMTs.

As with fingolimod, a full course of vaccination with varicella vaccine is recommended for antibody-negative patients prior to commencing treatment with siponimod, following which initiation of treatment should be postponed for 1 month to allow the full effect of vaccination to occur.[21]

As with fingolimod, an ophthalmic evaluation is recommended 3-4 months after treatment initiation to confirm presence or absence of macular oedema. It is recommended that patients with diabetes mellitus, uveitis or a history of retinal disease undergo an ophthalmic evaluation prior to initiating therapy and have follow up evaluations while receiving therapy.[21]

2. Describe the equipment required to use the technology.

No additional requirements; siponimod is administered orally as a film coated tablet.

3. Describe the supplies required to use the technology.

No additional requirements; siponimod is administered orally as a film coated tablet.

5 Clinical effectiveness and safety

Summary of the clinical effectiveness

- In the ITT population, EXPAND met its primary endpoint, with siponimod reducing the risk of 3-month confirmed disability progression (CDP), determined using a time-to-event analysis, by 21% versus placebo (p = 0.013; Hazard ratio [HR] 0.79, 95% confidence interval [CI] 0.65–0.95).[24] Siponimod also reduced the risk of 6-month CDP, which is considered the more robust disability measure, by 26% versus placebo (p = 0.0058; HR 0.74, 95% CI 0.60–0.92).[24] A consistency of effect on CDP outcomes was observed across all pre-specified subgroups considered for the primary endpoint; for 3-month CDP, the favourable outcomes were seen for patients with (HR, 0.67) and without (HR, 0.87) superimposed relapses in the 2 years prior to the study.
- In patients with active disease, *post hoc* analyses to support the label demonstrate the clinical efficacy of siponimod in patients with active SPMS in reducing the risk of disability progression. Siponimod significantly delayed the time to 3-month and 6-month confirmed disability progression (CDP), displaying a 30.7%% (HR 0.69, 95% CI 0.53–0.91) and 36.5% (HR 0.63, 95% CI 0.47–0.86) risk reduction compared with placebo for these endpoints. A 46.1% annualised relapse rate reduction for confirmed relapses was observed for siponimod versus placebo (ARR ratio 0.539, p=0.0004). For the key secondary endpoint of time to 3-month confirmed worsening in timed 25-foot walk (T25FW), there was an observed risk reduction of 14.3% in favour of the siponimod group, although this result was not significant (p=0.1879). Research published after EXPAND was designed has suggested that T25FW may have suboptimal sensitivity to change in patients with pronounced ambulatory disability (such as those in the EXPAND trial, with median EDSS of 6.0 at baseline, i.e. over 50% of patents requiring at least one walking aid),[24] as small increases in the EDSS can substantially affect their mobility.The change in patient-reported impact of disease on walking ability (MSWS-12) assessed as a secondary endpoint, was significantly improved with siponimod therapy (p=0.0494). However, baseline MSWS-12 scores near the maximal possible score, reflecting the high disability of the study population, only allowed modest further increase (ceiling effect), narrowing the ability to show a treatment effect.
- EXPAND is the first study to demonstrate the positive effect of an intervention on cognitive processing speed in SPMS patients, as measured using SDMT. Compared with placebo, a nominally statistically significant difference in adjusted means over all time-points assessed was observed for siponimod in the ITT population (1.384, p=0.007, unadjusted for multiplicity). In a *post hoc* exploratory analysis, siponimod also significantly reduced the risk of SDMT score worsening (decline ≥ 4 points) by 21% (p = 0.0157); a 4-point change is considered to be the minimum clinically important difference.[26, 27]
- No direct evidence for the clinical effectiveness of siponimod versus the specified comparators exists, therefore an indirect treatment comparison was necessary. Trials in SPMS are only available for interferon β-1b, interferon β-1a and natalizumab, and 6-month CDP data are only available for two studies other than EXPAND (ASCEND and the North American Study). Furthermore, there is limited comparator data for the active SPMS sub-population; results, but not baseline characteristics, are available for interferon β in the "relapsing" sub population, but no data is available for an "active" sub population. Only one comparator study, of interferon β-1b, showed any statistically significant effect on the primary endpoint of disability progression compared to placebo. However, this study enrolled a very different study population of younger patients with shorter disease

duration and more inflammatory disease activity. This result could not be replicated in another study with interferon β-1b nor with any other interferon-β studied in SPMS.

- Due to significant heterogeneity between the EXPAND and the comparator trials when considering patient populations (inclusion/exclusion criteria and baseline characteristics of effect modifiers) and trial outcomes (dissimilar placebo-arm outcomes), the assumptions of similarity and homogeneity required for an NMA approach were not met. Whilst the results of an NMA would be unreliable and biased due to significant clinical heterogeneity and dissimilarity, as well as an imbalance of effect modifiers between EXPAND and each of the comparator trials, the availability of patient-level data for the EXPAND trial allowed individual comparisons to each of the SPMS trials identified, using a matching-adjusted indirect comparison (MAIC) approach. Notably, MAICs were not feasible in any subgroups, due to the lack of comparator subgroup data.
- In the pairwise MAICs, assuming ITT population data, siponimod demonstrated numerical superiority for all CDP-related outcomes; in particular, siponimod was determined to be statistically significantly more effective for the outcome of time to 6-month CDP, which is seen as the more relevant measure of CDP, compared with Betaferon®. For ARR, siponimod was numerically but not statistically superior to Avonex®, and Betaferon® but statistically superior to both regimens of Rebif® (22 or 44 µg TIW); siponimod was numerically inferior with regards to ARR in the comparison with natalizumab, although the result was not statistically significant.
- In the active SPMS sub-population, the only available data are derived from the European Study; baseline data from the European study reveal that the population is very dissimilar to both the full EXPAND population as well as the active sub-population. Therefore a MAIC and NMA were deemed not to be feasible in the active sub-population, however an exploratory Bucher ITC was conducted against interferon β-1a and interferon β-1b. Siponimod demonstrated numerical superiority for 3-month CDP outcomes, however substantial limitations of the Bucher ITC approach undermine the clinical validity of this approach. Although a separate MAIC in the active SPMS subgroup itself is infeasible, the results of the matching and adjusting process show that the base case comparison to interferon β-1b is selective for a more active subset of the EXPAND trial: average age and baseline EDSS are lowered, the proportion of patients experiencing relapses in the two years prior to the trial is increased, as is the average number of relapses per patients in the two years prior to the trial. Therefore, although the extrapolation of the MAIC results to the active SPMS subgroup has inherent limitations, it remains preferable to an unadjusted naïve comparison of subgroup data between two trials which are known to differ in many respects

Summary of safety

- In the overall EXPAND trial, a numerically higher proportion in the siponimod group versus the placebo group reported treatment-related AEs or SAEs; AEs led to permanent study discontinuation in 8% and 5% of participants in each group, respectively. Deaths were balanced between treatment groups.
- The most commonly reported SAEs in both treatment groups were urinary tract infections, basal cell carcinoma and increased alanine aminotransferase levels.

- Siponimod has a safety profile that was consistent with the known profile of S1P receptor modulators. These included herpes zoster infections (2.3% vs 0.7%), macular oedema (1.8% vs 0.2%), hypertension (10.5% vs 7.5%), convulsions (1.7% vs 0.4%), grade 4 lymphopenia (2.7% vs 0.2%) and elevated liver function tests (10.1% vs 3.7%).
- Initiation of siponimod treatment results in a transient decrease in heart rate; a titration scheme to reach the maintenance dose on day 6 is therefore applied at the start of treatment which mitigates this risk, allowing treatment initiation without monitoring for patients without cardiac risks.[21]
- The efficacy studies of relevant comparators described in the clinical effectiveness section provide summary data for these treatments; these are aligned with the known safety profiles of these DMTs from RRMS.
- Due to a lack of sufficient comparable data, no formal indirect comparison of siponimod with active comparators is possible.

5.1 Identification and selection of relevant studies

1. State the databases and trial registries searched and, when relevant, the platforms used to do this.

The following databases were searched from their inception dates to 17 October 2018 in the original SLR:

- MEDLINE, including MEDLINE Daily and Epub Ahead of Print (via the Embase.com platform), and MEDLINE In-Process (via PubMed) from 1946 to the date of search
- Embase (via the Embase.com platform) from 1974 to the date of search
- Cochrane Database of Systematic Reviews (CDSR) up to Issue 10 of 12, October 2018 (via the Wiley Online platform)
- Cochrane Central Register of Controlled Trials (CENTRAL) up to Issue 10 of 12, October 2018 (via the Wiley online platform)
- Database of Abstracts of Reviews of Effect (DARE) up to Issue 2 of 4, April 2015 [last database update] (via the Centre for Reviews and Dissemination (CRD) platform)
- Health Technology Assessment Database (HTAD) (via the CRD platform)
- MEDLINE and Embase were searched simultaneously via the Embase.com platform; CDSR and CENTRAL were searched simultaneously via the Wiley Online platform; DARE and HTAD were searched simultaneously via the CRD platform. Deduplication of records was performed alongside the title/abstract sifting stage.

The SLR update searches were conducted on 21 March 2019 in the following databases:

- MEDLINE, including MEDLINE In-Process, MEDLINE Daily, Epub Ahead of Print and Versions (via Ovid SP) from 1946 to 21st March 2019
- Embase (via Ovid SP) from 1974 to 21st March 2019
- CDSR up to Issue 3 of 12, March 2019 (via the Wiley Online platform)
- CENTRAL up to Issue 3 of 12, March 2019 (via the Wiley Online platform)

Conference Abstract Books

Manual searches of abstracts from conference proceedings of the following major conferences from 2016 to October 2018 were conducted in the original SLR:

- American Academy of Neurology (AAN) 2016, 2017 and 2018
- European Academy of Neurology (EAN) 2016, 2017 and 2018
- Consortium of Multiple Sclerosis Centres (CMSC) 2016, 2017 and 2018
- Americas Committee for Treatment and Research in Multiple Sclerosis (ACTRIMS) 2016, 2017 and 2018
- European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) 2016, 2017 and 2018
- Association of British Neurologists' conference (ABN) 2016, 2017 and 2018

The SLR update conducted in March 2019 identified one conference (ACTRIMS 2019) that that had taken place since the previous SLR.

HTA Websites and Grey Literature Sources

A search of the following sources was conducted for additional relevant studies:

- NICE (https://www.nice.org.uk/)
- Canadian Agency for Drugs and Technologies in Health (CADTH; https://www.cadth.ca/)
- Institute for Quality and Efficiency in Health Care (IQWiG; https://www.iqwig.de/)
- Utility-weight collection collated by Tufts New England Medical Center's Catalogue of Preference Scores (http://healtheconomics.tuftsmedicalcenter.org/cear4/aboutus/whatisthecearegistry.aspx)
- Haute Autorite de Sante (HAS; https://www.has-sante.fr/)
- AWMSG (http://www.awmsg.org/)
- SMC (https://www.scottishmedicines.org.uk/)
- European Medicines Agency (EMA; https://www.ema.europa.eu/)
- ClinicalTrials.gov
- WHO ICTRP (https://www.who.int/ictrp/en/)
- Centre for Reviews and Dissemination (CRD; https://www.york.ac.uk/crd/)
- NIHR HTA Programme (https://www.nihr.ac.uk/)
- EU Clinical Trials Register (https://www.clinicaltrialsregister.eu/)

Bibliography Searches

The bibliographies of relevant SLRs and (network) meta-analyses identified through the electronic database searches and grey literature searches, as well as all ultimately included articles, were hand-searched to identify any additional studies of relevance.

2. State the date the searches were done and any limits (for example date, language) placed on the searches.

The systematic literature review (SLR) was initially conducted in October 2018, with a subsequent update conducted in March 2019. Any date limits, where relevant, have been noted in the answer to question 1.

3. Include as an appendix the search terms and strategies used to interrogate each database or registry.

Please refer to Appendix A (Section 6.1) for details of the search strategy.

4. In Table 11, state the inclusion and exclusion criteria used to select studies and justify these.

The inclusion and exclusion criteria used for study selection are stated in Table 11. For the purpose of the SLR, comparators were not restricted to those within the scope of this submission, but were kept deliberately broad, including experimental therapies.

Table 11. Inclusion and Exclusion Criteria

PICOS domain	Inclusion criteria	Exclusion criteria
Population	Adults (≥18 years) diagnosed with SPMS	Children (<18 years) Relevant outcomes were not presented separately for adults with SPMS*
	* Studies reporting results for mixed MS population were included, if more than 80% population met the inclusion criteria for disease	
Interventions	• Siponimod • Fingolimod • Interferon β • Ocrelizumab • MIS416 • Glatiramer acetate • Natalizumab • Masitinib • Peginterferon beta • Stem cell transplantation • Alemtuzumab • Dimethyl fumarate • Imilecleucel T • Idebenone • Simvastatin • Mitoxantrone • Teriflunomide • Ibudilast • Opicinumab • Fluoxetine • Rituximab • Cladribine • Biotin • Riluzole • Amiloride	Studies not investigating at least one of the relevant interventions
Comparators	• Any intervention listed above • Placebo	Any other comparator

PICOS domain	Inclusion criteria	Exclusion criteria
	• Best supportive care • Dose-ranging studies were included; extension studies were only included if they contained a placebo or comparator arm.	
Outcomes	Any efficacy, HRQoL or safety outcomes, including: • Disability (e.g. EDSS, confirmed disability progression at 3 months, confirmed disability progression at 6 months) • Timed 25-foot walk test, 9-hole peg test, MSFC • Relapses (e.g. annualised relapse rate, time to first relapse, proportion of patients relapse free) • MRI parameters (e.g. number of new/enlarging T2 lesions, number of T1 Gd+ lesions, T1 lesion volume, T2 lesion volume, brain volume) • Cognition (e.g. SDMT, PASAT, BVMTR) • HRQoL (e.g. MSIS-29, MSWS-12, EQ-5D) • Safety and tolerability (e.g. adverse events, serious adverse events, specific adverse events, treatment discontinuation)	Studies not reporting any eligible outcomes Studies reporting eligible outcomes in a mixed population, without separately reporting data for the population of interest (unless more than 80% of study population are adults with SPMS)
Study design	• RCTs • Non-randomised interventional studies • Prospective observational studies • Retrospective observational studies • Cross-sectional studies • Case-control studies	Any other study design
	SLR/NMAs were included at the abstract stage but subsequently excluded at the full text stage and their bibliographies hand searched for additional articles of relevance to this review.	
Other considerations	• Abstract or full text in the English language • Human subjects	• Non-English language abstract or full text • Studies not on human subjects

BVMTR, Brief Visuospatial Memory Test-Revised; EDSS, Expanded Disability Status Scale; EQ-5D, EuroQol five dimension scale; HRQoL, health-related quality of life, MSFC, Multiple Sclerosis Functional Composite; MSIS-29, Multiple Sclerosis Impact Scale-29; MSWS-12, Multiple Sclerosis Walking Scale-12; PASAT, Paced Auditory Serial Addition Test; RCT, randomised controlled trial; SDMT, Symbol Digit Modalities Test; SPMS, secondary progressive multiple sclerosis.

5. Provide a flow chart showing the number of studies identified and excluded. The PRISMA statement can be used; the PRISMA flow chart is included below, as an example.

The number of studies identified and excluded in the SLR for both the original and updated SLR are shown in Figure 2 and Figure 3, respectively.

Figure 2: Original SLR – flow of studies through the systematic review process

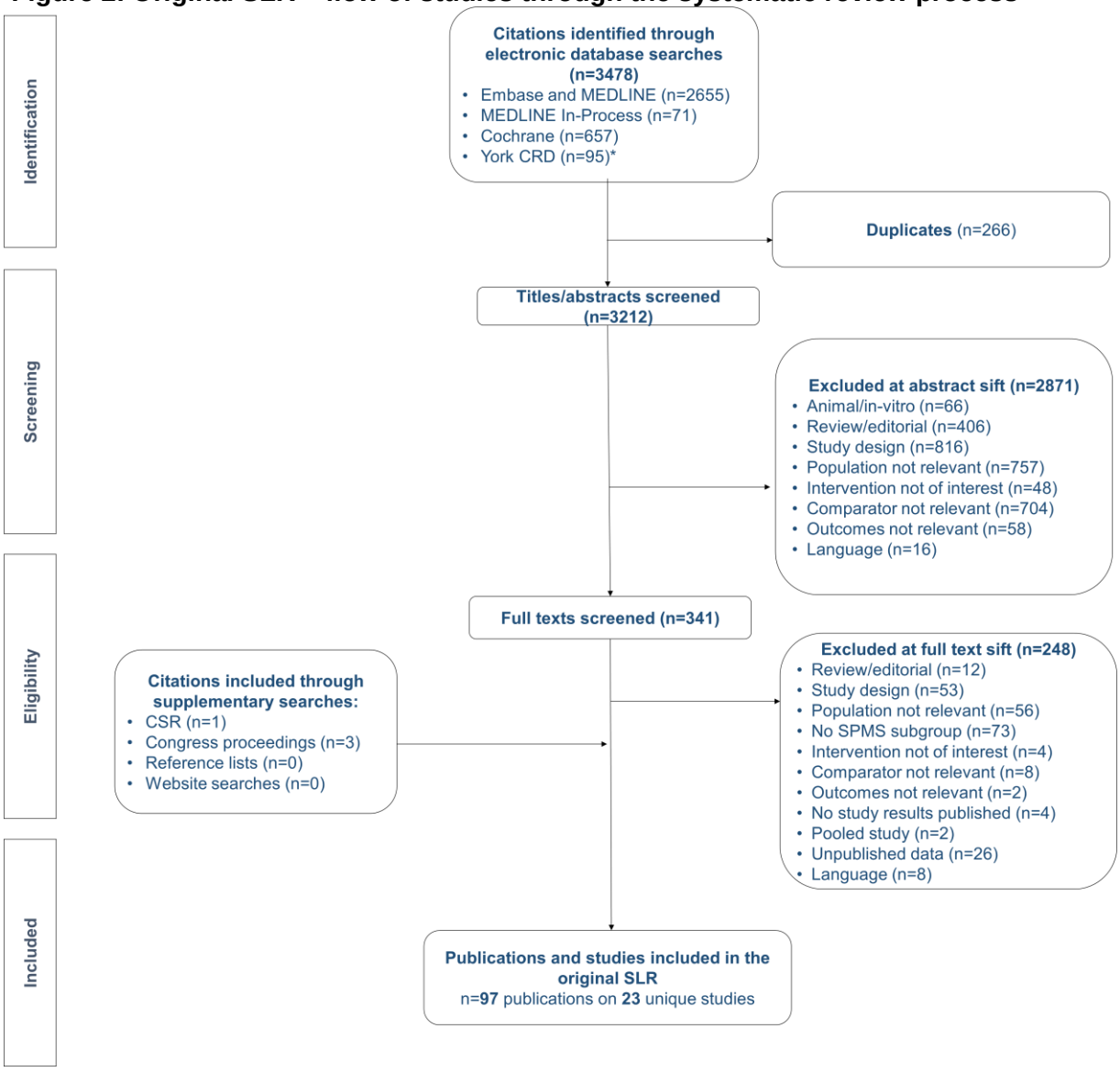
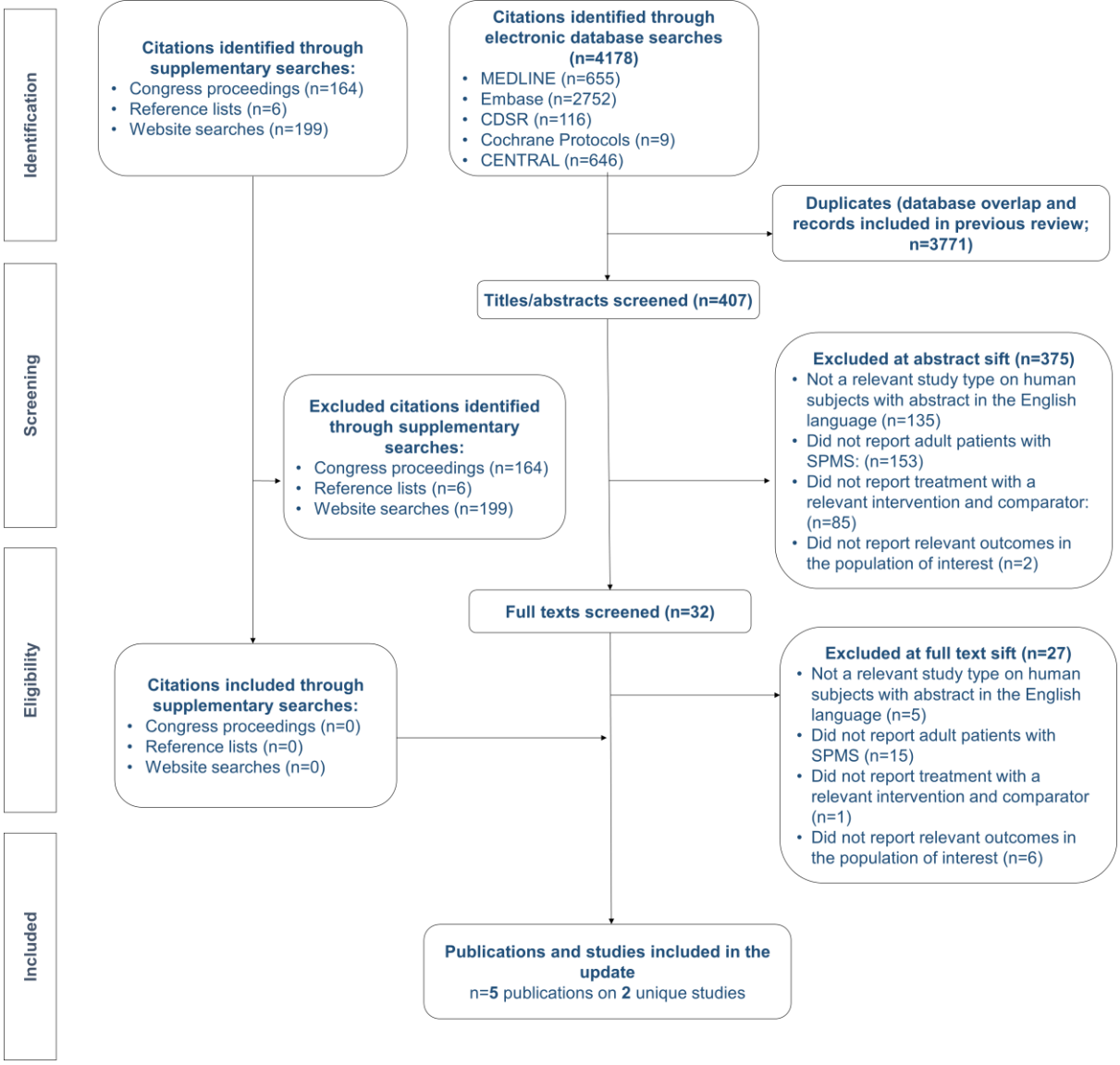


Figure 3. SLR update – flow of studies through the systematic review process



CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Controlled Register of Trials; Embase: Excerpta Medica Database; MEDLINE: Medical Literature Analysis and Retrieval System Online; SPMS: secondary progressive multiple sclerosis

Relevant studies

1. In Table 12 provide a list of the relevant studies identified.

A list of the relevant studies identified is presented in Table 12. The studies that satisfied the inclusion criteria for the SLR were further refined to those studying a relevant comparator (one study investigating a considerable underdose of a licensed comparator was also excluded) and reporting relevant outcomes. Including EXPAND, this resulted in six unique RCTs. The rationale for the exclusion of the studies prior to the MAIC is provided in Appendix A (Section 6.1.1).

Table 12: List of all relevant studies

Study reference/ID	**Available documentation***	**Status (ongoing**/ complete)**
Randomised controlled trials		
EXPAND	Kappos (2018)[24]	Complete
ASCEND	Kapoor (2018)[42]	Complete
SPECTRIMS	SPECTRIMS Study Group (2001)[103]; Li (2001)[117]	Complete
North American Study	Panitch (2004)[118]	Complete
European Study	European Study Group (1998)[113]; Kappos (2001)[114]	Complete
IMPACT	Cohen (2002)[104]	Complete
*Include references to all linked documents and indicate the expected date of publication for any unpublished clinical studies **Include expected date of completion		

5.2 Main characteristics of studies

1. In Table 17, describe the main characteristics of the studies.

Please refer to Table 17 for a description of the main characteristics of the studies of patients with SPMS. The included studies cover the whole SPMS population, not specifically those patients with active SPMS.

2. For each study provide a flow diagram of the numbers of patients moving through the trial.

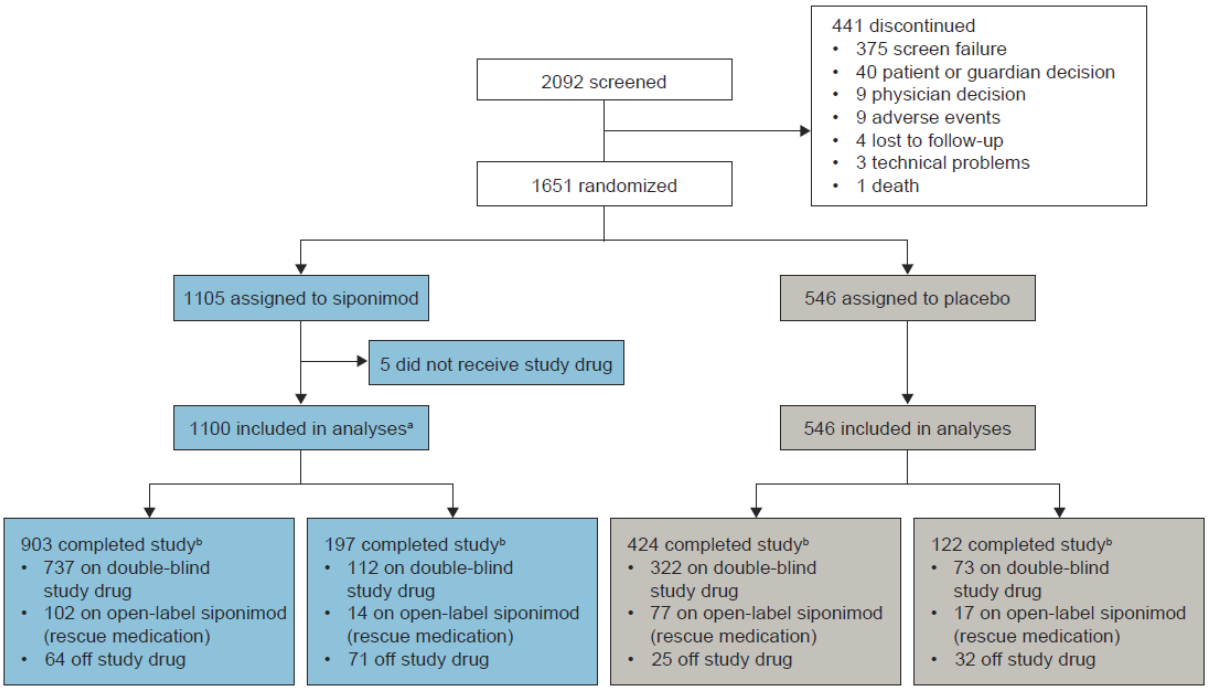
5.2.1 Patient disposition

EXPAND

A total of 1,651 patients entered the study (2:1 randomization with 1,105 in the siponimod group and 546 in the placebo group) (Figure 4).[24] In the siponimod group, five participants never received study drug and one participant did not provide a signed consent form before starting the study procedures. These participants were excluded from the analysis.

Median time on the study was 21 months (range: 0.2–37 months) and median exposure to the study drug was 18 months (range: 0–37 months). In total, 80% of participants (n = 1327/1651) completed the study (siponimod: 82% [n = 903]; placebo: 78% [n = 424]). Of all included participants, 11% (n = 179) switched to open-label siponimod (siponimod: 9% [n = 102]; placebo: 14% [n = 77]) and 5% (n = 89) stopped study medication (siponimod: 6% [n = 64]; placebo: 5% [n = 25]). Patients were analysed in their randomised treatment group, regardless of subsequent rescue therapy or treatment switching.

Figure 4: Patient disposition in the EXPAND study



[a]One participant randomly assigned to siponimod was excluded from all safety and efficacy analyses because no signed consent form was supplied before study start; [b]Double-blind placebo-controlled core part of EXPAND.

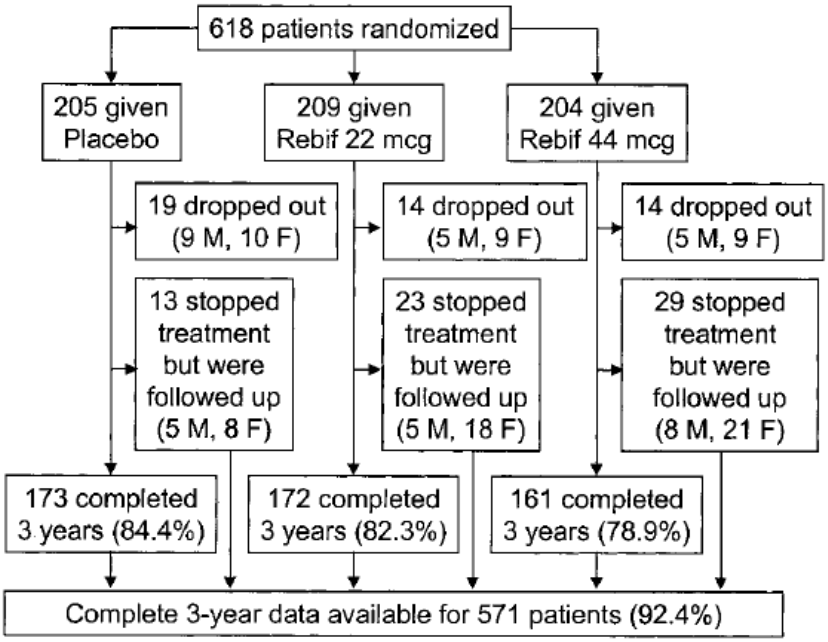
EXPAND, EXploring the efficacy and safety of siponimod in PAtients with SecoNDary progressive multiple sclerosis.

Source: Kappos et al., 2018[24]

Relevant comparator studies

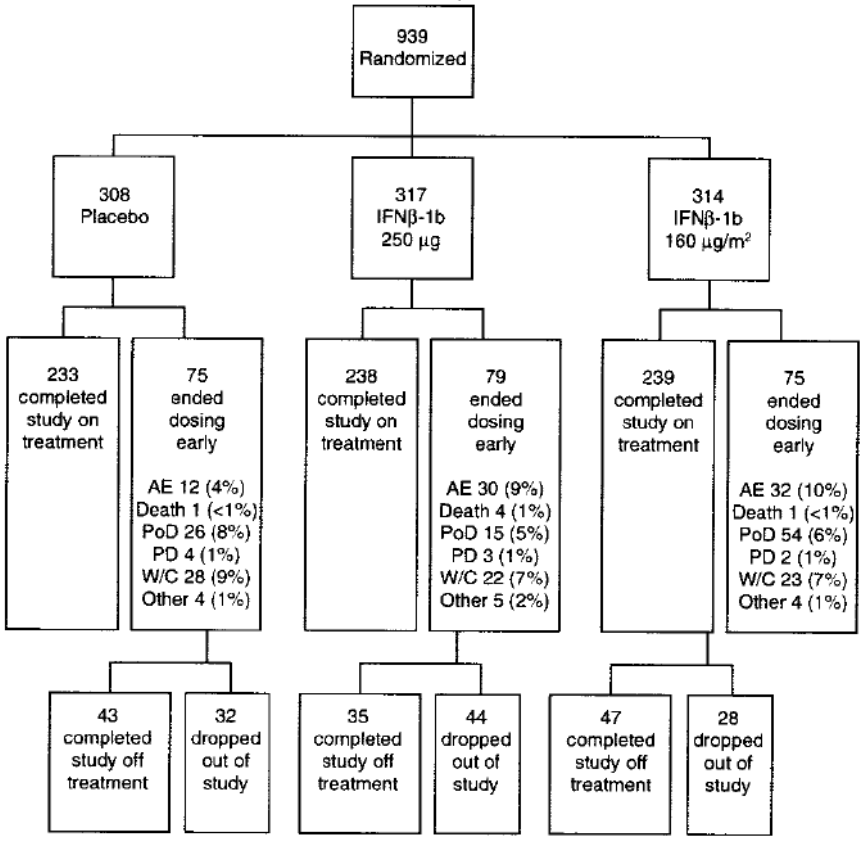
Patient disposition in each of the studies of comparators in SPMS is shown in Figure 8, Figure 5, Figure 6, Figure 7 and Figure 9.

Figure 5: Patient disposition in the SPECTRIMS study



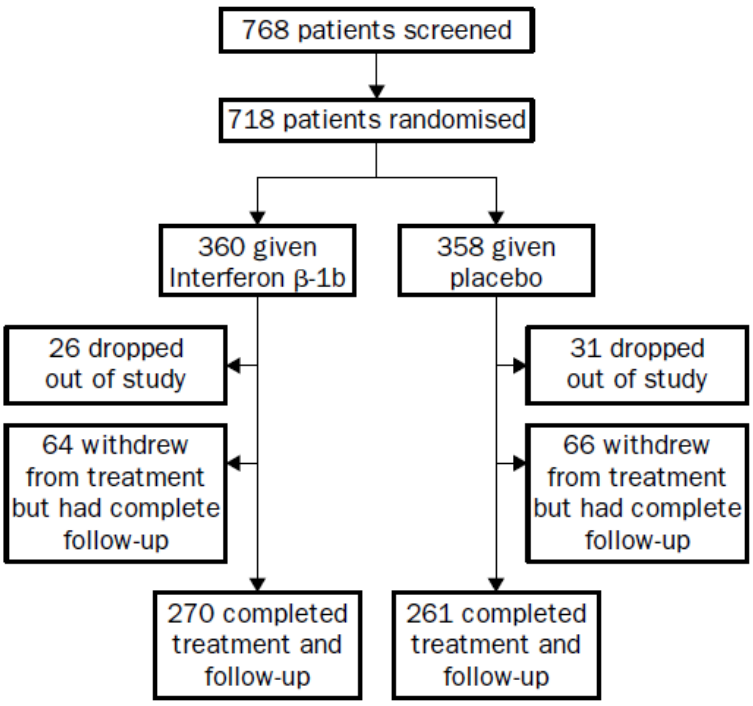
Source: SPECTRIMS study group, 2001[103]

Figure 6: Patient disposition in the North American Study



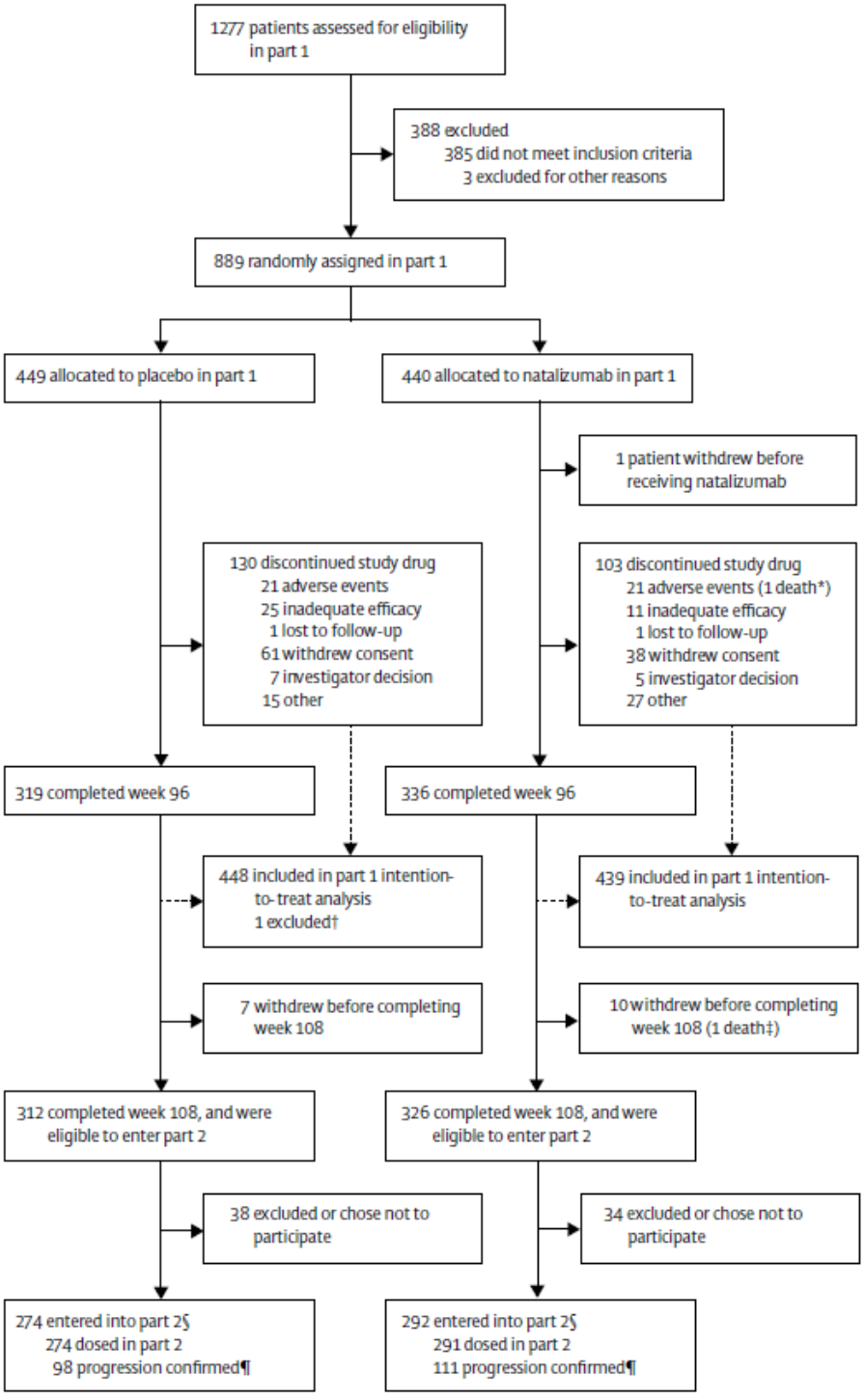
Source: Panitch et al., 2004[118]

Figure 7: Patient disposition in the European Study



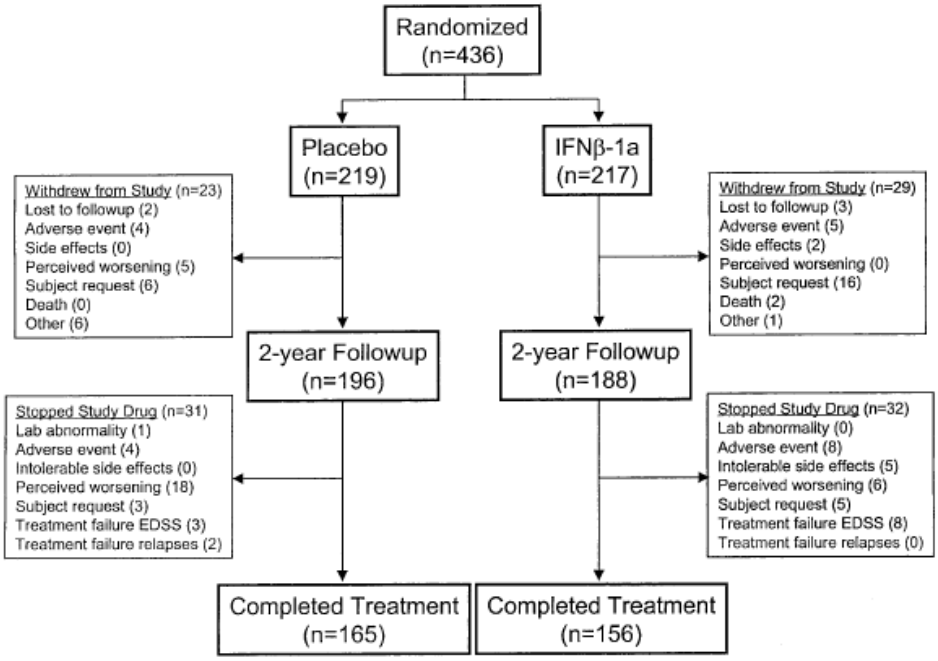
Source: European Study Group, 1998[113]

Figure 8: Patient disposition in the ASCEND study



Source: Kapoor et al, 2018[42]

Figure 9: Patient disposition in the IMPACT study



Source: Cohen et al., 2002[104]

3. For each study provide a comparison of patients (including demographic, clinical and social information [if applicable]) in treatment arms at baseline.

5.2.2 Demographic and baseline characteristics

EXPAND

Demographic and baseline characteristics for participants randomised in EXPAND are presented in Table 13. The siponimod and placebo groups were well matched for age, proportion of female participants, baseline EDSS score and baseline MRI and relapse outcomes. Furthermore, similar proportions in both groups had not received previous disease-modifying therapies (DMTs) (siponimod: 22%; placebo: 21%). Importantly, the population included in EXPAND is representative of an SPMS population, with characteristics that are compatible with natural history data and with other studies in SPMS.[24]

Importantly, levels of inflammatory disease activity were low in the EXPAND population, and levels of disability were high. Nearly 80% of participants had not relapsed in the year before study entry, over 60% had not relapsed in the 2 years before study entry and over 70% had no Gd^+ lesions at baseline. Furthermore, the population in EXPAND had higher levels of disability at baseline than those included in other MS trials.[24] This ensures that outcomes in EXPAND are relevant to a representative population of participants with SPMS.[102, 114, 118]

Table 13: Demographic and other baseline characteristics in the randomised set

Characteristic	Siponimod N = 1105	Placebo N = 546
Age, years Mean Median (range)	48.0 ± 7.8 49.0 (22–61)	48.1 ± 7.9 49.0 (21–61)

Characteristic	Siponimod N = 1105	Placebo N = 546
Age group, n (%) 18–40 years > 41 years	 188 (17) 917 (83.0)	 103 (19) 443 (81)
Female, n (%)	669 (61)	323 (59)
Time since diagnosis of MS, years Mean (± SD) Median (range)	 12.9 ± 7.9 12.0 (0.1–44.4)	 12.1 ± 7.5 11.2 (0.4–39.4)
Time since onset of MS symptoms, years Mean (± SD) Median (range)	 17.1 ± 8.4 16.4 (1.4–45.0)	 16.2 ± 8.2 15.4 (1.3–43.0)
Time since conversion to SPMS, years Mean (± SD) Median (range)	 3.9 ± 3.6 2.6 (0.1–24.2)	 3.6 ± 3.3 2.5 (0.1–21.7)
No previous use of DMT, n (%)	242 (22)	114 (21)
Participants with no relapses in the year before screening, n (%)	878 (79)	416 (76)
Participants with no relapses in the 2 years before screening, n (%)[a]	712 (64)	343 (63)
Number of relapses in the year before screening Mean (± SD) Median (range)	 0.2 ± 0.5 0 (0–4)	 0.3 ± 0.6 0 (0–4)
Number of relapses in the 2 years before screening Mean (± SD) Median (range)	 0.7 ± 1.2 0 (0–12)	 0.7 ± 1.2 0 (0–8)
EDSS score Mean (± SD) Median (range)	 5.4 ± 1.1 6.0 (2.0–7.0)	 5.4 ± 1.0 6.0 (2.5–7.0)
EDSS categories, n (%) < 3.0 3.0–4.5 5.0–5.5 6.0–6.5 > 6.5	 6 (0.5) 312 (28) 165 (15) 620 (56) 2 (0.2)	 2 (0.4) 148 (27) 100 (18) 295 (54) 1 (0.2)
Gd^+ lesions on T1-weighted images, n (%) Yes No	 237 (21) 833 (75)	 114 (21) 415 (76)
Total volume of lesions on T2-weighted images, mm^3 [b] Mean (± SD) Median (range)	 15 632 ± 16 268 10 286 (23–116664)	 14 694 ± 15 620 9994 (0–103560)
Normalised brain volume, cm^3 [c] Mean (± SD) Median (range)	 1422 ± 86 1421 (1136–1723)	 1425 ± 88 1425 (1199–1691)

[a]For three participants in the siponimod and one participant in the placebo group, information on the number of relapses in the past 2 years was not available; [b]1074 participants were assessed in the siponimod group, and 531 participants were assessed in the placebo group; [c]1071 participants were assessed in the siponimod group, and 531 participants were assessed in the placebo group.

Some percentages do not add up to 100 because of rounding.

DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; Gd^+, gadolinium-enhancing; MS, multiple sclerosis; SD, standard deviation; SPMS, secondary progressive multiple sclerosis.

Source: Kappos et al., 2018.[24]

Active SPMS Subgroup

The active SPMS subgroup is defined by relapses and/or MRI activity in patients with SPMS.[2] In the EXPAND trial, the *post hoc* active SPMS subgroup analyses included patients who experienced relapses in the two years prior to the study and/or who had gadolinium-enhanced T1 lesions at baseline. This choice of subgroup data cut reflected the available baseline characteristics from the EXPAND trial. Of note, in clinical practive new T2 lesions compared to previous scan could also be used to establish activity via MRI.

A total of 779 patients (out of the total trial population of 1649 patients) formed part of the *post hoc* active SPMS subgroup: 516 were in the siponimod group and 263 in the placebo arm, reflecting the 2:1 randomisation of the overall trial.

The baseline characteristics of patients included in the active SPMS subgroup of the EXPAND study are presented in Table 14. Patient characteristics at baseline in the subgroup were well balanced between the treatment groups and were similar to the baseline characteristics of the overall population except the criteria defining active SPMS.

The active SPMS subgroup of the EXPAND trial included a higher number of patients experiencing relapses in the previous 2 years prior to screening (24.1% had no relapses in that time, and 54.6% did not have relapses within the year prior to screening, compared with 63.9% and 78.4%, respectively, in the overall population). There was also a higher percentage of patients with Gd-enhancing T1 lesions (45.9% compared with 21.3%) and a larger volume of T2 lesions (17659 mm^3 compared with 15322 mm^3). Patients in the active SPMS subgroup were slightly younger (mean age of 46.6 years, compared with 48.0 in the ITT population); all other baseline characteristics were similar between the subgroup and the overall trial population.

Table 14: Summary of EXPAND baseline characteristics for active SPMS subgroup

Demographic Variable	Siponimod N=516	Placebo N=263
Age groups – n (%)		
18–40	119 (23.1)	61 (23.2)
>40	397 (77.0)	202 (76.8)
Age (years)		
Mean (SD)	46.2 (8.12)	47.2 (8.52)
Median	46.0	48.0
Min – Max	23–61	21–60
Sex – n (%)		
Female	331 (64.1)	166 (63.1)
Male	185 (35.9)	97 (36.9)
Duration of MS since diagnosis (years)		
Mean (SD)	11.68 (7.42)	11.12 (6.69)
Median	10.66	10.29
Min – Max	0.1–37.2	0.4–33.2
Duration of MS since first symptom (years)		
Mean (SD)	15.57 (7.90)	15.53 (8.18)

Demographic Variable	Siponimod N=516	Placebo N=263
Median	14.78	14.66
Min – Max	1.4–41.7	1.3–41.4
Time since conversion to SPMS (years)		
Mean (SD)	3.24 (3.32)	3.09 (3.20)
Median	2.11	1.89
Min – Max	0.1–24.2	0.1–21.7
Number of relapses in the last 2 years prior to screening		
Mean (SD)	1.4 (1.42)	1.4 (1.33)
Median	1.0	1.0
Min – Max	0–12	0–8
Number of relapses in the last 2 years prior to screening (categories) – n (%)		
None	127 (24.6)	61 (23.2)
Number of relapses in the last year prior to screening		
Mean (SD)	0.5 (0.69)	0.6 (0.70)
Median	0.0	0.0
Min – Max	0–4	0–4
Number of relapses in the last year prior to screening (categories) – n (%)		
None	291 (56.5)	134 (51.0)
Time since the onset of the most recent relapse (months)		
Mean (SD)	31.51 (42.28)	28.61 (41.24)
Median	17.03	15.00
Min – Max	3.1–321.5	2.7–307.4
EDSS		
Mean (SD)	5.46 (1.06)	5.41 (1.04)
Median	6.00	6.00
Min – Max	2.0–7.0	2.5–6.5
EDSS (categories) – n (%)		
<3.0	3 (0.6)	2 (0.8)
3.0–4.5	138 (26.7)	68 (25.9)
5.0–5.5	84 (16.3)	50 (19.0)
6.0–6.5	290 (56.2)	143 (54.4)
>6.5	1 (0.2)	0 (0.0)
Number of Gd-enhancing T1 lesions (categories) – n (%)		
0	269 (53.3)	144 (55.8)
≥1	236 (46.7)	114 (44.2)
Volume of T2 lesions (mm^3)		
Mean (SD)	17864 (11758)	17259 (16759)
Median	12020	12737
Min – Max	23–116664	0–103560
Normalised brain volume (cc)		
Mean (SD)	1421.7 (87.96)	1419.7 (91.27)

Demographic Variable	Siponimod N=516	Placebo N=263
Median	1417.7	1417.8
Min – Max	1171–1723	1228–1679
MS-DMTs		
Any MS DMT	396 (76.3)	203 (77.2)

DMT, disease-modifying therapy; EDSS, expanded disability status scale; MS, multiple sclerosis; SD, standard deviation; SPMS, secondary progressive multiple sclerosis.

Relevant comparator studies

Table 15 presents the baseline characteristics for the relevant comparator study populations alongside that of the EXPAND study.

Patient characteristics show that the EXPAND study population was broadly similar to populations of other large and relevant SPMS trials, but quite different from those of RRMS studies (Table 15 and Table 16). The EXPAND population had a high level of disability (median EDSS score of 6.0 at baseline) with a low level of clinical relapse and MRI inflammatory activity and was representative of a typical SPMS population. Studies with broadly similar population, such as the SPMS study of natalizumab (ASCEND) or the North American SPMS study of IFNB-1b (Table 15), all failed to demonstrate efficacy on disability progression on EDSS. The only positive study in an SPMS population to date, the European study of IFNB-1b, enrolled younger patients (mean age 41.0 years compared with 48.0 years in EXPAND) with shorter disease duration (2.2 years, compared with 3.8 years in EXPAND) and considerably more inflammatory disease activity pre-study and on-study (in the placebo group) than the other SPMS studies (Table 15). The proportion of patients relapse-free in the prior 2 years was 30% in the European SPMS study compared with 64% in EXPAND.

Seventy-eight per cent of the EXPAND study population had received prior treatment for their MS, similar to the portion of patients pre-treated in the natalizumab (ASCEND) study (77%,Table 15).

Compared to patients enrolled in in R(R)MS studies, the EXPAND patients were older by more than 10 years, had longer disease duration and much higher EDSS scores. They also showed substantially less inflammatory disease activity before and during the study (Table 16), supporting that inflammation is not the primary driver of disease progression. In EXPAND 64% of patients were relapse free in the last 2 years and 78% were relapse free in the last 12 months prior to enrolment, and only approximately 22% (of those with an assessment) had Gd-enhancing lesions at baseline. The low on-study relapse rate of 0.16 in the placebo group also supports this. This contrasts with R(R)MS studies where 38–44% of the patients have Gd-enhancing lesions at baseline and where on-study annualized relapse rates in the placebo/IFNB comparator groups ranges from 0.4 to 0.5.

Table 15. Baseline patient characteristics in relevant comparator studies

Characteristic	EXPAND (siponimod) 2018	ASCEND (natalizumab) 2018	North American (IFN β-1b, Betaferon®) 2004	IMPACT (IFN β-1a, Avonex®) 2002	SPECTRIMS (IFNβ-1a, Rebif®) 2001	European (IFN β-1b, Betaferon®) 1998
Age (mean years)	48.0	47.2	46.8	47.6	42.8	41.0
Proportion female (%)	60	62	63	64	63	61
Mean EDSS score	5.4	5.6	5.1	5.2	5.4	5.1
Proportion of patients with EDSS score ≥6.0 (%)	56	63	NR	48	NR	45
Time since onset of MS symptoms (mean years)	16.8	16.5	NR	NR	NR	NR
Duration of MS (mean years)	12.6	12.1	14.7	16.5	13.3	13.1
Duration of SPMS (mean years)	3.8	4.8	4.0	NR	4.0	2.2
Normalised brain volume (mean cm^3) [c]	1423	1423	NR	NR	NR	NR
Proportion of patients with Gd+ lesions of T1-weighted images (%)	21	24	NR	36	NR	NR
Total volume of T2 lesions on T2-weighted images (mean mm^3)	15,321	16,793	NR	NR	NR	NR
Proportion of patients without previous use of a DMT (%)	22	NR	NR	NR	NR	NR
Mean Timed 25-Foot Walk Test (seconds)	16.7	11.2 [a]	NR	14.5	NR	NR
Time since most recent relapse (months)	59	57	NR	44.4	NR	NR

Proportion of patients relapse-free in prior year (%)	78	84	NR	61	NR	NR
Proportion of patients relapse-free in prior 2 years (%)	64	71	55	NR	53	30
Number of relapses per patient in the prior year (mean)	0.2	NR	NR	0.6	NR	NR
Number of relapses per patient in the previous 2 years (mean)	0.7	NR	0.8	NR	0.9	NR

The European Study, with a younger and more active population, was the only trial with a positive result.

DMT, disease modifying therapy; EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; MS, multiple sclerosis; NR, not reported; n/a, not applicable; SPMS, secondary progressive multiple sclerosis.

Table 16: Contrasting SPMS baseline characteristics in EXPAND to typical RRMS and RMS studies

	EXPAND Siponimod N=1651	**FREEDOMS I Fingolimod N=1272**	**CONFIRM Dimethyl Fumarate N=1430**	**CARE-MS II Alemtuzumab N=840 (N=426***)**
Mean age (years)	48.0	37.1	38	34.8***
Mean time since onset (years)	16.8	8.2	n.a.	4.5***
Mean time since MS diagnosis	12.6	5.1	4.9	n.a.
% relapse-free in prior 2 years	63.9%	0%**	0%**	1%**
On-study annualized relapse rate (placebo/ comparator)	0.16‡	0.40‡	0.29‡	0.52‡+
EDSS score (mean)	5.4	2.4	2.6	2.7
% with EDSS ≥6.0	55.6%	0%**	<1%	0%**
% with T1 Gd lesion	21.3%	38%	53.5%	42.4%***
T2 lesion volume (mean)	15.3 cm^3	6.4 cm^3	13.9 cm^3	6.0 cm^{2}*** (median)

**based on inclusion criteria; ***alemtuzumab 12 mg arm; ‡ based on confirmed relapses; +IFN beta-1a.
Source: Kappos et al., 2018;[24] Kappos et al., 2010;[34] Fox et al., 2012;[35] Coles et al., 2012.[36]

Table 17: Characteristics of the studies

Study reference/ID	Objective	Study design	Eligibility criteria	Intervention and Comparator (N enrolled)	Primary outcome measure and follow-up time point	Secondary outcome measures and follow-up time points
EXPAND (NCT01665144)	To investigate the safety and efficacy of siponimod	Randomised (2:1) Double-blind Parallel group Placebo-controlled	Age 18–60 years; history of RRMS; SPMS diagnosis; moderate-to-advanced disability (EDSS score of 3.0–6.5 at screening); evidence for EDSS score progression in the 2 years prior to study; no evidence of relapses in the 3 months before randomisation.	Intervention: siponimod (n=1,105) Comparator: Placebo (n=546)	Time to 3-month CDP (Baseline, every 3 months up to a maximum of approximately 3 years).	The following outcomes were recorded at baseline and followed-up every 3 months for a maximum of approximately 3 years: • Time to 6-month CDP • Confirmed worsening of 25 foot walk test • Reduction in the increase of T2 lesion volume • ARR and Time to the First Relapse • Time to 3-month CDP in pre-defined subgroups The following outcomes were recorded at baseline and followed-up every 6 months for a maximum of approximately 3 years:

						• Time to 6-month CDP • Overall response rate on MSWS-12 The following outcome was recorded at baseline and followed-up every 12 months for a maximum of approximately 3 years: • Inflammatory Disease Activity and Burden of Disease as Measured by MRI
ASCEND (NCT01665144)	To evaluate the efficacy and safety of 300 mg intravenous natalizumab (Tysabri®) administered every four weeks, vs. placebo	Randomised Double-blind Parallel group Placebo-controlled	Natalizumab-naive patients aged 18–58 years with onset of secondary progressive multiple sclerosis 2 or more years before enrolment, an EDSS score of 3.0–6.5 (inclusive), a MSSS of 4 or more, and disability progression not related to clinical relapses during the year before enrolment, as assessed by clinical historical findings	Intervention: Natalizumab (n=1,651) Comparator: Placebo (n=889)	Percentage of participants with confirmed progression of disability in one or more of the EDSS, T25FW, or 9HP (up to 96 weeks).	Proportion of patients with consistent improvement in T25FW; MSWS-12; ABILHAND questionnaire; MSIS-29 physical score; whole brain volume; EDSS; functional system scores; safety; tolerability.

			with a standardised form.			
SPECTRIMS	To assess the efficacy and safety of two doses of interferon β in patients with SPMS.	Randomised Double-blind Parallel-group Placebo-controlled	Eligible patients had clinically definite SPMS, defined as progressive deterioration of disability for at least 6 months with an increase of at least 1 EDSS point over the last 2 years (or 0.5 point between EDSS score of 6.0 and 6.5), with or without superimposed exacerbations, following an initial RR course. At study entry, patients were between 18 and 55 years old, with EDSS scores from 3.0 to 6.5 and pyramidal functional score of at least 2.	Intervention: Interferon β-1a 22 µg (n=209) Interferon β-1a 44 µg (n=204) Comparator: Placebo (n=205)	Time to first confirmed progression in disability.	Proportion of patients progressing, exacerbation count, time to first exacerbation, time between first and second exacerbations, number of moderate and severe exacerbations, number of steroid courses for MS, number of hospitalisations for MS, and IDSS (defined by area under an EDSS time-curve adjusted for baseline).
North American Study	To evaluate the efficacy and safety of interferon β-1b in subjects with SPMS.	Randomised Double-blind Parallel-group Placebo-controlled	Age 18 to 65 years with clinically definite or laboratory supported definite MS of at least 2 years' duration and a history of at least one relapse followed by progressive deterioration sustained for at least 6 months. Patients required an EDSS	Intervention: Interferon β-1b 250 µg/m^2 (n=317) Interferon β-1b 160 µg/m^2 (n=314) (unlicensed dose) Comparator: Placebo (n=308)	EDSS progression. 3 years follow-up.	EDSS score, relapse-related measures, MRI activity, and a standardised neuropsychological function test, safety, tolerability. 3 years follow-up.

			score at screening of 3.0 to 6.5 inclusive, and an increase in EDSS score of at least 1.0 point in the 2 years prior to screening (at least a 0.5-point increase for subjects with a screening EDSS score of 6.5).			
European Study	To evaluate the efficacy and safety of interferon β-1b in subjects with SPMS.	Randomised Double-blind Parallel-group Placebo-controlled	Outpatients eligible for randomisation had a clinically or laboratory supported definite diagnosis of MS. Secondary progression was defined as a period of deterioration, independent of relapses, sustained for at least 6 months, and that followed a period of relapsing-remitting MS. Superimposed relapses were allowed. Patients were aged 18–55 years, with a baseline EDSS score of 3·0–6·5 inclusive and a recorded history of either two relapses or more or 1·0 point or more increase in	Intervention: Interferon β-1b (250 µg) (n=360) Comparator: Placebo (n=358)	3-month CDP. 3 years follow-up.	Time to becoming wheelchair-bound, EDSS, relapse, MRI outcomes, QoL, safety, tolerability. 3 years follow-up.

			EDSS in the previous 2 years.			
IMPACT			Aged 18 to 60 years inclusive, clinically definite SPMS with or without recent relapses, disease progression over the previous year, cranial MRI demonstrating lesions consistent with MS, and an EDSS score of 3.5 to 6.5 inclusive.	Intervention: Interferon β-1a 60 µg (n=217) Comparator: Placebo (n=219)	MSFC	T25W, 9HPT, and cognition (PASAT).

ARR, annualised relapse rate; CDP, confirmed disability progression; EDSS, expanded disability status scale; IDSS, integrated disability status scale; MRI, magnetic resonance imaging; MS, multiple sclerosis; MSFC, multiple sclerosis functional composite; MSIS-29, Multiple Sclerosis Impact Scale 29; MSSS, Multiple Sclerosis Severity Score; MSWS, multiple sclerosis walking scale; PASAT, Paced Auditory Serial Addition Test; QoL, quality of life; SPMS, secondary progressive multiple sclerosis; T25FW, timed 25-foot walk; 9HPT, 9-hole peg test;

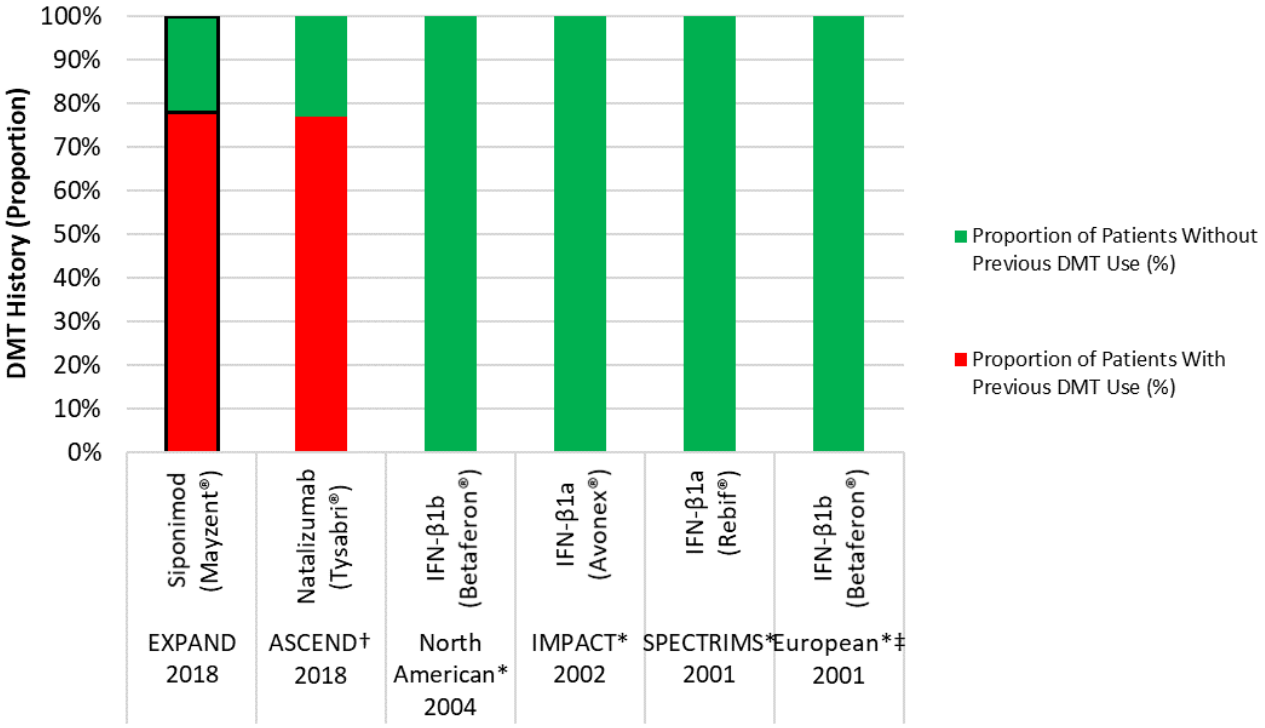
5.2.3 Heterogeneity between EXPAND and relevant comparator studies

As evidenced in Section 5.2.2, substantial heterogeneity exists between the EXPAND ITT population at baseline and those of the relevant comparator studies. Of note, there are two key areas of heterogeneity. Firstly, the proportion of patients with a history of prior DMT treatment was substantially higher in the two most recent studies (EXPAND and ASCEND) than in the older interferon β studies (Figure 10). The interferon studies started enrolment in the 1990s, and actively excluded patients with a history of interferon treatment. As there were no other approved DMTs for relapsing MS or SPMS at this time, these patients are considered to be DMT-naïve. Treatment history is a known confounder in MS outcomes, therefore the differences between the trials in terms of prior DMT treatment should be considered when evaluating the relative effectiveness of siponimod. Furthermore, additional differences in baseline characteristics exist between the interferon β studies and EXPAND: specifically, the population enrolled in the European Study had the lowest proportion of patients relapse-free in the 2 years prior to the study, lower mean age, shorter disease duration and considerably more inflammatory disease activity pre-study and on-study (in the placebo group) (Table 15).

Secondly, the proportion of patients that were relapse-free prior to study entry was greater, although possibly influenced by prior DMT treatment, in the more recent studies (EXPAND and ASCEND) than in the interferon β studies performed between 1994 and 2004 (Figure 11). Relapse history is thought to be an effect modifier in MS, so these baseline differences could have an impact on the overall treatment effect observed in the trials. In addition, the on-study placebo arm relapse rate differed across trials (Figure 12), highlighting that there are differences in the baseline risk of relapse between the different SPMS trial populations that appears to trend with the year of publication. This temporal trend further highlights the time difference between the studies, with EXPAND published in 2018 and the most recent interferon β study published in 2004 (North American Study).

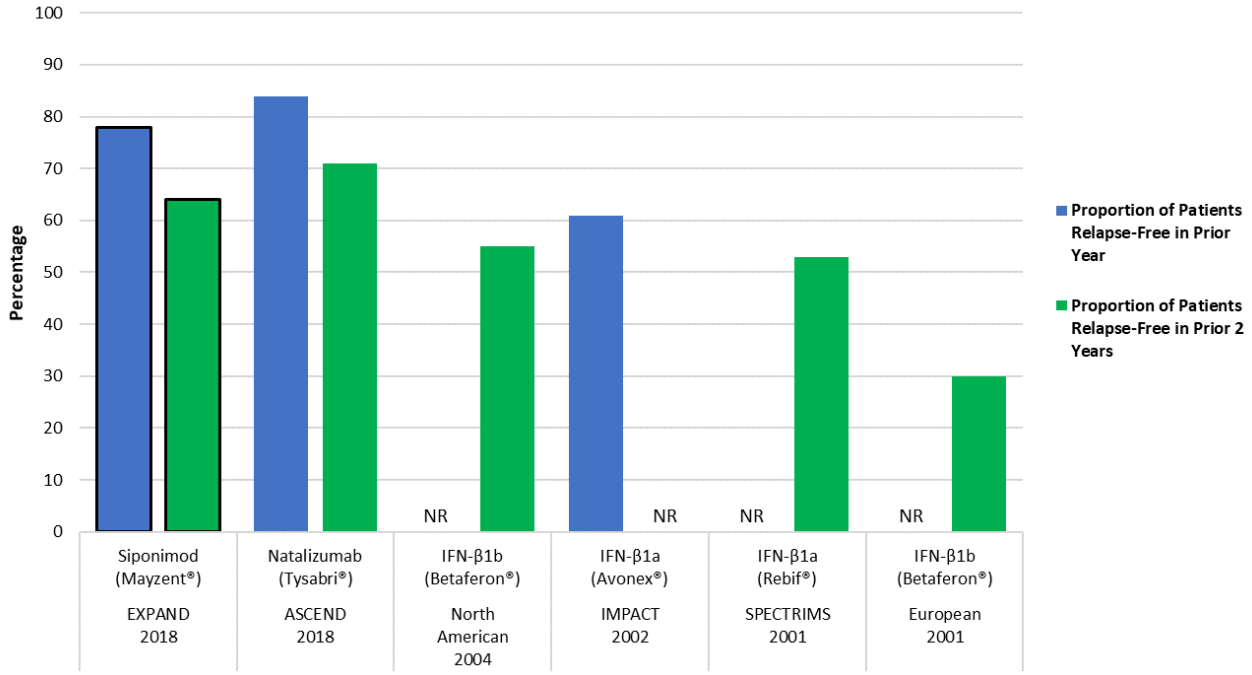
Given the substantial heterogeneity in trial populations and temporal differences between EXPAND and the relevant comparator trials, an unadjusted comparison of published effect estimates (Section 5.3.1) is not appropriate. Furthermore, a feasibility analysis has demonstrated that the level of heterogeneity between EXPAND and the comparator studies precludes a meaningful summary-level indirect treatment comparison or network meta-analysis, and results from these analyses would be biased and unreliable (Section 5.3.3). Therefore a matching-adjusted indirect comparison (MAIC) was undertaken (Section 5.3.6).

Figure 10: Prior DMT history in EXPAND and comparator trials



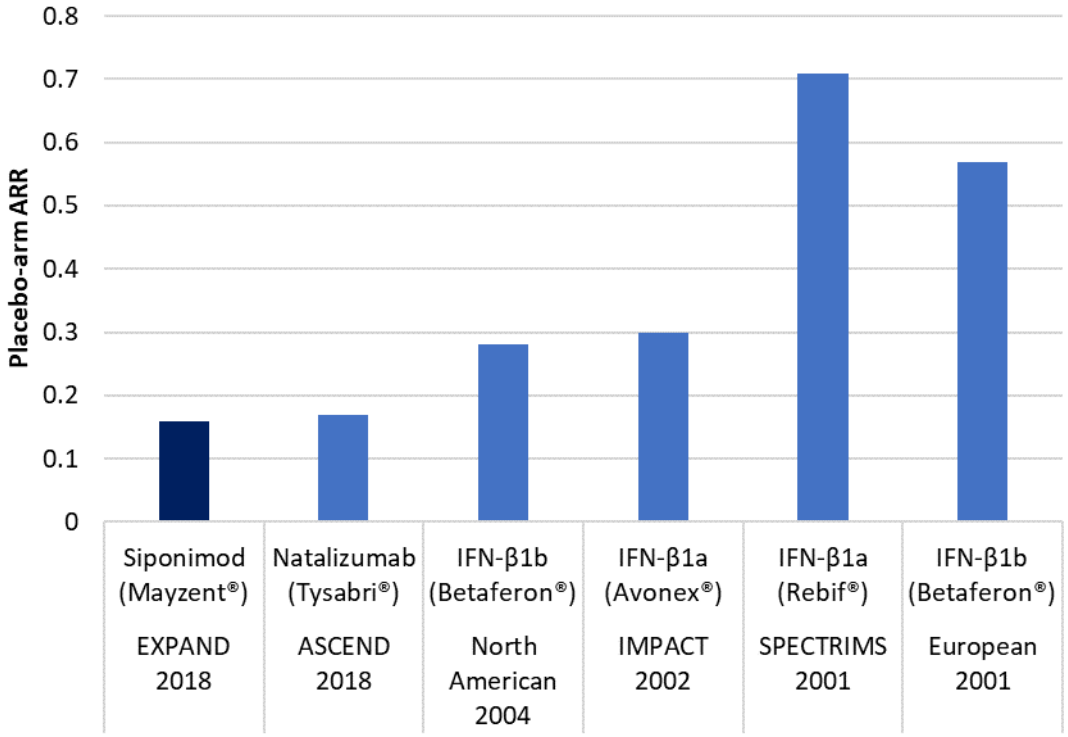
* A value of 100% was assumed because IFN(β)-experienced patients were excluded at screening and no other DMTs were approved before the study began.† Gold R et al. (2017) Impact of Primary Endpoint Definitions and Patient Baseline Characteristics on Study Outcomes in Progressive Multiple Sclerosis. *Poster presented at the 7th Joint Congress of the European Committee for Treatment and Research in Multiple Sclerosis-Americas Committee for Treatment and Research in Multiple Sclerosis; 25-28 October 2017; Paris, France*. *P1239*. Value derived using DigitizeIt: Bormann I (Web Page) DigitizeIt V 2.3.3. Updated 2016. Available online at: http://www.digitizeit.de. Accessed: 2019 July 3. ‡ The EU SPMS study recruited patients prior to the availability of Betaferon as first MS DMT I. F. Dahlke, personal correspondence, November 30th, 2018.
DMT, disease-modifying therapy; IFN, interferon; MS, multiple sclerosis; NR, not reported; SPMS, secondary progressive multiple sclerosis.

Figure 11: Proportion of patients relapse-free in EXPAND and comparator trials



IFN, interferon; NR, not reported.

Figure 12: Placebo arm relapse rate in EXPAND and comparator trials



ARR, annualised relapse rate; IFN, interferon.

It is important to note that the placebo response rates in Figure 12 are intended to serve as a proxy for differences in patient characteristics across trials, for example, if studies included the same patient population and were studied under similar conditions there should be similar placebo response rates. It is common to report placebo response rates without measures of uncertainty given the intent is to visually depict differences across trials, and there is also a lack of reporting of measures of uncertainty among trial publications, which therefore required assumptions to generate measures of uncertainty around event rates. Estimates of uncertainty for the placebo response rates in Figure 12 are provided in Table 18 as well as the related assumptions. Note that rounding may introduce slight differences in results.

Table 18: Annualised Relapse Rate and Estimated Uncertainty by Treatment Arm

Study	Treatment	Sample size (n)	Study Duration	Estimated Person-years	Reported ARR	Estimated Number of Events	Estimated 95% Confidence Interval
EXPAND	PO Placebo qd	546	3 years	1638.00	0.16	262.08	0.143–0.179
	PO Siponimod 2 mg qd	1099	3 years	3297.00	0.07	230.79	0.062–0.079
ASCEND	IV Placebo q4w	448	96 weeks	824.86	0.17	140.23	0.146–0.198
	IV Natalizumab q4w	439	96 weeks	808.29	0.08	64.66	0.063–0.101
IMPACT	IM Placebo qw	219	2 years	438.00	0.30	131.40	0.260–0.346
	IM 60 ug IFN-beta-1a qw	217	2 years	434.00	0.20	86.80	0.166–0.241
North American Study	SC Placebo q2d	308	3 years	924.00	0.28	258.72	0.252–0.311
	SC 250 ug IFN-beta-1b q2d	317	3 years	951.00	0.16	152.16	0.138–0.185
SPECTRIMS	SC Placebo tiw	205	3 years	615.00	0.71	436.65	0.675–0.747
	SC 22 ug IFN-beta-1a tiw	209	3 years	627.00	0.50	313.50	0.462–0.541
	SC 44 ug IFN-beta-1a tiw	204	3 years	612.00	0.50	306.00	0.462–0.541
European Study	SC Placebo q2d	358	3 years	1074.00	0.57	612.18	0.541–0.600
	SC 250 ug IFN-beta-1b q2d	360	3 years	1080.00	0.42	453.60	0.391–0.450

ARR, annualised relapse rate; IFN, interferon; IV, intravenous; PO, oral; qd, daily; q2d, every other day; qw, weekly; SC, subcutaneous; tiw, three times weekly.

5.3 Individual study results (clinical outcomes)

1. Describe the relevant endpoints, including the definition of the endpoint, and method of analysis (Table 19).

The population considered in this submission is patients with active SPMS; in the EXPAND trial, the *post hoc* active SPMS subgroup analyses included patients who experienced relapses in the two years prior to the study and/or who had gadolinium-enhanced T1 lesions at baseline.

Descriptions of the efficacy endpoints across the SPMS studies and considered in the indirect comparison are provided in Table 19, Table 20, Table 21 and Table 22. The outcome definitions were identical to EXPAND across all studies for discontinuation and annualised relapse rate, and the definition of 3-month CDP was similar in SPECTRIMS vs. EXPAND. However, where reported, differences exist between the outcome definitions for the other studies and endpoints.

Notably, the definition of time to 6-month CDP in ASCEND differed substantially, primarily because the time to 6-month reported by ASCEND was a composite outcome of multiple scales: CDP was achieved by a patient if there was sufficient change in any one or any combination of three different scales (including EDSS, the T25FW, and the 9-hole peg test [9-HPT]).

The EUnetHTA Project Plan for this submission specifies a number of additional outcomes; data for the additional outcomes that are available for EXPAND are detailed in Appendix B. However,

data for a number of outcomes cannot be reported as they were not incorporated in the clinical trial design. For example, in short term clinical trials the mortality benefit associated with the treatment is indirect and will not be realised for decades. Furthermore, as a number of the comparator trials were not performed recently, they did not include additional outcomes specified that had not been developed at the time of the trial (e.g. MSFC) or were not widely available to all patients included in the study at that time (e.g. MRI).

Table 19: Methods of data collection and analysis of time to 3-month CDP

Study reference/ID	Endpoint definition	Method of analysis
EXPAND (siponimod)	1.0-point increase in EDSS score: 3.0-5.0 0.5-point increase in EDSS score: 5.5-6.5	Differences were assessed using a Cox proportional hazards model and log-rank test. Kaplan–Meier estimates presented event rates by treatment group over time. Covariates in the Cox model were treatment, country, baseline EDSS score and SPMS group (with or without superimposed relapses, baseline definition). For the Cox proportional hazard model, participants with missing covariates were excluded from the analyses. Risk reduction was derived as (1 − hazard ratio) × 100. Observation of ≥ 374 events for 3-month CDP 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%.
SPECTRIMS (IFNβ-1a, Rebif®)	1.0-point increase in EDSS score: 3.0-5.0 0.5-point increase in EDSS score:5.5-6.5	Time to confirmed progression was analysed using the Cox proportional hazards model.
North American Study (IFN β-1b, Betaferon®)	–	–
European Study (IFN β-1b, Betaferon®)	1.0-point increase in EDSS score: 3.0-5.5 0.5-point increase in EDSS score: 6.0-6.5	The primary method for time to confirmed progression was an analysis of covariance with adjustment for centre and baseline EDSS and stratification adjustment for centre.
ASCEND (natalizumab)	–	–
IMPACT (IFN β-1a, Avonex®)	1.0-point increase in EDSS score: 3.0-5.5 0.5-point increase in EDSS score: 6.0-6.5	NR

CDP, confirmed disease progression; EDSS, Expanded Disability Status Scale; NR, not reported; SPMS, secondary progressive multiple sclerosis.

Table 20: Methods of data collection and analysis of time to 6-month CDP

Study reference/ID	Endpoint definition	Method of analysis
EXPAND (siponimod)	1.0-point increase in EDSS score: 3.0-5.0 0.5-point increase in EDSS score: 5.5-6.5	Differences were assessed using a Cox proportional hazards model and log-rank test. Kaplan–Meier estimates presented event rates by treatment group over time. Covariates in the Cox model were treatment, country, baseline EDSS score and SPMS group (with or without superimposed relapses, baseline definition).

		For the Cox proportional hazard model, participants with missing covariates were excluded from the analyses. Risk reduction was derived as (1 − hazard ratio) × 100. Observation of ≥ 374 events for 3-month CDP 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%.
SPECTRIMS (IFNβ-1a, Rebif®)	–	–
North American Study (IFN β-1b, Betaferon®)	1.0-point increase in EDSS score: 3.0-5.5 0.5-point increase in EDSS score:6.0-6.5	The distributions of time to confirmed progression by treatment group were described by the Kaplan–Meier product–limit approach, and differences between curves were assessed using the log rank test.
European Study (IFN β-1b, Betaferon®)	–	–
ASCEND (natalizumab)	Any one of: • 1.0-point increase in EDSS score: 3.0-5.5 • 0.5-point increase in EDSS score: 6.0-6.5 • Increase of ≥20% in T25FW • Increase ≥20% in 9-HPT	The primary endpoint of the percentage of patients with confirmed progression was analysed by use of logistic regression with baseline EDSS (≤5·5 or ≥6·0), T25FW, and 9HPT of each hand as covariates.
IMPACT (IFN β-1a, Avonex®)	–	–

CDP, confirmed disease progression; EDSS, Expanded Disability Status Scale; SPMS, secondary progressive multiple sclerosis.

Table 21: Methods of data collection and analysis of proportion of patients with 6-month CDP at 96 weeks[a]

Study reference/ID	Endpoint definition	Method of analysis
EXPAND (siponimod)	1.0-point increase in EDSS score: 3.0-5.0 0.5-point increase in EDSS score: 5.5-6.5	Calculated using methods analogous to those used in ASCEND. It was assumed that all patients who were censored at or before 96 weeks in EXPAND experienced a 6-month CDP event. The method used for censoring in ASCEND was not reported, ergo the assumption stated herein may or may not be analogous to ASCEND. As it was not described in ASCEND, the most conservative approach was used.
SPECTRIMS (IFNβ-1a, Rebif®)	–	–
North American Study (IFN β-1b, Betaferon®)	–	–
European Study (IFN β-1b, Betaferon®)	–	–

ASCEND (natalizumab)	1.0-point increase in EDSS score: 3.0-5.5 0.5-point increase in EDSS score: 6.0-6.5	The percentage of patients with confirmed progression was analysed by use of logistic regression.
IMPACT (IFN β-1a, Avonex®)	–	–

[a]Because ASCEND reported time to 6-month CDP only as a composite of multiple scales, which is not comparable with the EDSS-specific outcome in other trials such as EXPAND, indirect comparisons for this outcome are instead based on the proportion of patients who experienced 6-month CDP over the 96 week long as measured by the EDSS scale alone.
EDSS, Expanded Disability Status Scale.

Table 22: Methods of data collection and analysis of ARR

Study reference/ID	Endpoint definition	Method of analysis
EXPAND (siponimod)	Number of total relapses per patient-years	Estimated by negative binomial regression.
SPECTRIMS (IFNβ-1a, Rebif®)		NR
North American Study (IFN β-1b, Betaferon®)		Subject specific annual relapse rates were computed by dividing the number of confirmed relapses by the time on study for each subject. Treatment group differences in annual relapse rate were assessed using an ANOVA model.
European Study (IFN β-1b, Betaferon®)		NR
ASCEND (natalizumab)		Analysis of covariance and mixed-effects models for repeated measures were used to analyse continuous outcomes, with baseline measurement and baseline EDSS (≤5·5 or ≥6·0) as covariates.
IMPACT (IFN β-1a, Avonex®)		NR

ANOVA, analysis of variance; EDSS, Expanded Disability Status Scale; NR, not reported.

2. Provide a summary of the study results for each relevant comparison and outcome.

In MS broadly, the key clinical outcomes are 6-month CDP and ARR and these outcomes are therefore the most important for indirect comparisons; in the SPMS phenotype specifically, CDP is of central relevance, unlike ARR, although the latter is not irrelevant. The CHMP has highlighted the importance of these outcomes in MS, stating that the primary efficacy parameter in confirmatory trials should be clinically measured prevention or delay of disability progression, although relapsed based endpoints may also be acceptable in individuals with superimposed relapses.[119] Additionally, economic models in MS (both RRMS models which capture progression through SPMS, and PPMS models) are based around CDP and ARR; Novartis consider that, in line with previous European MS appraisals, this appraisal should focus on relative effectiveness for these two outcomes, with CDP the central focus as the only driver of modelled disease progression. This submission therefore presents the published effect estimates of 3-month and 6-month CDP, and ARR for each of the available comparator studies (Table 32, Table 33 and Table 34, respectively). Furthermore, these were the only outcomes where comparisons could consistently be made between studies.

The following subsections present relevant clinical data for the relative effectiveness of siponimod in the active SPMS population. This includes efficacy data for siponimod in the active SPMS sub-population, in line with the siponimod marketing authorisation, and published effect estimates for the outcomes of 3-month and 6-month CDP, and ARR, for both EXPAND and relevant comparator trials. Furthermore, a feasibility assessment for indirect comparisons in both the active SPMS sub-population and the EXPAND ITT population is presented, followed by results from a matching adjusted indirect comparison (MAIC) in the ITT population. Notably, the relevant comparator studies do not present sufficient data for a robust analysis of the relative effectiveness of siponimod in the active SPMS subgroup; specifically, a lack of baseline data for the active SPMS sub-population in the European Study precludes a MAIC. The published effect estimates and MAIC therefore consider the EXPAND ITT population.

5.3.1 EXPAND: Active SPMS Subgroup

The active SPMS subgroup is defined by relapses and/or MRI activity in patients with SPMS.[2] In the EXPAND trial, the *post hoc* active SPMS subgroup analyses included patients who experienced relapses in the two years prior to the study and/or who had gadolinium-enhanced T1 lesions at baseline. This choice of subgroup data cut reflected the available baseline characteristics from the EXPAND trial.

Data for the EXPAND ITT population are detailed in Appendix B (Section 6.2.2).

Time to 3-month CDP

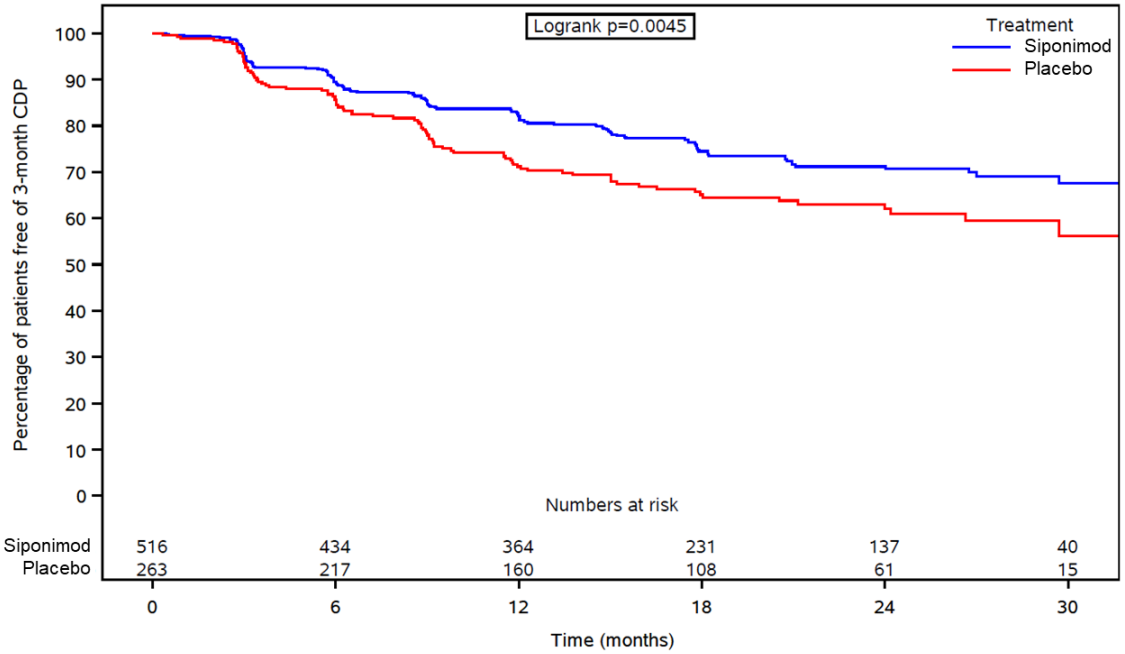
Siponimod treatment significantly delayed the time to 3-month CDP in the active SPMS subgroup compared with placebo (Table 23, hazard ratio [HR] 0.69, p=0.0094). Kaplan–Meier curves (Figure 13) represent the same results.

Table 23: Active SPMS subgroup: Time to 3-month CDP based on EDSS – Cox proportional hazards model

Treatment	n/N’	(%)	Comparison: Siponimod vs Placebo		
			Hazard Ratio (95% CI)	Risk Reduction	p-value
Siponimod (N=516)	128/515	24.9	0.69 (0.53, 0.91)	30.7%	0.0094
Placebo (N=263)	91/263	34.6			

N=number of subjects in treatment arm and subgroup, n=number of patients with event, N’=number of patients included in the analysis, (i.e. with non-missing covariates).
The Cox regression model includes the predictors treatment and baseline EDSS.
CDP, confirmed disability progression; CI, confidence interval; EDSS, expanded disability status scale; SPMS, secondary progressive multiple sclerosis.
Source: Novartis Data on File

Figure 13: Active SPMS subgroup: Percentage free of 3-month CDP based on EDSS – Kaplan–Meier curves



Last known date to be at risk is defined as the last EDSS assessment date in core part.
CDP, confirmed disability progression; EDSS, expanded disability status scale; SPMS, secondary progressive multiple sclerosis.
Source: Novartis Data on File

Time to 6-month CDP

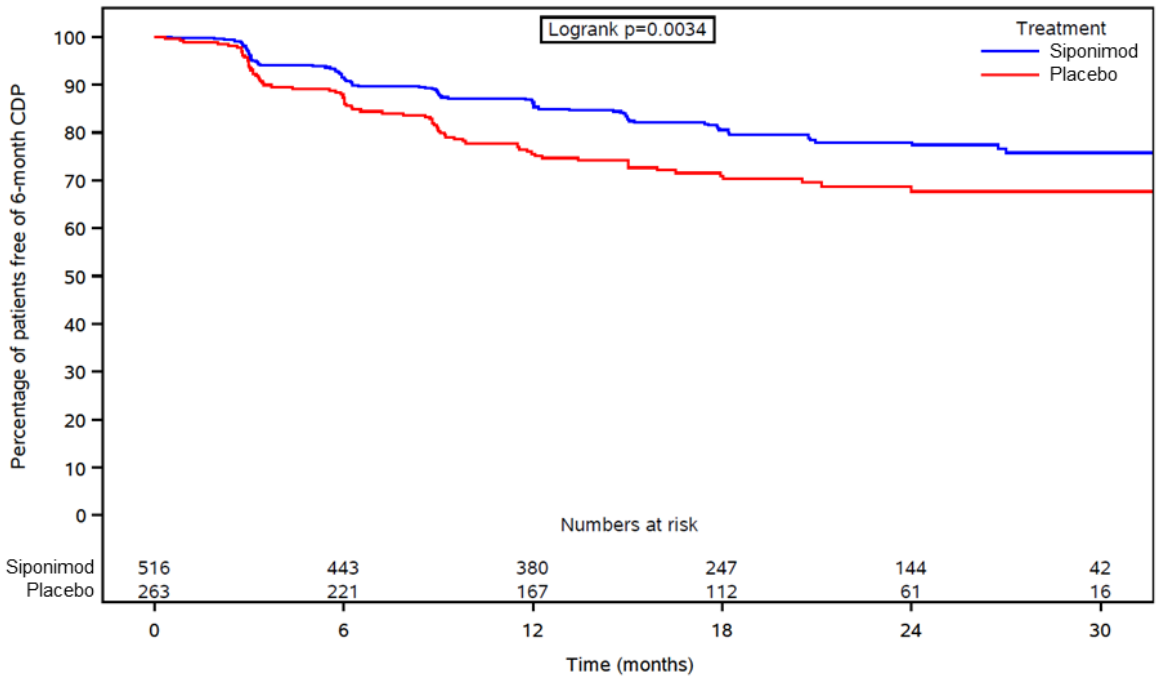
Siponimod treatment also significantly delayed the time to 6-month CDP in the active SPMS subgroup compared with placebo (Table 24, HR 0.63, p=0.0040). Kaplan–Meier curves (Figure 14) represent the same results.

Table 24: Active SPMS subgroup: Time to 6-month CDP based on EDSS – Cox proportional hazards model

Treatment	n/N'	(%)	Comparison: Siponimod vs Placebo		
			Hazard Ratio (95% CI)	Risk reduction	p-value
Siponimod (N=516)	98/515	19.0	0.63 (0.47, 0.86)	36.5%	0.0040
Placebo (N=263)	74/263	28.1			

N=number of subjects in treatment arm and subgroup, n=number of patients with event, N'=number of patients included in the analysis, (i.e. with non-missing covariates).
The Cox regression model includes the predictors treatment and baseline EDSS.
CDP, confirmed disability progression; CI, confidence interval; EDSS, expanded disability status scale; SPMS, secondary progressive multiple sclerosis.
Source: Novartis Data on File

Figure 14: Active SPMS subgroup: Percentage free of 6-month CDP based on EDSS – Kaplan–Meier curves



Last known date to be at risk is defined as the last EDSS assessment date in core part.
CDP, confirmed disability progression; EDSS, expanded disability status scale; SPMS, secondary progressive multiple sclerosis.
Source: Novartis Data on File

ARR

Negative binomial regression analysis of ARR for patients in the active SPMS subgroup demonstrated an ARR ratio of 0.539 (p=0.0004) for siponimod compared with placebo (Table 25).

Table 25: Active SPMS subgroup: Negative binomial regression of ARR for confirmed relapses

Treatment	n/N'	Time (days)	Raw ARR	Adjusted ARR (95% CI)	Comparison: Siponimod vs Placebo		
					ARR Ratio (95% CI)	% Difference	p-value
Siponimod (N=516)	99/516	330385	0.109	0.109 (0.087, 0.136)	0.539 (0.383, 0.757)	−46.1	0.0004
Placebo (N=263)	91/263	172056	0.193	0.202 (0.157, 0.260)			

N=number of subjects in treatment arm and subgroup, n=overall number of relapses in the analysis period for all subjects, N'=number of patients included in the analysis, time = total number of days in the analysis period for all subjects.
The negative binomial includes the predictors treatment and baseline EDSS.
ARR, annualised relapse rate; CI, confidence interval; EDSS, expanded disability status scale; SPMS, secondary progressive multiple sclerosis.
Source: Novartis Data on File

Time to 3-month confirmed worsening in T25FW

The results for time to 3-month confirmed worsening in T25FW of at least 20% from the baseline in the active SPMS population are summarised in Table 26. There was an observed risk reduction of 14.3% in favour of the siponimod group (p=0.1879).

Table 26: Active SPMS subgroup: Time to 3-month confirmed worsening in T25FW of at least 20% from baseline – Cox proportional hazards model

Treatment	n/N'	%	Comparison: Siponimod vs Placebo*		
			Risk reduction	Hazard ratio (95% CI)	p-value
Siponimod (N=516)	215/515	41.7	14.3%	0.86 (0.68; 1.08)	0.1879
Placebo (N=263)	120/263	45.6			

n/N': n= number of subjects with events/N'=number of subjects included in the analysis (i.e. with non-missing covariates). *Using a Cox proportional hazards model with treatment, country/region, baseline EDSS, baseline T25FW, and SPMS group (with/without superimposed relapses, baseline definition) as covariates. Risk reduction is derived as (1-hazard ratio) * 100.
CI, confidence interval; EDSS, expanded disability status scale; SPMS, secondary progressive multiple sclerosis; T25FW, timed 25-foot walk test.
Source: Novartis Data on File

Multiple Sclerosis Walking Scale (MSWS-12)

Patient walking ability was self-assessed by patients using the MSWS-12. Change from baseline in MSWS-12 converted score for the active SPMS subgroup is provided in Table 27. Total transformed scores on the MSWS-12 can range from 0-100 with higher scores reflecting greater impairment. The difference in adjusted means in the siponimod group showed smaller increases from baseline compared with placebo; however, the differences between groups were not statistically significant (the difference at Month 12 was nominally significant). When averaged over all visits, this difference was signficiant (-2.60 [-5.20, -0.02]; p=0.0494). The apparently smaller between-group differences at Month 24 compared with Month 12 should be interpreted in light of the smaller sample size (event driven design) and higher variability at Month 24.

Table 27: Active SPMS subgroup: Change from baseline in MSWS-12 converted score, by time point – repeated measures model

Time-point	Adjusted means (SE)		Comparison of adjusted means Siponimod vs Placebo			
	Siponimod (N'=482)	Placebo (N'=250)	Difference	SE	95% CI	p-value
Month 12	1.67 (1.033)	4.17 (1.323)	−2.50	1.486	−5.42; 0.42	0.0926
Month 24	4.48 (1.255)	6.23 (1.632)	−1.76	1.898	−5.49; 1.97	0.3552
Difference in average over all visits	–	–	–2.60	–	-5.20; -0.01	0.0494

N'=number of subjects included in the analysis (i.e. with a baseline and at least one post-baseline MSWS-12 converted score). Obtained from fitting a repeated measures model (assumes normally distributed data) with visit as categorical factor. Model was adjusted for treatment, region/country, baseline MSWS-12 converted score. Adjusted means refers to the change from baseline in MSWS-12.
CI, confidence interval; MSWS-12, multiple sclerosis walking scale; SE, standard error
Source: Novartis Data on File

MRI Activity: T2 Lesion Volume

Results for change from baseline in T2 volume at Month 12 and Month 24 for the active SPMS population are summarised in Table 28. The adjusted mean refers to the change from baseline in T2 lesion volume at each time point. In the active SPMS population, the change from baseline in T2 lesion volume at both Month 12 and Month 24 was statistically significant, nominal p-values of <0.0001 were observed for between-treatment comparisons at both time points as well as for the average over Month 12 and Month 24.

Table 28: Active SPMS Subgroup: Change from baseline in T2 lesion volume (mm^3) by time point – repeated measures model

Time-point	Adjusted means (SE)		Comparison of adjusted means Siponimod vs Placebo			
	Siponimod (N'=473)	Placebo (N'=244)	Difference	SE	95% CI	p-value
Month 12	93.485 (129.700)	1117.15 (160.760)	-1023.7	169.094	-1355.7; -691.66	<0.0001
Month 24	13.286 (139.710)	1316.32 (175.924)	-1303.0	189.745	-1675.8; -930.31	<0.0001
Average over Months 12 and 24	56.570 (132.490)	1218.10 (165.972)	-1161.5	175.548	-1506.4; -816.67	<0.0001

N'=number of subjects included in the analysis (i.e. with at least MRI scan post-baseline and non-missing covariates). Obtained from fitting a repeated measures model (model assumes normally distributed data) with visit as a categorical factor. Model was adjusted for treatment, country/region, baseline T2 lesion volume, number of T1 Gd-enhancing lesions at baseline, SPMS group (with/without superimposed relapses, baseline definition). Adjusted mean refers to the change from baseline in T2 lesion volume.
CI, confidence interval; MRI, magnetic resonance imaging; SE, standard error; SPMS, secondary progressive multiple sclerosis.
Source: Novartis Data on File

MRI Activity: New or Enlarging T2 Lesions

The results for number of new or enlarging T2 lesions for the active SPMS population by time point are summarised in Table 29. The rate ratio was the ratio of adjusted mean number of new/enlarging T2 lesions for siponimod versus placebo and rate reduction was derived from rate ratio. In the active SPMS population, the mean number of new/enlarging T2 lesions compared with the previous scan favored siponimod over placebo at Month 12 (74.1% rate reduction) and Month 24 (85.0%), and was statistically significant (p<0.0001), showing fewer patients with new/enlarging T2 lesions relative to placebo.

Table 29: Active SPMS subgroup: Number of new or enlarging T2 lesions – repeated measures negative binomial regression

Time-point	Adjusted means (95% CI)		Between treatment comparison[a] Siponimod vs Placebo			
	Siponimod (N'=474)	Placebo (N'=244)	Rate reduction	Rate ratio	95% CI	p-value
Number of new or enlarging T2 lesions (relative to previous scheduled scan)						
Month 12	1.687 (1.399, 2.034)	6.508 (5.344, 7.924)	74.1%	0.259	0.202; 0.332	<0.0001

Month 24	0.780 (0.550, 1.107)	5.189 (4.138, 6.506)	85.0%	0.150	0.100; 0.226	<0.0001
Average over all visits	1.147 (0.911, 1.445)	5.811 (4.811, 7.018)	80.3%	0.197	0.149; 0.261	<0.0001

N' = number of subjects included in the analysis (i.e with at least one MRI scan post-baseline and non-missing values for the co-variates included in the model). Adjusted mean (or rate) refers to the adjusted number of lesions per subject per scan. Rate reduction is derived as (1- rate ratio) * 100.
[a]Obtained from fitting negative binomial regression model adjusted for treatment, age, baseline number of T1 Gd-enhancing lesions (offset = number of scheduled MRI scans).
CI, confidence interval.
Source: Novartis Data on File

MRI Activity: T1 Gd-enhancing lesions

The results for number of T1 Gd-enhancing lesions for the active SPMS population by time point are summarised in Table 30. Statistically significant differences, favouring siponimod, were seen for number of T1 Gd-enhancing lesions at Month 12 and Month 24 (p<0.0001).

Table 30: Active SPMS subgroup: T1 Gd-enhancing lesions per patient per scan, by time point – repeated measures negative binomial regression

Time-point	Adjusted mean (95% CI)*		Between-treatment comparison* Siponimod vs Placebo			
	Siponimod (N'=474)	Placebo (N'=244)	Rate reduction	Rate ratio	95% CI	p-value
Number of T1 Gd-enhancing lesions (in this scan)**						
Month 12	0.165 (0.112, 0.243)	1.198 (0.877, 1.635)	86.3	0.137	0.083; 0.226	<0.0001
Month 24	0.127 (0.061, 0.266)	0.614 (0.432, 0.873)	79.2	0.208	0.091; 0.471	<0.0002
Cumulative number of T1 Gd-enhancing lesions (all post-baseline scans)						
Up to and including Month 24	0.169 (0.130, 0.219)	1.088 (0.807, 1.467)	84.5	0.155	0.104; 0.231	<0.0001
Up to and including last assessment	0.158 (0.122, 0.204)	1.069 (0.792, 1.442)	85.3	0.147	0.099; 0.220	<0.0001

N'=number of patients included in the analysis (i.e. with at least one MRI scan post baseline and non-missing values for the covariates included in the model). Adjusted mean (or rate) refers to the adjusted number of lesions per subject per scan. Rate reduction is derived as (1- rate ratio) * 100. *Obtained from fitting negative binomial regression model adjusted for treatment, age, baseline number of T1 Gd-enhancing lesions (offset=number of scheduled MRI scans). **A repeated measures regression model was implemented with visit as a categorical factor.
CI, confidence interval; MRI, magnetic resonance imaging.
Source: Novartis Data on File

MRI Activity: Percentage Brain Volume Change (PBVC)

The analysis of PBVC relative to baseline for the active SPMS population is provided by time-point in Table 31. The PBVC relative to baseline was −0.385% for siponimod and −0.559% for placebo at Month 12 (p=0.0020). The decrease in PBVC was also numerically lower in patients treated with siponimod at Month 24 (p=0.1657).

Table 31: Active SPMS subgroup: PBVC relative to baseline, by time point – repeated measures model

Time-point	Adjusted mean (SE)		Comparison of adjusted means Siponimod vs Placebo			
	Siponimod (N'=431)	Placebo (N'=222)	Difference	SE	95% CI	p-value
Month 12	-0.385 (0.044)	-0.559 (0.055)	0.173	0.0560	0.064; 0.283	0.0020
Month 24	-0.861 (0.055)	-0.969 (0.070)	0.108	0.0779	-0.045; 0.261	0.1657
Average over Months 12 and 24	-0.783 (0.056)	-0.911 (0.072)	0.128	0.0810	-0.031; 0.287	0.1153

N'=number of subjects included in the analysis (i.e. with at least MRI scan post-baseline and non-missing covariates).
Obtained from fitting a repeated measures model (for normally distributed data) with visit as a categorical factor. Model was adjusted for treatment, country/region, age, normalised brain volume at baseline, number of T1 Gd-enhancing lesions at baseline, T2 volume at baseline, and SPMS group (with/without superimposed relapses, baseline definition). Adjusted mean refers to PBVC relative to baseline. All post-baseline visits up to and including Month 36 have been included.
CI, confidence interval; PBVC, percentage brain volume change; SE, standard error; SPMS, secondary progressive multiple sclerosis.
Source: Novartis Data on File

5.3.2 Published Effect Estimates

The outcomes additionally specified in the Project Plan were not consistently reported across the comparator studies, although some data are available for the following outcomes: brain volume (ASCEND, EXPAND), proportion of patients with and without T1 Gd+ lesions (European Study, IMPACT, EXPAND), proportion of patients with and without T2 lesions (SPECTRIMS, IMPACT, EXPAND), number of T1 Gd+ lesions (ASCEND, European Study, IMPACT, EXPAND) and number of T2 lesions (ASCEND, European Study, IMPACT, EXPAND). It is important to note that in the older studies, the MRI outcomes are only available for a subset of patients and not for the ITT population. Data for the additional outcomes that are available for the EXPAND ITT population are detailed in Appendix B (Section 6.2.2).

As the comparator studies do not present sufficient data to facilitate comparison in the active SPMS subgroup, the published effect estimates presented below refer to the EXPAND ITT population, as these inform the MAIC.

Table 32: Results summary for time to 3-month CDP

Study ID(s)	Intervention	Regimen	Published Effect Estimates (95% CI)	
			Type	Intervention vs. Placebo
EXPAND	Siponimod	2 mg qd	HR	0.79 (0.65 to 0.95)
SPECTRIMS	Rebif® (SC IFNβ-1a)	22 µg tiw	HR	0.88 (0.69 to 1.12) [a]
SPECTRIMS	Rebif® (SC IFNβ-1a)	44 µg tiw	HR	0.83 (0.65 to 1.07)
European Study	Betaferon® (SC IFNβ-1b)	250 µg q2d	HR	0.74 (0.60 to 0.91) [a]

Study ID(s)	Intervention	Regimen	Published Effect Estimates (95% CI)	
			Type	Intervention vs. Placebo
IMPACT	Avonex® (IM IFNβ-1a)	60 µg qw	HR	0.977 (0.68 to 1.41)

[a]The HR and/or CI were not reported in the publication. Missing values were estimated using either the reported HR and p-value, the reported Kaplan-Meier curve through curve-fitting, or through analysis of IPD, as appropriate.

CDP, confirmed disability progression; CI, confidence interval; HR, hazard ratio; IFNβ = interferon beta; IM, intramuscular; IV, intravenous; mg, milligram; qd, once daily; q2d, once every other day; qw, once weekly; SC, subcutaneous; tiw, three times weekly; µg, microgram.

Table 33: Results summary for time to 6-month CDP

Study ID(s)	Intervention	Regimen	Published Effect Estimates (95% CI)	
			Type	Intervention vs. Placebo
Time to 6-month CDP				
EXPAND	Siponimod	2 mg qd	HR	0.74 (0.60 to 0.92)
North American Study	Betaferon® (SC IFNβ-1b)	250 µg q2d	HR	0.92 (0.71 to 1.20) [a]
Proportion with 6-month CDP (96 weeks)				
EXPAND	Siponimod	2 mg qd	OR	0.77 (0.61 to 0.97) [a,b]
ASCEND	Tysabri® (IV Natalizumab)	300 mg q4w	OR	1.06 (0.74 to 1.53) [b]

[a]The HR and/or CI were not reported in the publication. Missing values were estimated using either the reported HR and p-value, the reported Kaplan-Meier curve through curve-fitting, or through analysis of IPD, as appropriate. [b]The proportion of patients who experienced 6-month CDP by 96 weeks based on an increase in EDSS alone. For ASCEND, this was reported in the Supplementary Appendix. For EXPAND, the proportion of patients with this outcome was calculated using the IPD, based on a conservative assumption that all patients censored at or before 96 weeks had experienced a 6-month CDP event.

CDP, confirmed disability progression; CI, confidence interval; HR, hazard ratio; IFNβ = interferon beta; IM, intramuscular; IV, intravenous; mg, milligram; OR, odds ratio; qd, once daily; q2d, once every other day; qw, once weekly; SC, subcutaneous; tiw, three times weekly; µg, microgram.

Table 34: Results summary for annualised relapse rate

Study ID(s)	Intervention	Regimen	Published Effect Estimates (95% CI)[a]	
			Type	Intervention vs. Placebo[a]
EXPAND	Siponimod	2 mg qd	RR	0.45 (0.34 to 0.59)
North American Study European Study[b]	Betaferon® (SC IFNβ-1b)	250 µg q2d	RR	0.65 (0.48 to 0.88)
SPECTRIMS	Rebif® (SC IFNβ-1a)	22 µg tiw	RR	0.69 (0.56 to 0.84)
SPECTRIMS	Rebif® (SC IFNβ-1a)	44 µg tiw	RR	0.69 (0.56 to 0.85)
ASCEND	Tysabri® (IV Natalizumab)	300 mg q4w	RR	0.453 (0.323 to 0.634)

Study ID(s)	Intervention	Regimen	Published Effect Estimates (95% CI)[a]	
			Type	Intervention vs. Placebo[a]
IMPACT	Avonex® (IM IFNβ-1a)	60 µg qw	RR	0.67 (0.49 to 0.90)[c]

[a]Extracted or derived from the EXPAND or comparator publication(s).
[b]Error has been estimated using the CI from the North American Study 160 µg/m2 treatment arm which has a similar effect size and sample size. The Handling Continuous Outcomes in Quantitative Synthesis (Fu et al., 2013) guide recommends that studies only missing error should not be excluded as this can lead to a biased combined estimate.
[c]Error was calculated from the reported RR and p-value.
CI, confidence interval; IFNβ = interferon beta; IM, intramuscular; IV, intravenous; mg, milligram; qd, once daily; q2d, once every other day; q4w, once every 4 days; qw, once weekly; RR, relative risk; SC, subcutaneous; tiw, three times weekly; µg, microgram.

5.3.3 Feasibility assessment for an indirect comparison: ITT populations

A feasibility assessment was undertaken to determine whether indirect treatment comparisons (ITCs) could be conducted in the absence of direct head-to-head trials comparing siponimod to other DMTs for the treatment of adult patients with SPMS, and to identify suitably comparable studies relative to EXPAND. The feasibility of conducting ITCs is dependent on the outcomes of interest, the availability of summary-level data and/or IPD, similarity of trial designs, and heterogeneity between the studies. Part of the objective was to summarise a qualitative assessment of similarity and heterogeneity based on the study design, inclusion/exclusion criteria, patient characteristics, and study-specific outcome definitions of EXPAND compared with comparator trials. Following the guidance of the NICE DSU Technical Support Document 18, the feasibility assessment focussed on determining if effect modifiers are present and if there is an imbalance between the trial populations.[120]

Treatment effect modifiers

In order to identify potential treatment effect modifiers, a structured review in SPMS was undertaken and Novartis consulted with 9 clinical experts from Canada and Europe. This was further supported by data-driven analyses of the EXPAND IPD to assess relationships between covariates and outcomes. Clinical experts experienced in the treatment of MS and in attendance at two Novartis-organised advisory boards (one in the UK, one in Canada) ranked the treatment effect modifiers separately for each outcome in question. The final ranked lists were created from the average of all participating physicians and are presented in Table 35 and Table 36.

Table 35: Treatment effect modifiers identified for CDP

Rank	Adjustment Factor (Treatment Effect Modifier)
1	Age
2	EDSS score at screening
3	Duration of MS since diagnosis
4	Treatment experience (IFN or DMT history)
5	Normalised brain volume
6	Gadolinium-enhancing lesions on T1-weighted images
7	Duration of SPMS
8	Total volume of T2 lesions on T2-weighted images
9	Number of relapses in prior 2 years (or any other relapse variable)

10	Sex

Abbreviations: CDP: confirmed disability progression; DMT: disease-modifying therapy; EDSS: expanded disability status scale; IFN: interferon; MS: multiple sclerosis; SPMS: secondary progressive multiple sclerosis.

Table 36: Treatment effect modifiers identified for ARR

Rank	Adjustment Factor (Treatment Effect Modifier)
1	Time since onset of most recent relapse
2	Number of relapses per patient in one year prior to study
3	Number of relapses per patient in two years prior to study
4	Gadolinium-enhancing lesions on T1-weighted images
5	Total volume of lesions on T2-weighted images

Abbreviations: ARR: annualised relapse rate.

The identified treatment effect modifiers for CDP were additionally tested by analysis of baseline characteristics in EXPAND. Analyses of the EXPAND IPD included univariate regressions of the available covariates to assess the potential treatment effects on the outcomes in EXPAND, assessment of heterogeneity in baseline characteristics across trials, and univariate ITCs to assess the potential impact of effect modifiers in combination with the degree of heterogeneity across trials in each ITC. The results of these tests, along with univariate exploration of early MAIC results, confirmed that the clinician-ranked lists capture the identifiable effect modifiers within the EXPAND trial data.

Qualitative assessment of imbalance in trial design and baseline patient characteristics

Pairwise comparisons were made to test the following aspects of feasibility: similarity of each comparator trial's study design compared with EXPAND; inclusion and exclusion criteria; outcome definitions; baseline patient characteristics; and consistency of placebo-arm outcomes. For studies where feasibility assessments concluded that an indirect comparison was possible, a summary of each of these is presented in Table 37, Table 38, Table 39 and Table 40, respectively. Further information on each comparison is provided in Appendix C.

For quantitative values, a threshold of +/-10% was chosen to communicate whether a characteristic was relatively similar (<10% difference in either direction) or dissimilar (>10% difference in either direction) to EXPAND. This was a subjective judgement and a difference of greater than 10% does not necessarily indicate that the characteristic in question is a driver for bias; however, relatively large differences in baseline characteristics may be considered as a potential source of heterogeneity and bias, which could present a weakness of unadjusted indirect comparisons such as Bucher ITCs or NMAs. In the MAIC, characteristics were adjusted irrespective of whether a 10% threshold was observed, as this was for qualitative visualisation purposes and did not dictate or influence the quantitative analyses in the indirect treatment comparisons.

Differences within the threshold of 10% were considered to be similar and marked with a check ("✓"). Differences that exceeded 10% were still considered feasibly comparable (marked with "!") if the criteria in EXPAND was broad enough that the difference could be potentially mitigated by matching or adjusting using IPD. Differences that exceeded 10% and were impossible to accommodate through matching or adjusting were marked with "X" to indicate a potential source of heterogeneity that must be considered in the interpretation of any results, whether summary-level ITC or MAIC.

Table 37: Pairwise comparisons of inclusion/exclusion criteria (vs. EXPAND)

Criteria	**ASCEND** (natalizumab)	**North American Study** (IFN β-1b, Betaferon®)	**IMPACT** (IFN β-1a, Avonex®)	**SPECTRIMS** (IFN β-1a, Rebif®)	**European Study** (IFN β-1b, Betaferon®)
MS Population	✓	✓	✓	✓	✓
Baseline EDSS range	✓	✓	!	✓	✓
Age range	!	X	✓	!	!
Prior IFN therapy	✓	!	!	!	!
Number of relapses in X months prior	✓	X	n/a	X	X
Documented progression within X months prior	!	✓	!	✓	✓
History of RRMS	n/a	✓	n/a	✓	✓
Duration of MS	n/a	!	n/a	n/a	n/a
Duration of SPMS	!	n/a	n/a	n/a	n/a
MS severity score	!	n/a	n/a	n/a	n/a
T25FW test	!	n/a	n/a	n/a	n/a

✓ = Criterion is identical; ! = Differences exist between trials and the EXPAND patient population is broader (i.e. matching may be possible); X = Differences exist between the trials and the EXPAND patient population is not broader (i.e. matching is not possible); n/a = not applicable as not reported in the comparator trial.

Abbreviations: EDSS: expanded disability status scale; IFN: interferon; MS: multiple sclerosis; RRMS: relapsing-remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis; T25FW: timed 25-foot walk.

Table 38: Pairwise comparisons of outcome definitions (vs. EXPAND)

Criteria	**ASCEND** (natalizumab)	**North American Study** (IFN β-1b, Betaferon®)	**IMPACT** (IFN β-1a, Avonex®)	**SPECTRIMS** (IFN β-1a, Rebif®)	**European Study** (IFN β-1b, Betaferon®)
ARR	✓	✓	✓	✓	✓
Time to 3-month CDP	n/a	n/a	!	✓	!
Time to 6-month CDP	!*	!	n/a	n/a	n/a
Discontinuation	✓	✓	✓	✓	✓

✓ = Outcome is reported in the comparator trial with the same or very similar definition to EXPAND; ! = Outcome is reported in the comparator trial, but the definition differs from EXPAND; n/a = not applicable as not reported in the comparator trial.

*Because ASCEND reported time to 6-month CDP only as a composite of multiple scales, which is not comparable with the EDSS-specific outcome in other trials such as EXPAND, indirect comparisons for this outcome are instead based on the proportion of patients who experienced 6-month CDP (96 weeks) as measured by the EDSS scale alone.

Abbreviations: ARR: annualised relapse rate; CDP: confirmed disability progression; EDSS: expanded disability status scale; IFN: interferon.

Table 39: Pairwise comparisons of baseline patient characteristics (vs. EXPAND)

Characteristic	ASCEND (natalizumab)	North American Study (IFN β-1b, Betaferon®)	IMPACT (IFN β-1a, Avonex®)	SPECTRIMS (IFN β-1a, Rebif®)	European Study (IFN β-1b, Betaferon®)
Age (mean years)	✓	✓	✓	!	!
Proportion female (%)	✓	✓	✓	✓	✓
Mean EDSS score	✓	✓	✓	✓	✓
Proportion of patients with EDSS score ≥6.0 (%)	!	n/a	!	n/a	!
Time since onset of MS symptoms (mean years)	✓	n/a	n/a	n/a	n/a
Duration of MS (mean years)	✓	!	!	✓	✓
Duration of SPMS (mean years)	!	✓	n/a	✓	!
Normalised brain volume (mean cm^3)	✓	n/a	n/a	n/a	n/a
Proportion of patients with Gd+ lesions of T1-weighted images (%)	!	n/a	!	n/a	n/a
Total volume of T2 lesions on T2-weighted images (mean mm^3)	✓	n/a	n/a	n/a	n/a
Proportion of patients without previous use of a DMT (%)	n/a	n/a	n/a	n/a	n/a
Mean T25FW Test (seconds)	!	n/a	!	n/a	n/a
Time since most recent relapse (months)	✓	n/a	!	n/a	n/a
Proportion of patients relapse-free in prior year (%)	✓	n/a	!	n/a	n/a
Proportion of patients relapse-free in prior 2 years (%)	✓	!	n/a	!	!
Number of relapses per patient in the prior year (mean)	n/a	n/a	!	n/a	n/a
Number of relapses per patient in the previous 2 years (mean)	n/a	!	n/a	!	n/a

✓ = Both studies report the characteristic and the values are similar (within 10%); ! = Both studies report the characteristic and the values are dissimilar (by >10%); n/a = not applicable as not reported in the comparator trial. A 10% threshold for similarity was subjectively selected to qualitatively assess heterogeneity; choice of the 10% threshold was supported by a quantitative analysis using estimated standardized mean differences.

Abbreviations: DMT: disease modifying therapy; EDSS: expanded disability status scale; IFN: interferon; MS: multiple sclerosis; RRMS: relapsing-remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis; T25FW: timed 25-foot walk.

Table 40: Pairwise comparisons of placebo-arm outcomes* (vs. EXPAND)

Criteria	**ASCEND** (natalizumab)	**North American Study** (IFN β-1b, Betaferon®)	**IMPACT** (IFN β-1a, Avonex®)	**SPECTRIMS** (IFN β-1a, Rebif®)	**European Study** (IFN β-1b, Betaferon®)
ARR	✓	!	!	!	!
Annualised Rate of Discontinuation	!	!	!	!	!

✓ = Outcome value is similar (within 10%) compared to EXPAND; ! = Outcome value is dissimilar (>10% different) compared to EXPAND. A 10% threshold for similarity was subjectively selected to qualitatively assess heterogeneity; choice of the 10% threshold was supported by a quantitative analysis using estimated standardized mean differences.

*The placebo-arm results for ARR and discontinuation were compared because these outcomes are reported by trial arm, whereas the time-to-event outcomes (i.e., 3-month CDP and 6-month CDP) are generally reported only as a HR between a treatment arm and the placebo arm.

Abbreviations: ARR: annualised relapse rate; IFN: interferon.

SMD assessment of imbalance in patient characteristics

SMD were also used to quantify the degree of heterogeneity between the trials for each baseline characteristic when compared to EXPAND. These are presented in Table 41 and demonstrate similar results to the qualitative 10% threshold analysis presented above. Both sets of analyses demonstrate there are moderate-to-major differences between EXPAND and the comparator trials.

Table 41: Imbalances in baseline characteristics between EXPAND and comparator trials based on SMD

Baseline patient characteristics	**EXPAND** (siponimod)	**ASCEND** (natalizumab)	**North American Study** (IFN β-1b, Betaferon®)	**IMPACT** (IFN β-1a, Avonex®)	**SPECTRIMS** (IFN β-1a, Rebif®)	**European Study** (IFN β-1b, Betaferon®)
Age (mean years)	48	47.2	46.8	47.6	42.8	41
Proportion female (%)	60	62	63	64	63	61
Mean EDSS score	5.4	5.6	5.1	5.2	5.4	5.1
Proportion of patients with EDSS score ⩾6.0 (%)	56	63	n/a	48	n/a	45
Time since onset of MS symptoms (mean years)	16.8	16.5	n/a	n/a	n/a	n/a
Duration of MS (mean years)	12.6	12.1	14.7	16.5	13.3	13.1
Duration of SPMS (mean years)	3.8	4.8	4.0	n/a	4.0	2.2

Normalised brain volume (mean cm^3)	1,423	1,423	n/a	n/a	n/a	n/a
Proportion of patients with Gd+ lesions of T1-weighted images (%)	21	24	n/a	36	n/a	n/a
Total volume of T2 lesions on T2-weighted images (mean mm^3)	15,321	16,793	n/a	n/a	n/a	n/a
Proportion of patients without previous use of a DMT (%)	22	23	100*	100*	100*	100
Mean Timed 25-Foot Walk Test (seconds)	16.7	n/a	n/a	14.5	n/a	n/a
Time since most recent relapse (months)	59	57	n/a	44.4	n/a	n/a
Proportion of patients relapse-free in prior year (%)	78	84	n/a	61	n/a	n/a
Proportion of patients relapse-free in prior 2 years (%)	64	71	55	n/a	53	30
Number of relapses per patient in the prior year (mean)	0.2	n/a	n/a	0.6	n/a	n/a
Number of relapses per patient in the previous 2 years (mean)	0.7	n/a	0.8	n/a	0.9	n/a

Green = minimal degree of difference (SMD <0.1); orange = moderate degree of difference (SMD ≥0.1 and <0.2); red = major degree of difference (SMD ≥0.2). SMD thresholds based on Austin 2009.[121]
Characteristics marked n/a if not reported in the comparator trial.
*A value of 100% was assumed because IFN-experienced patients were excluded at screening, as described in the exclusion criteria of the trial, and other DMTs were not available at the time of enrolment.
DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; IFN, interferon; MS, multiple sclerosis; n/a, not applicable; SMD, standardised mean difference; SPMS, secondary progressive multiple sclerosis.

Conclusions

Although creation of a connected network may initially seem possible through the connection of placebo arms between the trials of interest, the heterogeneity observed across identified trials in SPMS lead to a standard NMA approach being infeasible. The presence of significant clinical heterogeneity and dissimilarity, as well as an imbalance of effect modifiers between EXPAND and each of the comparator trials undermines the validity of ITC methods that are based on summary-level data, such as network meta-analysis (NMA). Failure to account for differences in trial designs and effect modifiers between trial populations can lead to misleading comparisons of treatment effect and can result in significant bias and clinically implausible results as a result of differences in the prognosis and treatment effect of disparate patient populations. Network meta-analysis results have nonetheless been presented in Appendix C (Section 6.3.4); as previously noted, there are major limitations with these estimates and Novartis do not consider them to be meaningfully interpretable or informative for the decision problem considered by this appraisal.

For the five included comparator studies (i.e., SPECTRIMS, the North American Study, the European Study, ASCEND, and IMPACT), following the guidance of the NICE DSU TSD18, anchored MAICs were determined to be the most appropriate and robust comparative method because the majority of important clinical differences between the trials could be adjusted for using MAIC methodology through use of IPD from EXPAND. Despite the caveat that not all differences could be accounted for, MAICs would still provide the most appropriate method for indirect comparisons.

A summary of the conclusions of the ITC feasibility assessments are presented in brief below (Table 42). Additional information and full details for the pairwise feasibility assessments can be found in Appendix C (Section 6.3.1 and Section 6.3.3).

It is notable that, in addition to the feasibility assessment presented here, the independent US-based Institute for Clinical and Economic Review (ICER) assessment of siponimod in people with SPMS arrived at the same conclusion, namely that summary-level indirect comparisons were infeasible for siponimod and the comparators discussed.[122]

Table 42: Summary of conclusions of the ITC feasibility assessments

Study ID	Key Sources of Potential Bias when Compared with EXPAND	Conclusions / Recommendations
SPECTRIMS North American Study European Study IMPACT	• Excluded IFN-experienced patients • Several major differences in inclusion/exclusion criteria • Several major differences in baseline patient characteristics • Inconsistencies in placebo-arm outcomes	• Summary-level ITCs may have low validity due to significant imbalances in average baseline characteristics • Nonetheless, the populations overlap generously with EXPAND, permitting adjustment of the EXPAND population to match that of the comparator trials using individual patient data • Outcome definitions are reasonably similar where reported, with some caveats • Therefore, conduct MAICs to account for heterogeneity where possible
ASCEND	• Some differences in inclusion/exclusion criteria • Some differences in baseline patient characteristics • Major difference in definitions of outcomes pertaining to time to CDP	• Summary-level ITCs may have reduced validity due to imbalances in patient populations • However, the populations overlap generously with EXPAND • With the exception of time to CDP (either measure), outcome definitions are reasonably similar where reported • Therefore, conduct MAICs to account for heterogeneity where possible

CDP: confirmed disability progression; IFN: interferon; ITC: indirect treatment comparison; MAIC: matching-adjusted indirect comparison; SPMS: secondary progressive multiple sclerosis.

5.3.4 Feasibility assessment for an indirect comparison: active SPMS subgroup

A feasibility assessment was also conducted to determine whether indirect comparisons could be conducted in the active SPMS population. Pairwise comparisons to determine the similarity of the definition of active SPMS and the baseline patient characteristics can be found in Table 43 and Table 44, respectively. Further information on each comparison is provided in Section 5.3.3 and Appendix C.

Baseline characteristics were not reported for the active SPMS subgroup in the SPECTRIMS trial. Therefore, it would have to be assumed that the characteristics for the overall population could be applied to the active subgroup to conduct an MAIC. Given that this assumption is known to be untrue, with patients with active SPMS by definition having a higher disease activity at baseline, in combination with the characteristics of the overall study population not aligning as closely with the EXPAND active SPMS population as with the overall EXPAND population, a MAIC focusing on active SPMS specifically is not possible.

Neither the North American study nor the ASCEND trial reported an active SPMS subgroup.

For the European study and the IMPACT trial, as neither baseline characteristics nor relevant outcomes were reported for the active SPMS subgroup, MAICs were not deemed feasible.

Table 43: Pairwise comparisons of active SPMS definition (vs. EXPAND active SPMS subgroup)

	Active SPMS Definition	Comparability
EXPAND	Presence of relapses in 2 years before study or Gd+ T1 lesions at baseline	n/a
SPECTRIMS (IFN β-1a, Rebif®)	Presence of relapses in the 2 years preceding the study	!
North American Study (IFN β-1b, Betaferon®)	None	n/a
European Study (IFN β-1b, Betaferon®)	Relapse within 2 years before the study	!
ASCEND (natalizumab)	None	n/a
IMPACT (IFN β-1a, Avonex®)	Presence of relapses in year before enrolment	!

! = Outcome definition is dissimilar (>10% different) compared to EXPAND.

IFN: interferon; SPMS: secondary progressive multiple sclerosis.

Table 44: Pairwise comparisons of baseline patient characteristics (comparator ITT vs. EXPAND active SPMS subgroup)

Characteristic	SPECTRIMS (IFN β-1a, Rebif®)	North American Study (IFN β-1b, Betaferon®)	European Study (IFN β-1b, Betaferon®)	ASCEND (natalizumab)	IMPACT (IFN β-1a, Avonex®)
Age (mean years)	✓	✓	!	✓	✓
Proportion female (%)	!	!	!	!	!
Mean EDSS score	✓	✓	✓	✓	✓
Proportion of patients with EDSS score ≥6.0 (%)	n/a	n/a	!	!	!
Time since onset of MS symptoms (mean years)	n/a	n/a	n/a	✓	n/a
Duration of MS (mean years)	!	!	!	✓	!
Duration of SPMS (mean years)	!	!	✓	!	n/a
Normalised brain volume (mean cm3) c	n/a	n/a	n/a	✓	n/a
Proportion of patients with Gd+ lesions of T1-weighted images (%)	n/a	n/a	n/a	!	!
Total volume of T2 lesions on T2-weighted images (mean mm3)	n/a	n/a	n/a	✓	n/a

Proportion of patients without previous use of a DMT (%)	n/a	n/a	n/a	n/a	n/a
Mean T25FW (seconds)	n/a	n/a	n/a	!	!
Time since most recent relapse (months)	n/a	n/a	n/a	!	!
Proportion of patients relapse-free in prior year (%)	n/a	n/a	n/a	!	!
Proportion of patients relapse-free in prior 2 years (%)	!	!	!	!	n/a
Number of relapses per patient in the prior year (mean)	n/a	n/a	n/a	n/a	!
Number of relapses per patient in the previous 2 years (mean)	!	!	n/a	n/a	n/a

✓ = Both studies report the characteristic and the values are similar (within 10%); ! = Both studies report the characteristic and the values are dissimilar (by >10%). A 10% threshold for similarity was subjectively selected to qualitatively assess heterogeneity; choice of the 10% threshold was supported by a quantitative analysis using estimated standardized mean differences.

DMT: disease modifying therapy; EDSS: expanded disability status scale; IFN: interferon; MS: multiple sclerosis; RRMS: relapsing-remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis; T25FW: timed 25-foot walk.

Relapsing SPMS subgroup

In the absence of sufficient data for the active SPMS population, the feasibility assessment additionally considered the subgroup of SPMS patients with relapsing SPMS. Four studies reported relapsing and non-relapsing SPMS subgroups: the European Study, SPECTRIMS, IMPACT, and ASCEND (Table 45). None of the studies reported subgroup-specific baseline patient characteristics; IMPACT and ASCEND did not report any subgroup-specific outcomes of interest.

Table 45: Reported Relapsing and Non-Relapsing Subgroups in SPMS

Study	Intervention	Contains a relevant "relapsing" or "non-relapsing" subgroup?	Reported Subgroups	Reported Subgroup-Specific Outcomes	Requirement to Conduct ITC
ASCEND	Natalizumab (Tysabri®)	Yes	Patients with and without relapses in the prior 12 or 24 months (Appendix)	None	n/a
North American Study	IFNβ-1b (Betaferon®)	No	None	n/a	n/a
SPECTRIMS	IFNβ-1a (Rebif®)	Yes	Patients with and without relapses in the 2 years before study	ARR Time to 3-month CDP	Calculate outcomes from EXPAND IPD
IMPACT	IFNβ-1a (Avonex®)	Yes	Patients with and without relapses in the 1 year before study	None	n/a
European Study	IFNβ-1b (Betaferon®)	Yes	Patients with and without relapses in the 2 years before study	Proportion of patients with 3-month CDP at 33 months	Calculate outcome from EXPAND IPD; requires imputation of censored patients

ARR, annualised relapse rate; CDP, confirmed disease progression; IFN, interferon; IPD, individual patient data; ITC, indirect treatment comparison.

Because none of the studies reported subgroup-specific baseline patient characteristics, MAICs were not possible. Due to the lack of common subgroup and outcome definitions, NMAs were also not possible; however pairwise Bucher ITCs could be conducted in the relapsing SPMS population. Bucher ITCs between these studies are undermined by substantial clinical heterogeneity and all results should be interpreted with caution. Subgroup-specific Bucher ITCs were performed using subgroups derived from the EXPAND IPD to match the subgroup and outcome definitions stated in Table 45.

The European Study did not report any outcomes of interest, but did report the proportion of patients with 3-month CDP at 33 months. This outcome was calculated from the EXPAND IPD in order to facilitate an ITC; however, to derive this outcome, an assumption was required pertaining to the handling of censored patients. Due to the high proportion of censored patients at 33 months in EXPAND, the *last observation carried forward* imputation method was conducted wherein censored patients were assumed to have the same status at 33 months as they did on the day that they were censored. Although *non-responder* imputation (i.e., assuming all censored patients would have 3-month CDP) would be a preferred conservative approach (that is, it would underestimate the efficacy of siponimod), it resulted in undefined estimates due to the high degree of censorship.

In the interest of exploratory analyses only, and with acknowledgment to the implausible assumptions, a Bucher ITC was also conducted wherein the HR for time to 3-month CDP derived from EXPAND IPD after following patients for 33 months was compared directly to the relative risk for the proportion with 3-month CDP at 33 months reported by the European Study (Section 5.3.5). A Bucher ITC was also conducted using the SPECTRIMS data.

5.3.5 Bucher indirect comparison: Relapsing SPMS population

Results for the unadjusted pairwise Bucher indirect comparison performed in the relapsing SPMS population are presented in Table 46.

The relapsing sub-group was used as a proxy for the active sub-group due to the absence of comparator data in active SPMS. Based on the results of the post-hoc subgroup analysis of EXPAND, the active subgroup (Section 5.3.1) and relapsing subgroup (Section 6.2.2.9) were similar with regards to the outcomes for time to 6-month and 3-month CDP compared to placebo. (3-month CDP: HR 0.68 [0.52, 0.89; p=0.0049]) in the active SPMS subgroup, HR 0.67 [0.50, 0.91; p=0.0108] in the relapsing SPMS subgroup); a comparison considering the relapsing SPMS sub-population may therefore be an appropriate indicator of relative effectiveness in the active SPMS population.

In the relapsing subgroup, siponimod was demonstrated to be numerically superior in most comparisons, although no comparison reached statistical significance. Because adjusted ITCs were not possible in the subgroups, the observed between-trial heterogeneity in patient populations undermines the clinical validity of these results. There were significant limitations in conducting the subgroup ITCs and they must be interpreted in the context of these weaknesses detailed previously.

Given the described limitations of these analyses, it is recommended that the MAICs conducted in the full SPMS population are considered representative of results in the active SPMS population; at least for siponimod, this would not be overestimating the efficacy in the active SPMS subgroup.

Table 46: Summary of subgroup Bucher ITC results for 3-month CDP and ARR in the relapsing subgroup

Comparator Intervention	Study ID(s)	Notable Assumptions	Siponimod vs. Placebo Subgroup from EXPAND IPD (95% CI)		Comparator vs. Placebo Subgroup from Publication (95% CI)		Subgroup Bucher ITC Results Siponimod vs. Comparator (95% CI)	
			Type	Value	Type	Value	Type	Value
Proportion with 3-month CDP (33 months) in Subgroup: Patients with Relapses in the 2 Years Before Study								
Betaferon® (SC IFNβ-1b 250 µg q2d)	European Study	Imputation of censored data for EXPAND: Last observation carried forward*	OR	**0.61 (0.42 - 0.88)**	OR	**0.69 (0.49 - 0.98)**	OR	0.88 (0.53 - 1.47)
Betaferon® (SC IFNβ-1b 250 µg q2d)	European Study	Compared subgroup ReR of European Study with subgroup time-to-event HR of EXPAND**	HR	**0.67 (0.50 - 0.91)**	ReR	**0.83 (0.69 - 0.99)**	ReR compared to HR**	0.81 (0.57 - 1.15)
Time to 3-month CDP in Subgroup: Patients with Relapses in the 2 Years Before Study								
Rebif® (SC IFNβ-1a 44 µg tiw‡)	SPECTRIMS	–	HR	**0.67 (0.49 - 0.91)**	HR	0.76 (0.53 - 1.10)	HR	0.88 (0.55 - 1.42)
ARR in Subgroup: Patients with Relapses in the 2 Years Before Study								
Rebif® (SC IFNβ-1a 22 µg tiw)	SPECTRIMS	SPECTRIMS: Assume the RR p-value = 0.001 in order to calculate the 95% CI†	RR	**0.58 (0.40 - 0.84)**	RR	**0.53 (0.36 - 0.77)** †	RR	1.10 (0.65 - 1.87)
Rebif® (SC IFNβ-1a 44 µg tiw)	SPECTRIMS		RR	**0.58 (0.40 - 0.84)**	RR	**0.62 (0.47 - 0.82)** †	RR	0.94 (0.59 - 1.49)

Note: Statistically significant values are bolded. *Last observation carried forward: censored patients are assumed to have the same status at the cut-off time-point as they did on the day they were censored. Note that Complete Case could not be derived from the EXPAND IPD due to the volume of censoring (in complete case, censored patients are removed from the data). **Must be interpreted with caution. †Analysis of the ARR outcome for the relapsing subgroup in SPECTRIMS required making an assumption about the p-value (reported as "<0.001 for both doses") in order to calculate the 95% CI, which was not reported. The p-value was assumed to equal 0.001 for each dose. ‡ Time to CDP-3 subgroup results not reported for the 22 µg dose in SPECTRIMS. ARR, annualised relapse rate; CDP, confirmed disease progression; CI, confidence interval; HR, hazard ratio; IFN, interferon; IPD, individual patient data; OR, odds ratio; qw, weekly; q2d, twice daily; RR, relative risk; SC, subcutaneous; tiw, three times weekly.

5.3.6 Matching-adjusted indirect treatment comparisons (MAICs)

MAICs were conducted using the methods outlined in the NICE DSU TSD18.[120] The MAIC method is designed to reduce cross-trial differences in baseline patient characteristics and reduce sensitivity to effect measures. Individual patient data from one trial (i.e. EXPAND) were weighted to match mean baseline characteristics (i.e. aggregate or summary data) as published from the included trials identified in the systematic review. Results of the trial with IPD were then reanalysed using the weighted patient-level data set.

This MAIC method was used to carry out “anchored” indirect comparisons, where there is a common comparator arm in each trial (in all cases in this submission the common comparator was placebo).

Matching was performed to align the population of EXPAND to the reported inclusion and exclusion criteria of trials pertaining to the comparator DMT by excluding EXPAND patients who would not have qualified for the comparator trials, where possible.

The matching step depends on the inclusion/exclusion criteria reported by comparator trials. As such, the precise list of factors matched varies by pairwise comparison. Overall, the factors included the following categories of inclusion/exclusion criteria:

- Baseline EDSS range
- Age range
- Prior interferon (IFN) therapy
- No relapses in X months prior
- Documented progression within X months prior
- Duration of MS
- Duration of SPMS
- MS severity score
- T25FW test score

Given that the comparisons were anchored, adjustment was only required for treatment effect modifiers; this was conducted using all the available clinically relevant baseline characteristics identified as treatment effect modifiers in Table 35 and Table 36, for CDP and ARR respectively. The identified characteristics were ranked by relative importance, as presented in Table 35 and Table 36, and were used to re-weight the outcomes of patients of the already-matched EXPAND population to simultaneously adjust the mean of all chosen treatment effect modifiers or “adjustment factors” (e.g. mean EDSS score at baseline).

MAIC results are presented herein for all feasible comparisons with siponimod, disaggregated by DMT, dose, and regimen: IFN β-1a (Rebif®) 22 µg thrice weekly (TIW), IFN β-1a (Rebif®) 44 µg TIW, IFN β-1b (Betaferon®) 250 µg every other day (Q2D), natalizumab 300 mg every 4 weeks (Q4W), and IFN β-1a (Avonex®) 60 µg QW (unlicensed dose, see below for rationale).

Avonex® 60 µg is not the licensed regimen of this treatment, however the Summary of Product Characteristics (SmPC) for Avonex® states that no additional benefit has been shown by administering a higher dose once a week, and so it can be assumed that the efficacy of the 60 µg dose, for which there is RCT data available in SPMS, is the same as for the licensed 30 µg dose.[93]

The matching and adjustment process (propensity score reweighting) for each pairwise comparison is reported in Appendix C. Please refer to Section 5.3.3 and Appendix C for a detailed breakdown of the imbalance in inclusion criteria and baseline patient characteristics between studies. The pairwise results of each MAIC are presented below. Although summary-level ITCs are considered to be invalid, as outlined in the feasibility assessment, for full transparency summary results for pairwise Bucher ITC and an NMA have also been presented

alongside the summary of MAIC results at the end of this section. In addition, as a scenario analysis for the MAIC, a simulated treatment comparison (STC) was also undertaken and has been presented alongside the summary of MAIC results at the end of this section. STC is another method of deriving population-adjusted ITCs using a mix of IPD and aggregate data from a comparator trial. Whereas MAICs "match" to a comparator trial by excluding patients in the EXPAND dataset who would not have met the eligibility criteria of the comparator trial, STCs retain the full EXPAND population. In an STC, a regression model incorporating prognostic effects and effect modifiers is estimated and the fitted model is used to predict ITCs in the comparator trial. Although MAICs and STCs are often presented as equivalent methods of estimating population-adjusted relative treatment effects, MAICs are more commonly used for health technology assessments, may be more intuitive to clinicians, and are considered more flexible for non-linear outcomes (such as ARR) and time-to-event outcomes (such as CDP).[120] For these reasons, MAICs are considered the preferred and primary method for deriving ITCs between siponimod and comparator treatments. STCs are used here as a sensitivity analysis to validate the MAIC results. Full results and methodology for the ITC, NMA and STC can be found in the appendix (Section 6.3.4 and 6.3.5).

Siponimod vs IFN β-1a (Rebif®) 22 µg TIW

There was a significant drop in sample size as a result of matching to the comparator trial (Table 47). This illustrates the imbalance between these studies and patient populations that undermines the validity of summary-level ITC results and supports the need for a MAIC.

Table 47: Results of population matching and adjustment for CDP – Siponimod vs IFN β-1a (Rebif®) 22 µg TIW

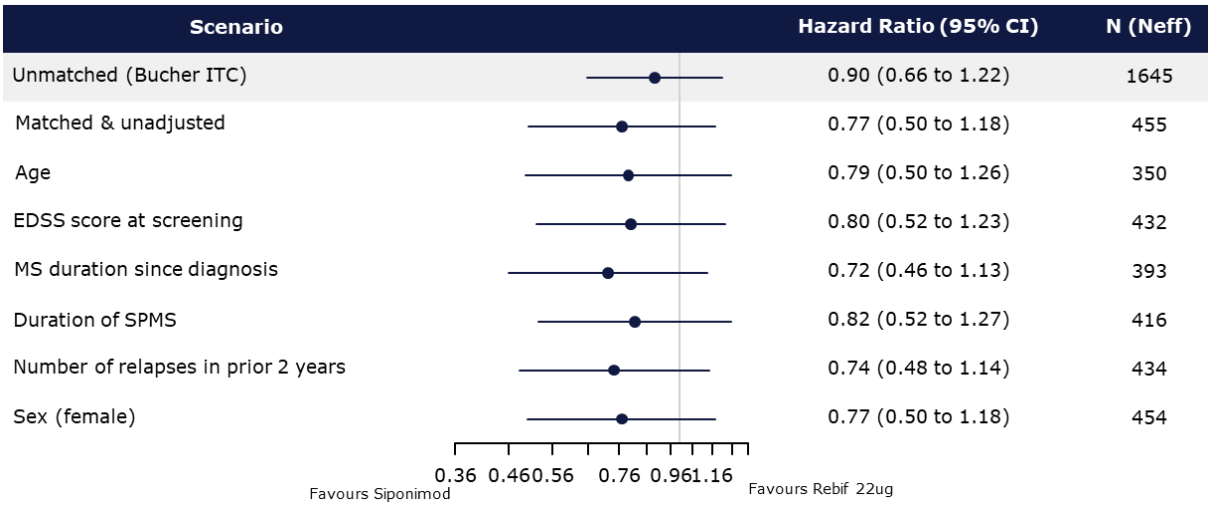
Variables	SPECTRIMS	EXPAND (unmatched)	EXPAND (matched and unadjusted)	Scenario A	Scenario B	Scenario C	Scenario D	Scenario E	Scenario F
N (Neff)	618	1638	455	237	239	253	268	325	350
Age (mean years [SD])	42.8 (7.1)	48.03 (7.84)	46.43 (6.81)	42.8 (7.11)	42.8 (7.11)	42.8 (7.11)	42.8 (7.11)	42.8 (7.11)	42.8 (7.11)
EDSS score at screening (mean [SD])	5.4 (1.1)	5.42 (1.06)	5.19 (1.11)	5.4 (1.1)	5.4 (1.1)	5.4 (1.1)	5.4 (1.1)	5.4 (1.1)	–
MS duration since diagnosis (mean years [SD])	13.3 (7.1)	12.62 (7.77)	11.06 (7.91)	13.3 (7.11)	13.3 (7.11)	13.3 (7.11)	13.3 (7.11)	–	–
Duration of SPMS (mean years [SD])	4 (3)	3.77 (3.51)	3.42 (3.19)	4 (3)	4 (3)	4 (3)	–	–	–
Number of relapses in prior 2	0.9 (1.3)	0.67 (1.19)	0.71 (1.08)	0.9 (1.3)	0.9 (1.3)	–	–	–	–

years (mean [SD])									
Sex (proportion female)	63.0%	60.01%	60.22%	63.0%	–	–	–	–	–

Scenario A adjusts for all available ranked characteristics, subsequent scenarios drop the least important characteristic from adjustment.
Matched sample excludes patients >55 years old, EDSS <3 or >6.5, and those with prior IFNβ therapy.
EDSS, expanded disability status scale; MS, multiple sclerosis; Neff, effective sample size; SD, standard deviation; SPMS, secondary progressive multiple sclerosis.

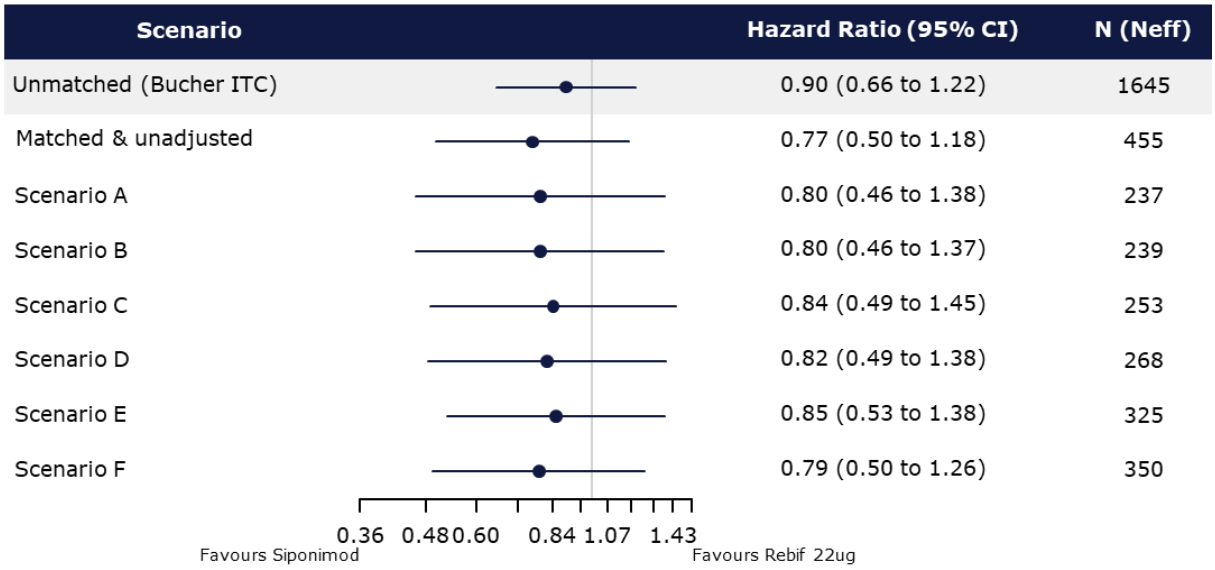
For the outcome of time to 3-month CDP, all univariate and scenario analyses were in favour of siponimod but were not statistically significant (Figure 15 and Figure 16). The fully matched-and-adjusted estimate was in favour of siponimod, but the result was not statistically significant.

Figure 15: MAIC univariate adjustment results for time to 3-month CDP – Siponimod vs IFN β-1a (Rebif®) 22 µg TIW



Matched sample excludes patients >55 years old, EDSS <3 or >6.5, and those with prior IFNβ therapy.
CI, confidence interval; EDSS, expanded disability status scale; ITC, indirect treatment comparison; MS, multiple sclerosis; Neff, effective sample size; SPMS, secondary progressive multiple sclerosis.

Figure 16: MAIC scenario analysis results for time to 3-month CDP – Siponimod vs IFN β-1a (Rebif®) 22 µg TIW



Scenario A adjusts for all available ranked characteristics, subsequent scenarios drop the least important characteristic from adjustment.
Matched sample excludes patients >55 years old, EDSS <3 or >6.5, and those with prior IFNβ therapy
CI, confidence interval; ITC, indirect treatment comparison; Neff, effective sample size.

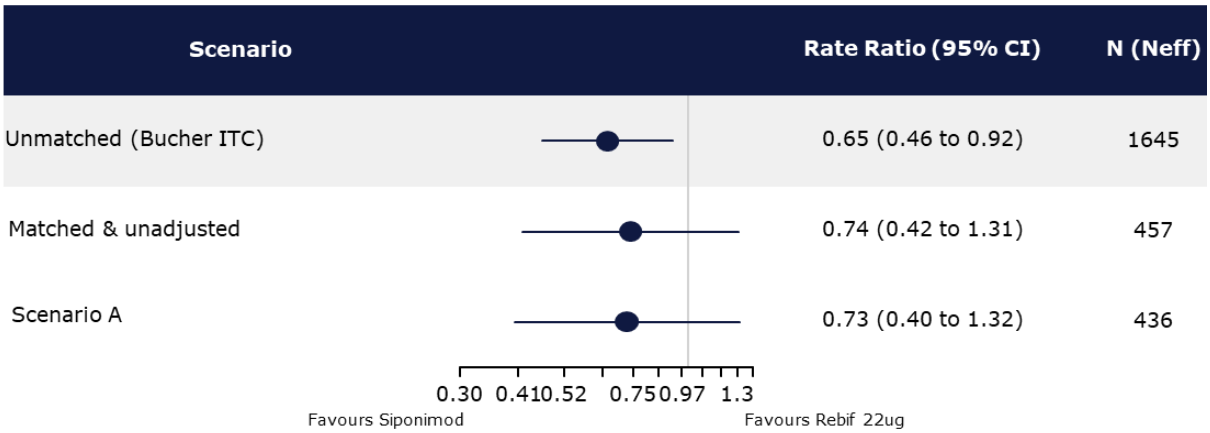
For the outcome of ARR, the fully matched and adjusted estimate was in favour of siponimod, although the result was not statistically significant (Table 48 and Figure 17).

Table 48: Results of population matching and adjustment for ARR – Siponimod vs IFN β-1a (Rebif®) 22 µg TIW

Variables	SPECTRIMS	EXPAND (unmatched)	EXPAND (matched and unadjusted)	Scenario A
N (Neff)	616	1641	457	436
Number of relapses in prior 2 years (mean [SD])	0.9 (1.3)	0.67 (1.19)	0.71 (1.07)	0.9 (1.3)

Scenario A adjusts for all available ranked characteristics, subsequent scenarios drop the least important characteristic from adjustment.
Matched sample excludes patients > 55 years old, baseline EDSS <3 or >6.5, and those with prior IFN therapy.
Neff, effective sample size; SD, standard deviation.

Figure 17: MAIC results for ARR – Siponimod vs IFN β-1a (Rebif®) 22 µg TIW



Matched sample excludes patients >55 years old, EDSS <3 or >6.5, and those with prior IFNβ therapy.

CI, confidence interval; ITC, indirect treatment comparison; Neff, effective sample size.

Siponimod vs IFN β-1a (Rebif®) 44 µg TIW

There was a significant drop in sample size as a result of matching to the comparator trial (Table 49). This illustrates the imbalance between these studies and patient populations that undermines the validity of summary-level ITC results and supports the need for a MAIC.

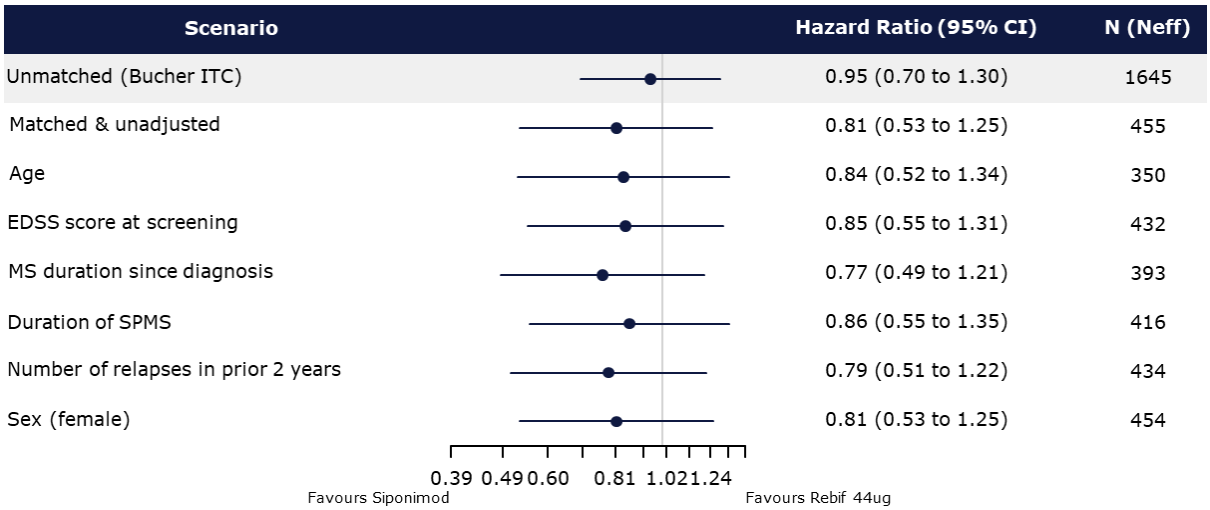
Table 49: Results of population matching and adjustment for CDP – Siponimod vs IFN β-1a (Rebif®) 44 µg TIW

Variables	SPECTRIMS	EXPAND (unmatched)	EXPAND (matched and unadjusted)	Scenario A	Scenario B	Scenario C	Scenario D	Scenario E	Scenario F
N (Neff)	618	1638	455	237	239	253	268	325	350
Age (mean years [SD])	42.8 (7.1)	48.03 (7.84)	46.43 (6.81)	42.8 (7.11)	42.8 (7.11)	42.8 (7.11)	42.8 (7.11)	42.8 (7.11)	42.8 (7.11)
EDSS score at screening (mean [SD])	5.4 (1.1)	5.42 (1.06)	5.19 (1.11)	5.4 (1.1)	5.4 (1.1)	5.4 (1.1)	5.4 (1.1)	5.4 (1.1)	–
MS duration since diagnosis (mean years [SD])	13.3 (7.1)	12.62 (7.77)	11.06 (7.91)	13.3 (7.11)	13.3 (7.11)	13.3 (7.11)	13.3 (7.11)	–	–
Duration of SPMS (mean years [SD])	4 (3)	3.77 (3.51)	3.42 (3.19)	4 (3)	4 (3)	4 (3)	–	–	–
Number of relapses in prior 2 years (mean [SD])	0.9 (1.3)	0.67 (1.19)	0.71 (1.08)	0.9 (1.3)	0.9 (1.3)	–	–	–	–
Sex (proportion female)	63.0%	60.01%	60.22%	63.0%	–	–	–	–	–

Scenario A adjusts for all available ranked characteristics, subsequent scenarios drop the least important characteristic from adjustment.
Matched sample excludes patients >55 years old, EDSS <3 or >6.5, and those with prior IFNβ therapy.
EDSS, expanded disability status scale; MS, multiple sclerosis; Neff, effective sample size; SD, standard deviation; SPMS, secondary progressive multiple sclerosis.

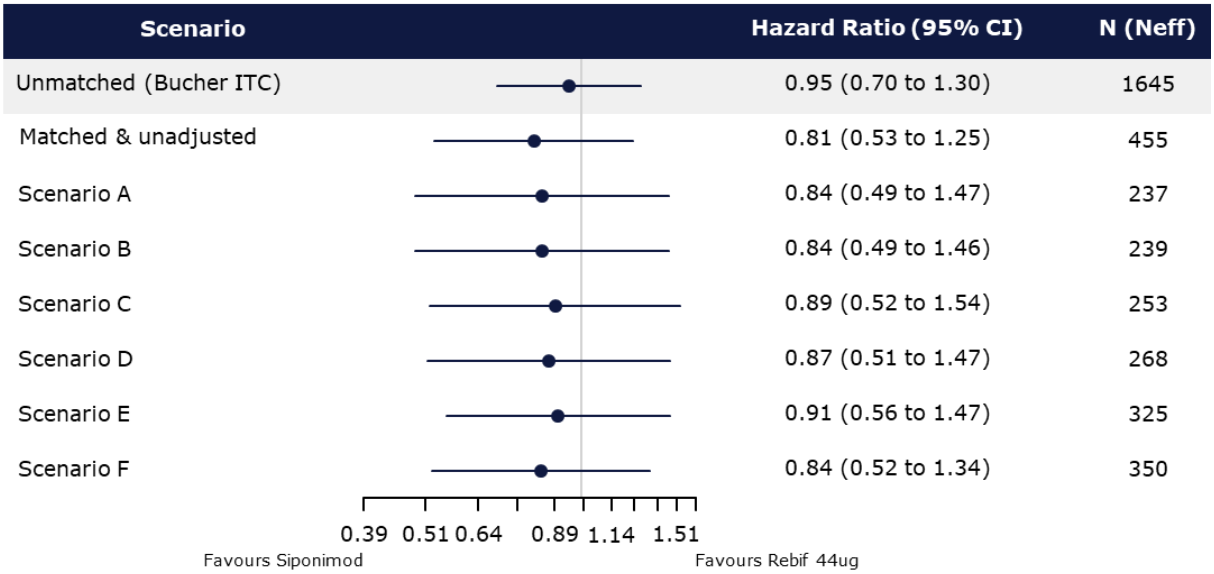
For the outcome of time to 3-month CDP, all univariate and scenario analyses were in favour of siponimod but were not statistically significant (Figure 18 and Figure 19). The fully matched-and-adjusted estimate was in favour of siponimod, but the result was not statistically significant.

Figure 18: MAIC Univariate Adjustment Results for Time to 3-month CDP – Siponimod vs. IFN β-1a (Rebif®) 44 µg TIW



Matched sample excludes patients >55 years old, EDSS <3 or >6.5, and those with prior IFNβ therapy.
CI, confidence interval; EDSS, expanded disability status scale; ITC, indirect treatment comparison; MS, multiple sclerosis; Neff, effective sample size; SD, standard deviation; SPMS, secondary progressive multiple sclerosis.

Figure 19: MAIC Scenario Analysis Results for Time to 3-month CDP – Siponimod vs. IFN β-1a (Rebif®) 44 µg TIW



Scenario A adjusts for all available ranked characteristics, subsequent scenarios drop the least important characteristic from adjustment.
Matched sample excludes patients >55 years old, EDSS <3 or >6.5, and those with prior IFNβ therapy.
CI, confidence interval; ITC, indirect treatment comparison; Neff, effective sample size.

For the outcome of ARR, the fully matched and adjusted estimate was in favour of siponimod, although the result was not statistically significant (Table 50 and Figure 20).

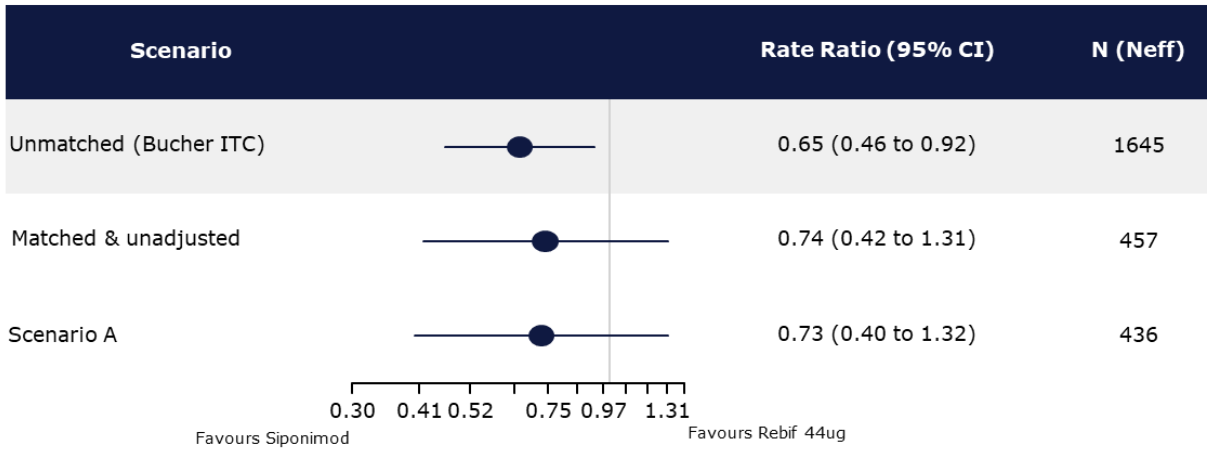
Table 50: Results of Population Matching and Adjustment for ARR – Siponimod vs. IFN β-1a (Rebif®) 44 µg TIW

Variables	SPECTRIMS	EXPAND (unmatched)	EXPAND (matched and unadjusted)	Scenario A
N (Neff)	616	1641	457	436

Number of relapses in prior 2 years (mean [SD])	0.9 (1.3)	0.67 (1.19)	0.71 (1.07)	0.9 (1.3)

Scenario A adjusts for all available ranked characteristics, subsequent scenarios drop the least important characteristic from adjustment.
Matched sample excludes patients > 55 years old, baseline EDSS <3 or >6.5, and those with prior IFN therapy.
Neff, effective sample size; SD, standard deviation.

Figure 20: MAIC Results for ARR – Siponimod vs. IFN β-1a (Rebif®) 44 µg TIW



Scenario A adjusts for all available ranked characteristics, subsequent scenarios drop the least important characteristic from adjustment.
Matched sample excludes patients >55 years old, EDSS <3 or >6.5, and those with prior IFNβ therapy.
CI, confidence interval; ITC, indirect treatment comparison; Neff, effective sample size.

Siponimod vs. IFN β-1b (Betaferon®) 250 µg Q2D

There was a significant drop in sample size as a result of matching to the comparator trials for every outcome (Table 51). This illustrates the imbalance between these studies and patient populations that undermines the validity of summary-level ITC results and supports the need for a MAIC.

Table 51: Results of Population Matching and Adjustment for 6-month CDP – Siponimod vs. IFN β-1b (Betaferon®) 250 µg Q2D

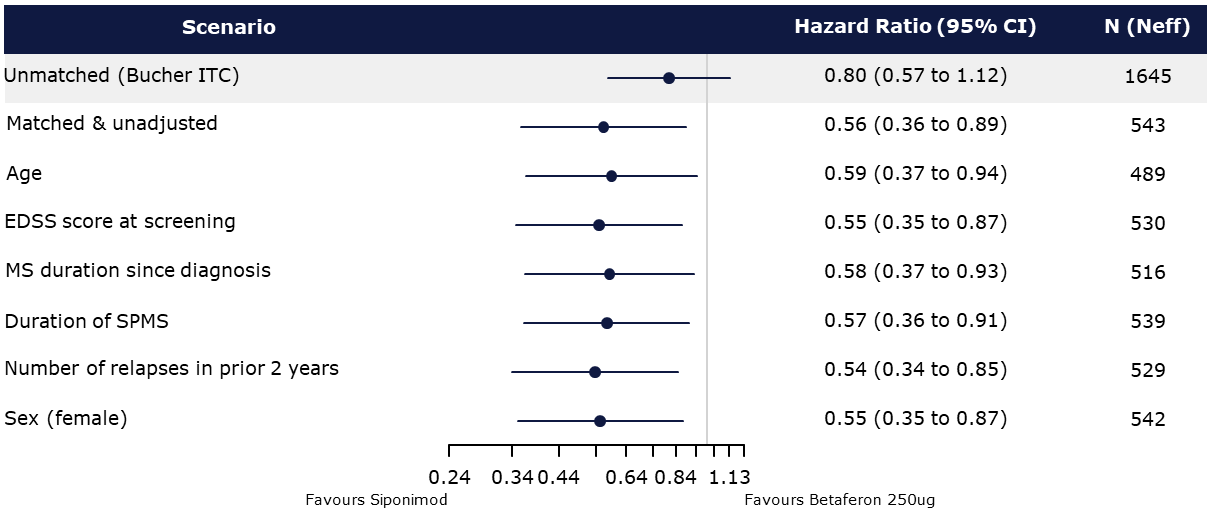
Variables	North American Study	EXPAND (unmatched)	EXPAND (matched and unadjusted)	Scenario A	Scenario B	Scenario C	Scenario D	Scenario E	Scenario F
N (Neff)	939	1638	543	410	411	427	432	479	489
Age (mean years [SD])	46.83 (8.14)	48.03 (7.84)	49.4 (7.74)	46.83 (8.15)	46.83 (8.15)	46.83 (8.15)	46.83 (8.15)	46.83 (8.15)	46.83 (8.15)
EDSS score at screening (mean [SD])	5.13 (1.18)	5.42 (1.06)	5.27 (1.11)	5.13 (1.18)	5.13 (1.18)	5.13 (1.18)	5.13 (1.18)	5.13 (1.18)	–
MS duration since diagnosis (mean years [SD])	14.66 (8.32)	12.62 (7.77)	12.92 (8.24)	14.66 (8.33)	14.67 (8.33)	14.67 (8.33)	14.66 (8.33)	–	–

Duration of SPMS (mean years [SD])	4.03 (3.48)	3.77 (3.51)	3.84 (3.53)	4.03 (3.48)	4.03 (3.48)	4.03 (3.48)	–	–	–
Number of relapses in prior 2 years (mean [SD])	0.83 (1.32)	0.67 (1.19)	0.65 (1.1)	0.83 (1.32)	0.83 (1.32)	–	–	–	–
Sex (proportion female)	62.6%	60.01%	60.41%	62.6%	–	–	–	–	–

Scenario A adjusts for all available ranked characteristics, subsequent scenarios drop the least important characteristic from adjustment.
Matched sample excludes patients with MS duration <2 years, baseline EDSS <3 or >6.5, and patients with prior IFNβ therapy.
EDSS, expanded disability status scale; MS, multiple sclerosis; Neff, effective sample size; SD, standard deviation; SPMS, secondary progressive multiple sclerosis.

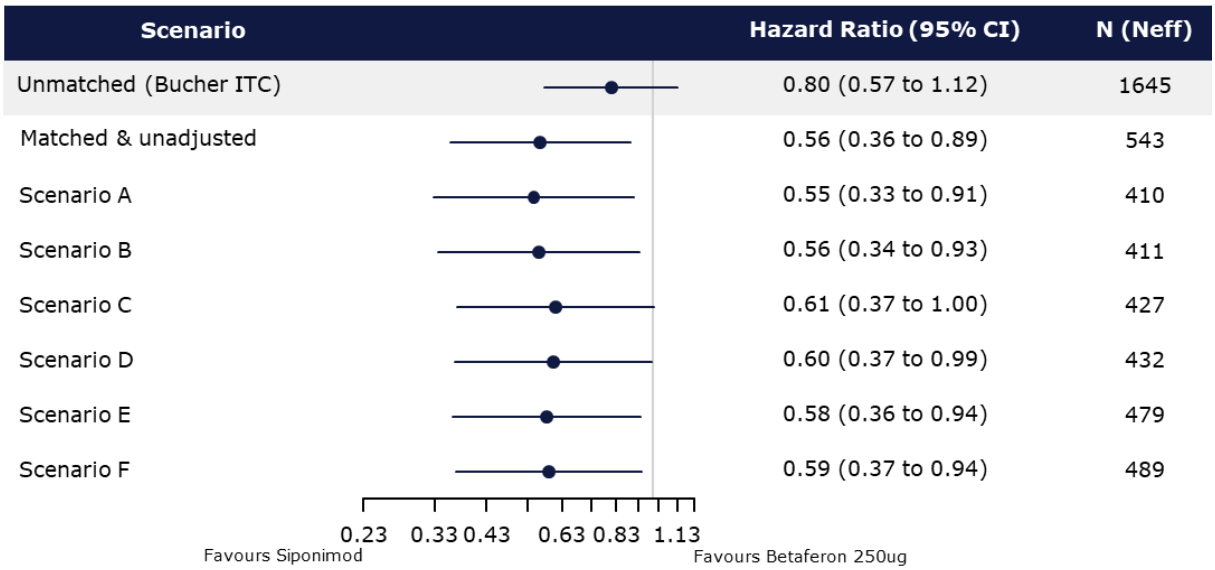
For the outcome of time to 6-month CDP, all univariate and scenario analyses were in favour of siponimod and were statistically significant (Figure 21and Figure 22). The fully matched-and-adjusted estimate was in favour of siponimod and the result was also statistically significant.

Figure 21: MAIC Univariate Adjustment Results for Time to 6-month CDP – Siponimod vs. IFN β-1b (Betaferon®) 250 µg Q2D



Matched sample excludes patients with MS duration <2 years, baseline EDSS <3 or >6.5, and patients with prior IFNβ therapy.
CI, confidence interval; EDSS, expanded disability status scale; ITC, indirect treatment comparison; MS, multiple sclerosis; Neff, effective sample size; SD, standard deviation; SPMS, secondary progressive multiple sclerosis.

Figure 22: MAIC Scenario Analysis Results for Time to 6-month CDP – Siponimod vs. IFN β-1b (Betaferon®) 250 µg Q2D



Scenario A adjusts for all available ranked characteristics, subsequent scenarios drop the least important characteristic from adjustment.
Matched sample excludes patients with MS duration <2 years, baseline EDSS <3 or >6.5, and patients with prior IFNβ therapy.
CI, confidence interval; ITC, indirect treatment comparison; Neff, effective sample size.

For the outcome of time to 3-month CDP, all univariate and scenario analyses were in favour of siponimod but were not statistically significant (Figure 23 and Figure 24). The fully matched-and-adjusted estimate was in favour of siponimod, but the result was also not statistically significant.

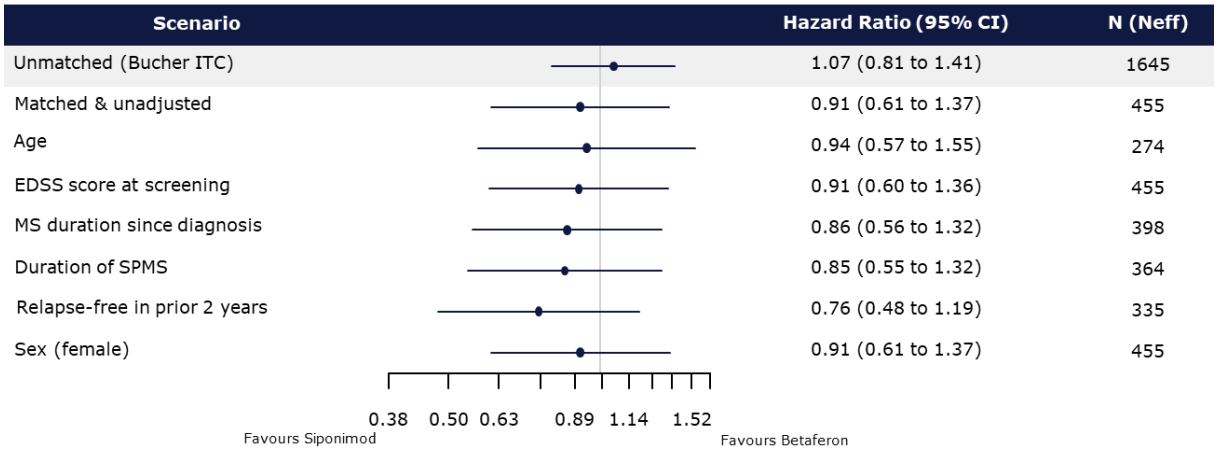
Table 52: Results of Population Matching and Adjustment for 3-month CDP – Siponimod vs. IFN β-1b (Betaferon®) 250 µg Q2D

Variables	European Study	EXPAND (unmatched)	EXPAND (matched and unadjusted)	Scenario A	Scenario B	Scenario C	Scenario D	Scenario E	Scenario F
N (Neff)	718	1638	455	140	141	163	205	274	274
Age (mean years [SD])	41 (7.2)	48.03 (7.84)	46.43 (6.81)	41 (7.22)	41 (7.22)	41 (7.21)	41 (7.21)	41 (7.21)	41 (7.21)
EDSS score at screening (mean [SD])	5.15 (1.1)	5.42 (1.06)	5.19 (1.11)	5.15 (1.1)	5.15 (1.1)	5.15 (1.1)	5.15 (1.1)	5.15 (1.1)	–
MS duration since diagnosis (mean years [SD])	13.1 (7.06)	12.62 (7.77)	11.06 (7.91)	13.1 (7.08)	13.1 (7.08)	13.1 (7.08)	13.1 (7.08)	–	–
Duration of SPMS (mean	2.15 (2.3)	3.77 (3.51)	3.42 (3.19)	2.15 (2.31)	2.15 (2.31)	2.15 (2.3)	–	–	–

years [SD])									
Relapse-free in prior 2 years (mean [SD])	30.4%	64.04%	59.78%	30.4%	30.4%	–	–	–	–
Sex (proportion female)	61.1%	60.01%	60.22%	61.1%	–	–	–	–	–

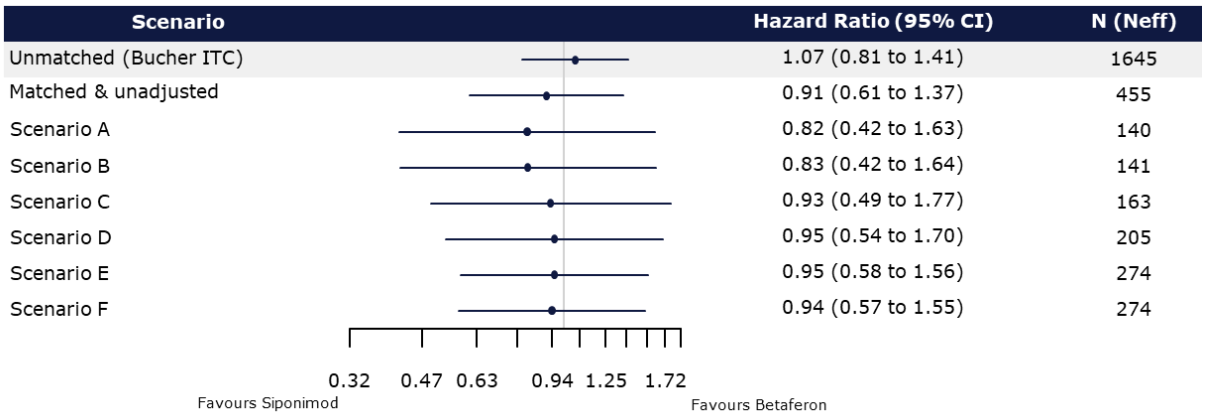
Scenario A adjusts for all available ranked characteristics, subsequent scenarios drop the least important characteristic from adjustment.
Matched sample excludes patients >55 years old, EDSS <3 or >6.5, and those with prior IFNβ therapy.
EDSS, expanded disability status scale; MS, multiple sclerosis; Neff, effective sample size; SD, standard deviation; SPMS, secondary progressive multiple sclerosis.

Figure 23: MAIC Univariate Adjustment Results for Time to 3-month CDP – Siponimod vs. IFN β-1b (Betaferon®) 250 µg Q2D



Matched sample excludes patients >55 years old, EDSS <3 or >6.5, and those with prior IFNβ therapy.
CI, confidence interval; EDSS, expanded disability status scale; ITC, indirect treatment comparison; MS, multiple sclerosis; Neff, effective sample size; SD, standard deviation; SPMS, secondary progressive multiple sclerosis.

Figure 24: MAIC Scenario Analysis Results for Time to 3-month CDP – Siponimod vs. IFN β-1b (Betaferon®) 250 µg Q2D



Scenario A adjusts for all available ranked characteristics, subsequent scenarios drop the least important characteristic from adjustment.
Matched sample excludes patients >55 years old, EDSS <3 or >6.5, and those with prior IFNβ therapy
CI, confidence interval; ITC, indirect treatment comparison; Neff, effective sample size.

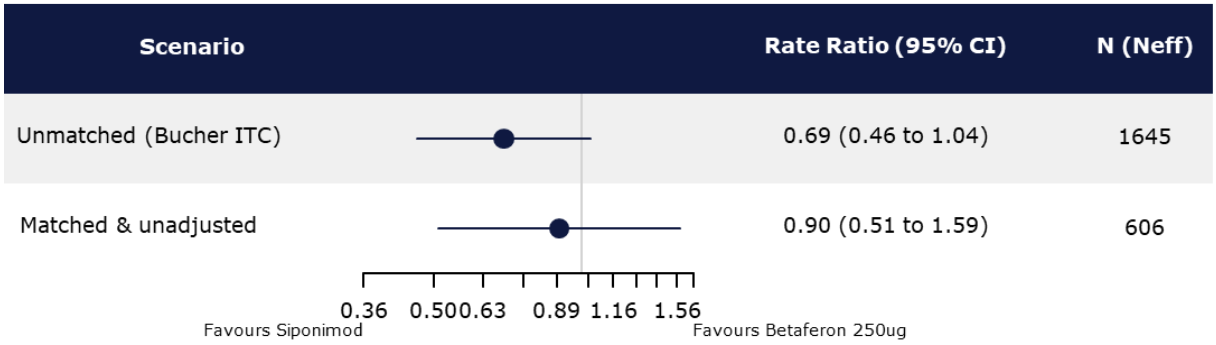
For the outcome of ARR, the matched estimate was in favour of siponimod, but the result was not statistically significant (Table 53 and Figure 25).

Table 53: Results of Population Matching and Adjustment for ARR – Siponimod vs. IFN β-1b (Betaferon®) 250 µg Q2D

Variables	European Study & North American Study	EXPAND (unmatched)	EXPAND (matched and unadjusted)
N (Neff)	1343	1645	606

Scenario A adjusts for all available ranked characteristics, subsequent scenarios drop the least important characteristic from adjustment.
Matched sample excludes patients with baseline EDSS <3 or >6.5, and those with prior IFN therapy.
Neff, effective sample size.

Figure 25: MAIC Results for ARR – Siponimod vs. IFN β-1b (Betaferon®) 250 µg Q2D



Matched sample excludes patients with baseline EDSS <3 or >6.5, and those with prior IFN therapy.
CI, confidence interval; ITC, indirect treatment comparison; Neff, effective sample size.

Siponimod vs natalizumab 300 mg Q4W

There was a significant drop in sample size as a result of matching to the comparator trial (Table 54 and Table 55). This illustrates the imbalance between these studies and patient populations that undermines the validity of summary-level ITC results and supports the need for a MAIC.

Table 54: Results of population matching and adjustment for CDP – Siponimod vs. natalizumab 300 mg Q4W

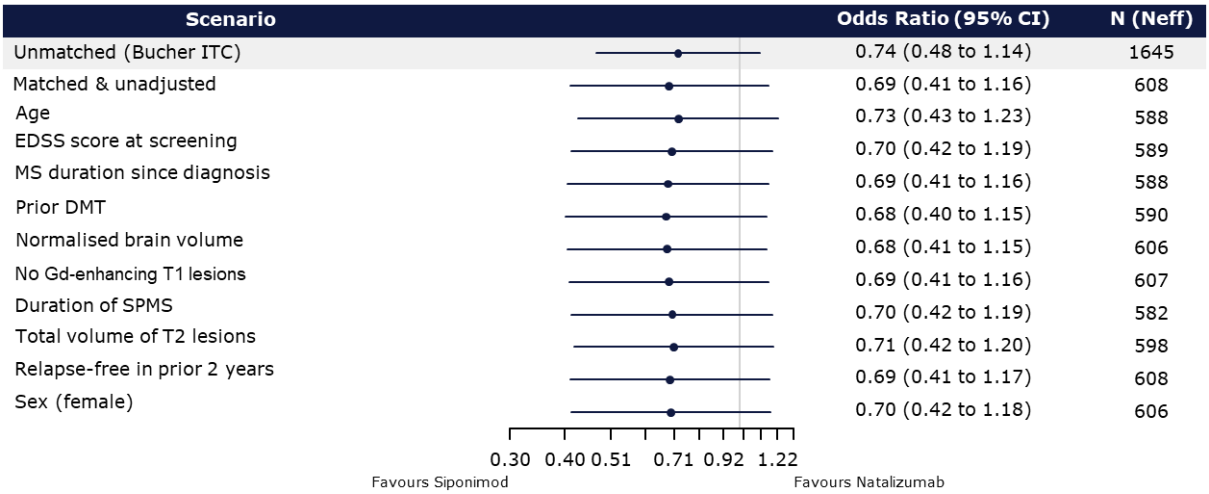
Variables	ASCEND	EXPAND (unmatched)	EXPAND (matched and unadjusted)	Scenario A	Scenario B	Scenario C	Scenario D	Scenario E	Scenario F	Scenario G	Scenario H	Scenario I	Scenario J
N (Neff)	887	1584	608	516	518	522	531	543	544	553	564	571	588
Age (mean years [SD])	47.25 (7.61)	48.07 (7.84)	47.77 (6.82)	47.25 (7.61)	47.25 (7.61)	47.25 (7.61)	47.25 (7.61)	47.25 (7.61)	47.25 (7.61)	47.25 (7.61)	47.25 (7.61)	47.25 (7.61)	47.25 (7.61)
EDSS score at screening (mean [SD])	5.6 (0.9)	5.41 (1.07)	5.75 (0.83)	5.6 (0.9)	5.6 (0.9)	5.6 (0.9)	5.6 (0.9)	5.6 (0.9)	5.6 (0.9)	5.6 (0.9)	5.6 (0.9)	5.6 (0.9)	–
MS duration since diagnosis (mean years [SD])	12.14 (6.88)	12.69 (7.8)	13.28 (6.93)	12.14 (6.89)	12.15 (6.89)	12.14 (6.89)	12.15 (6.89)	12.14 (6.89)	12.14 (6.89)	12.14 (6.89)	12.14 (6.89)	–	–
Prior DMT (proportion)	77.0%	78.41%	83.55%	77.0%	77.0%	77.0%	77.0%	77.0%	77.0%	77.0%	–	–	–
Normalised brain volume (mean cm^3 [SD])	1423.37 (82.95)	1422.95 (86.76)	1429.17 (83.49)	1423.37 (83.02)	1423.37 (83.02)	1423.37 (83.02)	1423.37 (83.02)	1423.37 (83.02)	1423.37 (83.02)	–	–	–	–
No Gd-enhancing T1 lesions (proportion)	76.2%	78.09%	78.12%	76.2%	76.2%	76.2%	76.2%	76.2%	–	–	–	–	–
Duration of SPMS (mean years [SD])	4.8 (3.37)	3.77 (3.51)	5.2 (3.32)	4.8 (3.38)	4.8 (3.38)	4.8 (3.37)	4.8 (3.37)	–	–	–	–	–	–

Total volume of T2 lesions (mean mm^3 [SD])	16793.21 (17003.8)	15231.14 (15942.01)	14961.27 (16181.56)	16793.2 (17018.97)	16793.24 (17018.96)	16793.21 (17018.86)	–	–	–	–	–	–	–
Relapse-free in prior 2 years (proportion])	70.7%	63.83%	68.91%	70.7%	70.7%	–	–	–	–	–	–	–	–
Sex (proportion female)	62.0%	60.29%	59.05%	62.0%	–	–	–	–	–	–	–	–	–

Scenario A adjusts for all available ranked characteristics, subsequent scenarios drop the least important characteristic from adjustment.
Matched sample excludes patients >58 years, SPMS onset within pervious 2 years of enrolment, baseline EDSS <3 or >6.5, MS severity score of <4, most recent relapses within 3 months, and patients with T25FW test of >30s during screening period.
DMT, disease modifying therapy; EDSS, expanded disability status scale; Gd, gadolinium; MS, multiple sclerosis; Neff, effective sample size; SD, standard deviation; SPMS, secondary progressive multiple sclerosis.

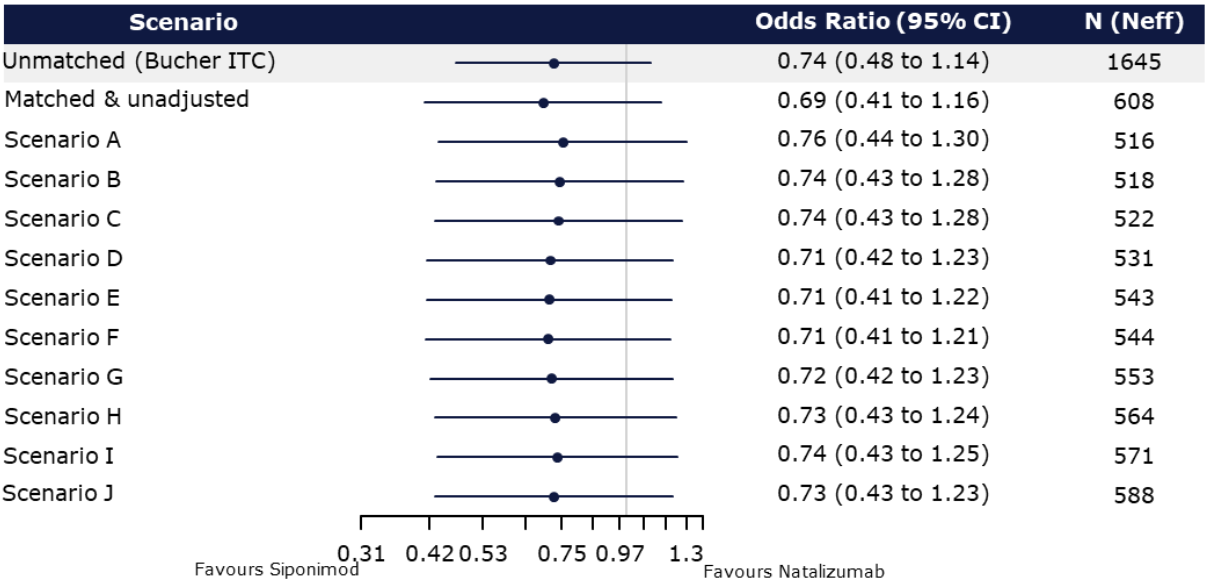
For the outcome of 6-month CDP at 96 weeks, all univariate and scenario analyses were in favour of siponimod but not statistically significant (Figure 26 and Figure 27). The fully matched-and-adjusted estimate was in favour of siponimod but the result was not statistically significant.

Figure 26: MAIC univariate adjustment results proportion of 6-month CDP at 96 weeks – Siponimod vs. natalizumab 300 mg Q4W



Matched sample excludes patients >58 years, SPMS onset within pervious 2 years of enrolment, baseline EDSS <3 or >6.5, MS severity score of <4, most recent relapses within 3 months, and patients with T25FW test of >30s during screening period.
CI, confidence interval; DMT, disease modifying therapy; EDSS, expanded disability status scale; ITC, indirect treatment comparison; MS, multiple sclerosis; Neff, effective sample size; SD, standard deviation; SPMS, secondary progressive multiple sclerosis.

Figure 27: MAIC scenario analysis results for proportion of 6-month CDP at 96 weeks – Siponimod vs. natalizumab 300 mg Q4W



Scenario A adjusts for all available ranked characteristics, subsequent scenarios drop the least important characteristic from adjustment.
Matched sample excludes patients >58 years, SPMS onset within pervious 2 years of enrolment, baseline EDSS <3 or >6.5, MS severity score of <4, most recent relapses within 3 months, and patients with T25FW test of >30s during screening period.
CI, confidence interval; ITC, indirect treatment comparison; Neff, effective sample size.

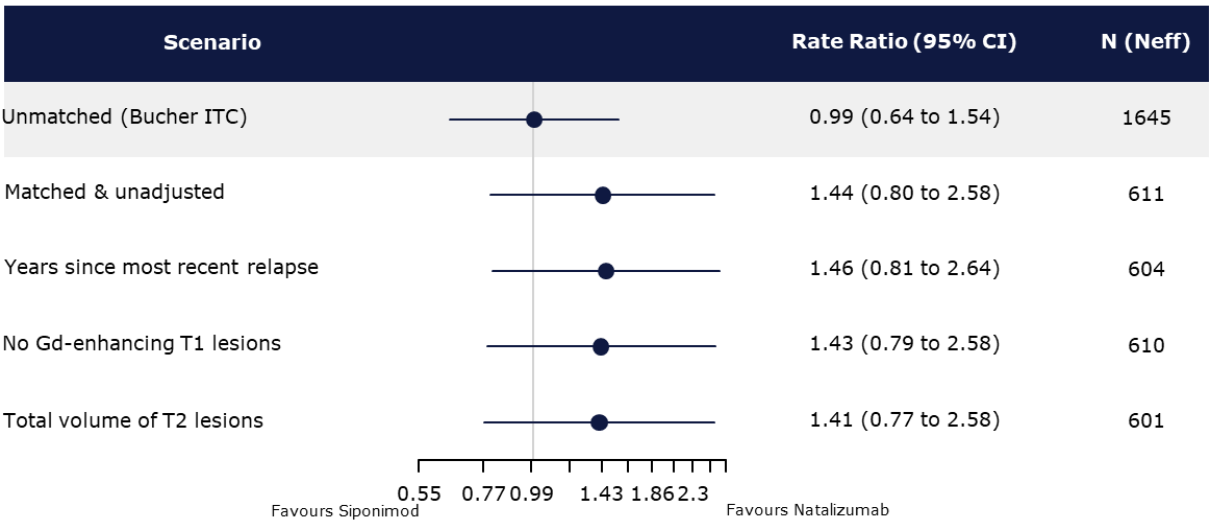
For the outcome of ARR, the matched estimate was not in favour of siponimod, although the result was not statistically significant (Figure 28).

Table 55: Results of population matching and adjustment for ARR – Siponimod vs. natalizumab 300 mg Q4W

Variables	ASCEND	EXPAND (unmatched)	EXPAND (matched and unadjusted)	Scenario A	Scenario B	Scenario C
N (Neff)	887	1551	611	594	604	604
Years since most recent relapse (mean [SD])	4.75 (4.25)	4.96 (5)	5.26 (4.76)	4.75 (4.25)	4.75 (4.25)	4.75 (4.25)
No Gd+ T1 lesions (proportion)	76.2%	77.76%	77.91%	76.2%	76.2%	–
Total volume of T2 lesions (mean mm^3 [SD])	16793.21 (17003.8)	15191.29 (15907.14)	14975.87 (16159.57)	16793.2 (17017.93)	–	–

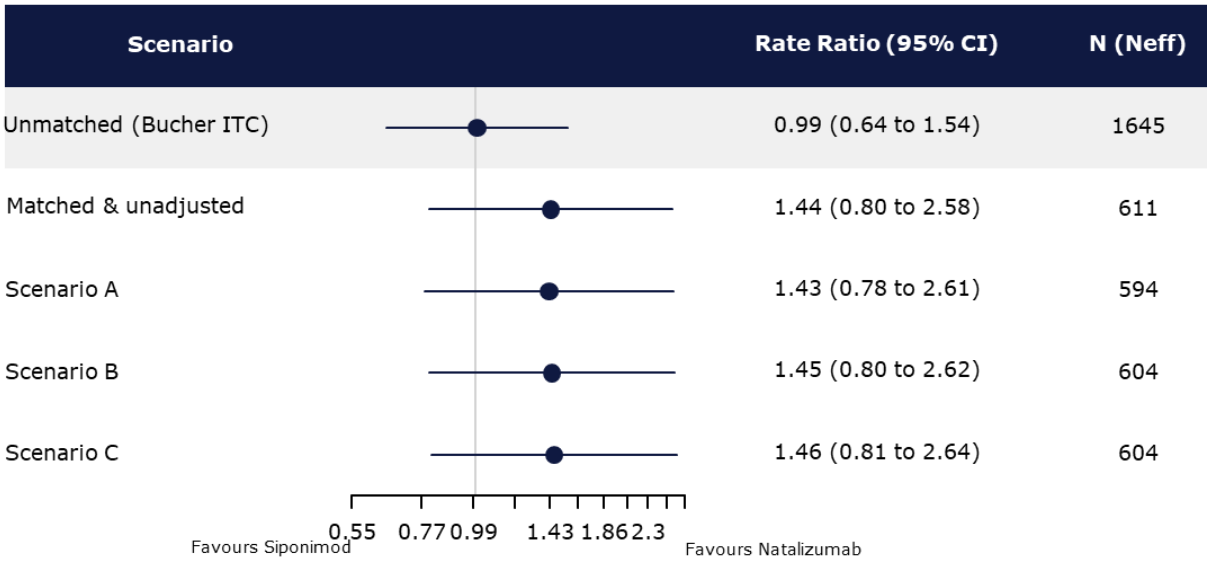
Scenario A adjusts for all available ranked characteristics, subsequent scenarios drop the least important characteristic from adjustment.
Matched sample excludes patients >58 years, SPMS onset within pervious 2 years of enrolment, baseline EDSS <3 or >6.5, MS severity score of <4, most recent relapses within 3 months, and patients with T25FW test of >30s during screening period.
Gd+, gadolinium-enhancing; Neff, effective sample size; SD, standard deviation.

Figure 28: MAIC univariate adjustment results for ARR – Siponimod vs. natalizumab 300 mg Q4W



Matched sample excludes patients >58 years, SPMS onset within pervious 2 years of enrolment, baseline EDSS <3 or >6.5, MS severity score of <4, most recent relapses within 3 months, and patients with T25FW test of >30s during screening period.
CI, confidence interval; Gd, gadolinium; ITC, indirect treatment comparison; Neff, effective sample size; SD, standard deviation.

Figure 29: MAIC scenario analysis results for ARR – Siponimod vs. natalizumab 300 mg Q4W



Scenario A adjusts for all available ranked characteristics, subsequent scenarios drop the least important characteristic from adjustment.
Matched sample excludes patients >58 years, SPMS onset within pervious 2 years of enrolment, baseline EDSS <3 or >6.5, MS severity score of <4, most recent relapses within 3 months, and patients with T25FW test of >30s during screening period.
CI, confidence interval; ITC, indirect treatment comparison; Neff, effective sample size.

Siponimod vs IFN β-1a (Avonex®) 60 µg QW

There was a significant drop in sample size as a result of matching to the comparator trial (Table 56 and Table 57). This illustrates the imbalance between these studies and patient populations that undermines the validity of summary-level ITC results and supports the need for a MAIC.

Table 56: Results of population matching and adjustment for CDP – Siponimod vs. IFN β-1a (Avonex®) QW

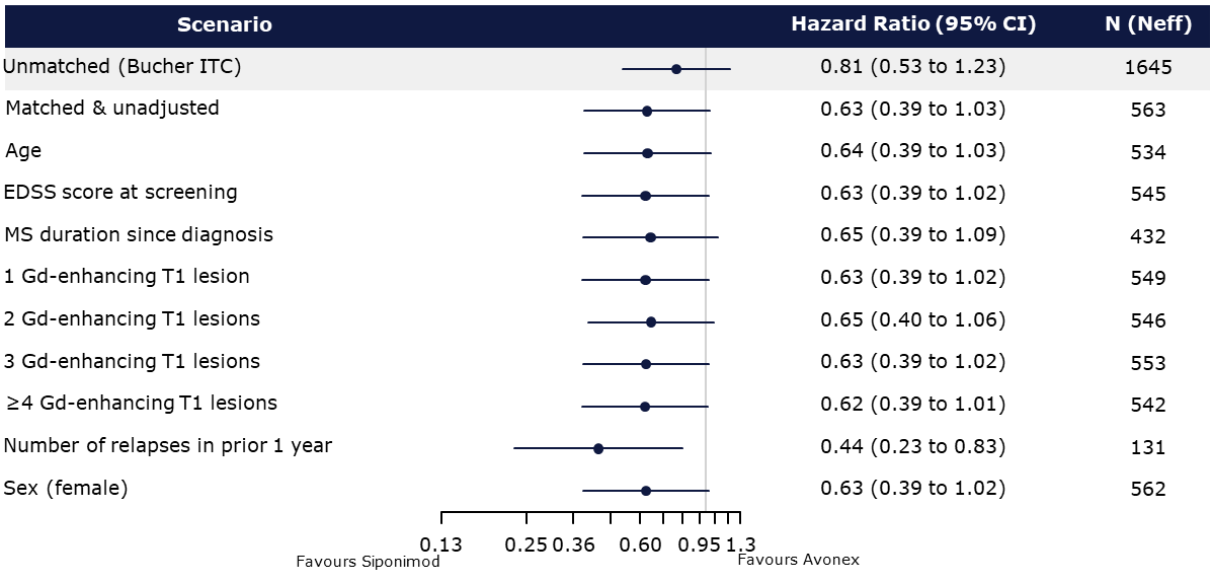
Variables	IMPACT	EXPAND (unmatched)	EXPAND (matched and unadjusted)	Scenario A	Scenario B	Scenario C	Scenario D	Scenario E	Scenario F
N (Neff)	**436**	1590	563	113	113	322	354	520	534
Age (mean years [SD])	**47.55 (7.95)**	48.05 (7.87)	49.31 (7.81)	47.55 (7.97)	47.55 (7.97)	47.55 (7.96)	47.55 (7.96)	47.55 (7.96)	47.55 (7.96)
EDSS score at screening (mean [SD])	**5.2 (1.1)**	5.41 (1.07)	5.33 (1.03)	5.2 (1.1)	5.2 (1.1)	5.2 (1.1)	5.2 (1.1)	5.2 (1.1)	–
MS duration since diagnosis (mean years [SD])	**16.45 (9)**	12.68 (7.79)	11.76 (8.57)	16.45 (9.02)	16.45 (9.02)	16.45 (9.01)	16.45 (9.01)	–	–
1 Gd-enhancing T1 lesion (proportion)	**16.5%**	10.88%	11.37%	16.5%	16.5%	16.5%	–	–	–

2 Gd-enhancing T1 lesions (proportion)	**5.8%**	3.4%	2.84%	5.8%	5.8%	5.8%	–	–	–
3 Gd-enhancing T1 lesions (proportion)	**3.6%**	2.2%	1.78%	3.6%	3.6%	3.6%	–	–	–
≥4 Gd-enhancing T1 lesions (proportion)	**10.3%**	5.47%	5.68%	10.3%	10.3%	10.3%	–	–	–
Number of relapses in prior 1 year (mean [SD])	**0.55 (1)**	0.26 (0.55)	0.26 (0.51)	0.55 (1.01)	0.55 (1.01)	–	–	–	–
Sex (proportion female)	**64%**	60.25%	61.81%	64%	–	–	–	–	–

Scenario A adjusts for all available ranked characteristics, subsequent scenarios drop the least important characteristic from adjustment.
Matched sample excludes patients >55 years old, EDSS <3 or >6.5, and those with prior IFNβ therapy.
EDSS, expanded disability status scale; Gd, gadolinium; MS, multiple sclerosis; Neff, effective sample size; SD, standard deviation.

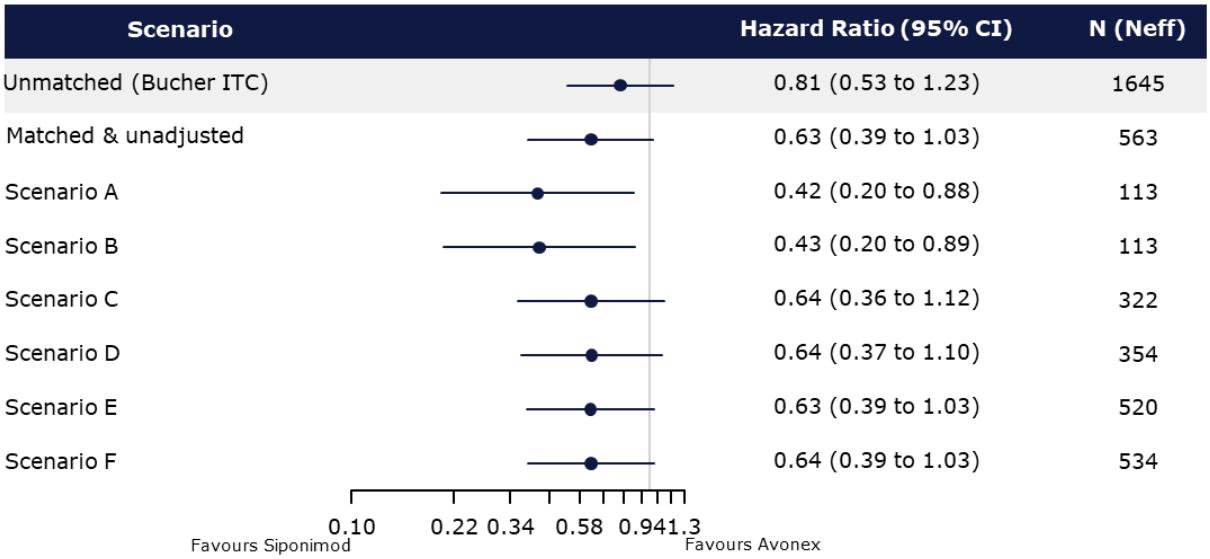
For the outcome of time to 3-month CDP, all univariate and scenario analyses were in favour of siponimod (Figure 30 and Figure 31). The fully matched-and-adjusted estimate was in favour of siponimod, and the result was statistically significant.

Figure 30: MAIC univariate adjustment results for time to 3-month CDP – Siponimod vs. IFN β-1a (Avonex®) QW



Matched sample excludes patients >55 years old, EDSS <3 or >6.5, and those with prior IFNβ therapy.
CI, confidence interval; EDSS, expanded disability status scale; Gd, gadolinium; ITC, indirect treatment comparison; MS, multiple sclerosis; Neff, effective sample size.

Figure 31: MAIC scenario analysis results for time to 3-month CDP – Siponimod vs. IFN β-1a (Avonex®) QW



Scenario A adjusts for all available ranked characteristics, subsequent scenarios drop the least important characteristic from adjustment.
CI, confidence interval; ITC, indirect treatment comparison; Neff, effective sample size; SPMS, secondary progressive multiple sclerosis.

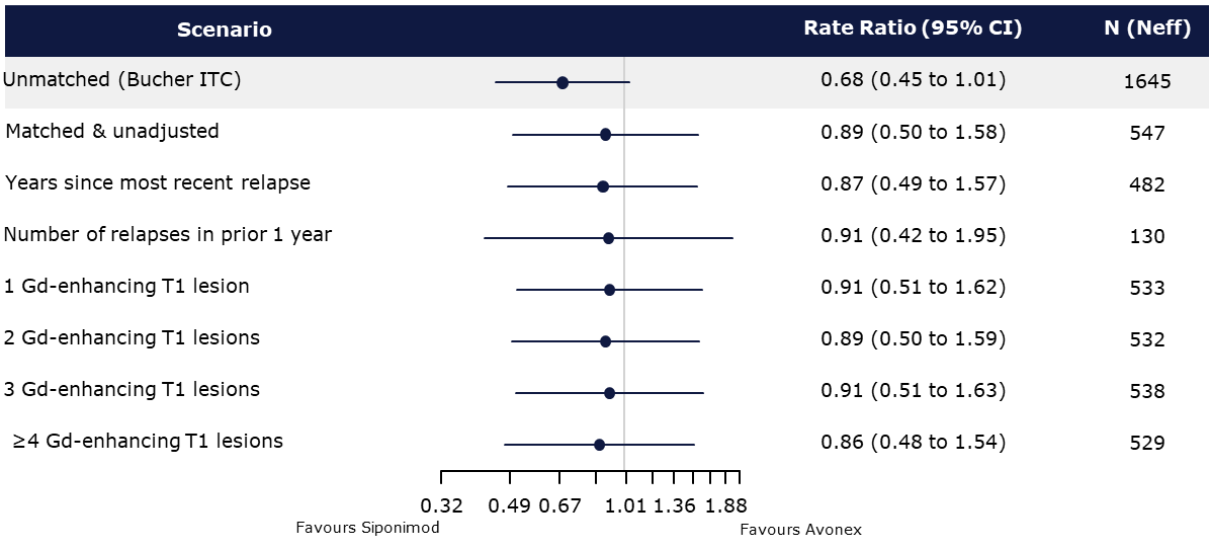
For the outcome of ARR, all univariate and scenario analyses were in favour of siponimod but were not statistically significant (Figure 32 and Figure 33). The fully matched and adjusted scenario was in favour of siponimod, but the result was not statistically significant.

Table 57: Results of population matching and adjustment for ARR – Siponimod vs. IFN β-1a (Avonex®) QW

Variables	IMPACT	EXPAND (unmatched)	EXPAND (matched and unadjusted)	Scenario A	Scenario B	Scenario C
N (Neff)	436	1550	547	119	122	482
Years since most recent relapse (mean [SD])	3.7 (5.1)	4.96 (5)	5.1 (5.55)	3.7 (5.11)	3.7 (5.11)	3.7 (5.11)
Number of relapses in prior 1 year (mean [SD])	0.55 (1)	0.27 (0.56)	0.27 (0.52)	0.55 (1.01)	0.55 (1.01)	–
1 Gd-enhancing T1 lesion (proportion)	16.5%	11.03%	11.33%	16.5%	–	–
2 Gd-enhancing T1 lesions (proportion)	5.8%	3.42%	2.93%	5.8%	–	–
3 Gd-enhancing T1 lesions (proportion)	3.6%	2.13%	1.83%	3.6%	–	–
≥4 Gd-enhancing T1 lesions (proportion)	10.3%	5.61%	5.85%	10.3%	–	–

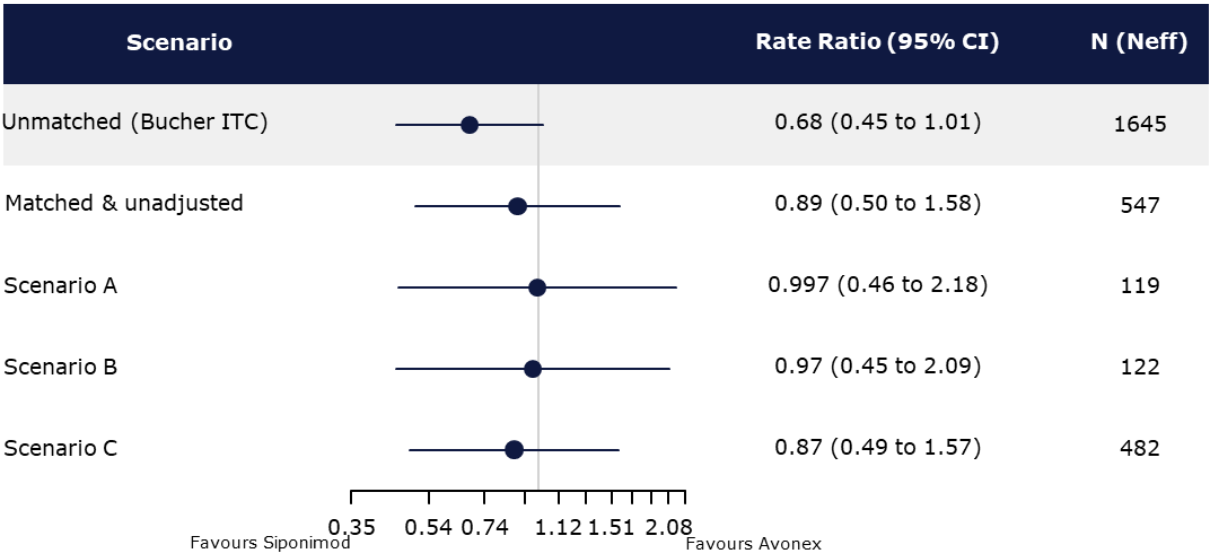
Scenario A adjusts for all available ranked characteristics, subsequent scenarios drop the least important characteristic from adjustment.
Matched sample excludes patients with baseline EDSS <3.5 or >6.5, and those with prior IFNβ therapy.
Gd, gadolinium; MS, multiple sclerosis; Neff, effective sample size; SD, standard deviation.

Figure 32: MAIC univariate adjustment results for ARR – Siponimod vs. IFN β-1a (Avonex®) QW



Matched sample excludes patients with baseline EDSS <3 or >6.5, and those with prior IFN therapy.
CI, confidence interval; Gd, gadolinium; ITC, indirect treatment comparison; Neff, effective sample size.

Figure 33: MAIC scenario analysis results for ARR – Siponimod vs. IFN β-1a (Avonex®) QW



Scenario A adjusts for all available ranked characteristics, subsequent scenarios drop the least important characteristic from adjustment.
Matched sample excludes patients with baseline EDSS <3.5 or >6.5, and those with prior IFNβ therapy.
CI, confidence interval; ITC, indirect treatment comparison; Neff, effective sample size.

MAIC Results Summary

Summaries of the results from the pairwise MAICs for CDP outcomes are presented in Table 58 , and the ARR outcome in Table 59. For transparency, these are presented alongside results from the pairwise Bucher ITC and NMA summary-level ITCs, as well as the STC that was performed as a scenario analysis; however, due to reasons previously described (Section 5.3.3), the summary-level ITC results are considered to be biased and uninterpretable given substantial heterogeneity in effect modifiers between trial populations and temporal differences between

EXPAND and the relevant comparator trials. Full results and methodology for the ITC, NMA and STC can be found in the appendix (Section 6.3.4 and 6.3.5).

Siponimod was determined to be more effective for the outcome of time to 6-month CDP, which is seen as the more relevant measure of CDP, compared with Betaferon®, and this result was statistically significant. Siponimod was numerically superior regarding the proportion of patients with 6-month CDP at 96 weeks compared with natalizumab, and the outcome of time to 3-month CDP compared with Betaferon®, Avonex®, and both regimens of Rebif® (22 or 44 µg TIW); the result for Avonex® was statistically significant.

For the outcome of ARR, siponimod was numerically but not statistically superior to Avonex®, Rebif® or Betaferon®; siponimod was numerically inferior with regards to ARR in the comparison with natalizumab, although the result was not statistically significant.

STC results were in general comparable to the MAIC results. Across all pairwise comparisons for CDP-related outcomes, siponimod demonstrated numerical favourability over the comparator of interest. Unlike the MAIC results, STC-derived ITCs did not reach statistical significance for comparisons of siponimod with Betaferon® for 6-month CDP, or Avonex® for 3-month CDP. The STCs validated that for the outcome of ARR, siponimod was numerically but not statistically superior to Avonex®, Betaferon® and Rebif®, and numerically but not statistically inferior to natalizumab.

Although MAICs and STCs are often presented as equivalent methods of estimating population-adjusted relative treatment effects, MAICs are more commonly used for health technology assessments, may be more intuitive to clinicians, and are considered more flexible for non-linear outcomes (such as ARR) and time-to-event outcomes (such as CDP).[120] For these reasons, MAICs are considered the preferred and primary method for deriving ITCs between siponimod and comparator treatments, and the MAIC results should therefore be those principally considered when evaluating the relative effectiveness of siponimod.

Table 58: Detailed MAIC Results (CDP)

Comparator Intervention	Regimen	Study ID(s)	Effect Estimate Type	Published Effect Estimates (95% CI) [c]		Bucher ITC Results (95% CI)	NMA Results (95% credible interval)	STC Results [d,e] (95% CI)	MAIC Results [e] (95% CI)	
				Comparator vs. Placebo [c]	Siponimod vs. Placebo [c]	Siponimod vs. Comparator	Siponimod vs. Comparator	Siponimod vs. Comparator	Siponimod vs. Comparator	Siponimod vs. Placebo
Time to 6-month CDP										
Betaferon® (SC IFNβ-1b)	250 µg q2d	North American Study	HR	0.92 (0.71 to 1.20) [a]	**0.74 (0.60 to 0.92)**	0.80 (0.57 to 1.12)	0.80 (0.57 to 1.13)	0.63 (0.39 to 1.01)	**0.55 (0.33 to 0.91)**	**0.50 (0.32 to 0.78)**
Proportion with 6-month CDP at 96 weeks[b]										
Tysabri® (IV Natalizumab)	300 mg q4w	ASCEND	OR	1.06 (0.74 to 1.53) [b]	**0.77 (0.61 to 0.97) [a,b]**	0.74 (0.48 to 1.14)	0.74 (0.48 to 1.14)	0.69 (0.44 to 1.09)	0.76 (0.44 to 1.30)	0.80 (0.53 to 1.21)
Time to 3-month CDP										
Avonex® (IM IFNβ-1a)	60 µg qw	IMPACT	HR	0.977 (0.68 to 1.41)	**0.79 (0.65 to 0.95)**	0.81 (0.53 to 1.23)	0.81 (0.54 to 1.22)	0.64 (0.38 to 1.08)	**0.42 (0.20 to 0.88)**	**0.41 (0.21 to 0.78)**
Betaferon® (SC IFNβ-1b)	8 MIU q2d	European Study	HR	**0.74 (0.60 to 0.91) [a]**		1.07 (0.81 to 1.41)	1.06 (0.81 to 1.41)	0.81 (0.53 to 1.23)	0.82 (0.42 to 1.63)	0.61 (0.32 to 1.16)
Rebif® (SC IFNβ-1a)	22 µg tiw	SPECTRIMS	HR	0.88 (0.69 to 1.12) [a]		0.90 (0.66 to 1.22)	0.90 (0.66 to 1.22)	0.72 (0.47 to 1.10)	0.80 (0.46 to 1.38)	0.70 (0.43 to 1.15)
Rebif® (SC IFNβ-1a)	44 µg tiw	SPECTRIMS	HR	0.83 (0.65 to 1.07)		0.95 (0.70 to 1.30)	0.95 (0.70 to 1.30)	0.76 (0.50 to 1.17)	0.84 (0.49 to 1.47)	0.70 (0.43 to 1.15)

Note: An effect size of <1 indicates that the intervention has a favourable outcome relative to the comparator or placebo. Statistically significant values are bolded.
[a]The HR and/or CI were not reported in the publication. Missing values were estimated using either the reported HR and p-value, the reported Kaplan-Meier curve through curve-fitting, or through analysis of IPD, as appropriate; [b]The proportion of patients who experienced CDP-6 by 96 weeks based on an increase in EDSS alone. For ASCEND,

this was reported in the publication. For EXPAND, the proportion of patients with this outcome was calculated using the IPD, based on a conservative assumption that all patients censored at or before 96 weeks had experienced a CDP-6 event; [c]Extracted or derived from the EXPAND or comparator publication(s); [d];Prior interferon beta is modelled as an effect modifier; [e]The target population is that of the comparator trial.
CDP, confirmed disability progression; CI, confidence interval; HR, hazard ratio; IFNβ, interferon beta; IM, intramuscular; IPD, individual patient data; ITC, indirect treatment comparison; IV, intravenous; MAIC, matching-adjusted indirect comparison; mg, milligram; n/a, not applicable; OR, odds ratio; PBO, placebo; PO, oral; qd, once daily; q2d, once every other day; qw, once weekly; q4w, once every four weeks; RR, rate ratio; SC, subcutaneous; tiw, three times weekly; µg, microgram.

Table 59: Detailed MAIC Results (ARR)

Comparator Intervention	Regimen	Study ID(s)	Effect Estimate Type	Published Effect Estimates (95% CI) [a]		Bucher ITC Results (95% CI)	NMA Results (95% credible interval)	STC Results [b,f] (95% CI)	MAIC Results [b] (95% CI)	
				Comparator vs. Placebo [a]	Siponimod vs. Placebo [a]	Siponimod vs. Comparator	Siponimod vs. Comparator	Siponimod vs. Comparator	Siponimod vs. Comparator	Siponimod vs. Placebo
Betaferon® (SC IFNβ-1b)	250 µg q2d	North American Study European Study [d]	RR	**0.65 (0.48 to 0.88)**	**0.45 (0.34 to 0.59)**	0.69 (0.46 to 1.04)	0.69 (0.46 to 1.04)	0.89 (0.50 to 1.56)	0.90 (0.51 to 1.59) [e]	**0.59 (0.36 to 0.95)** [e]
Tysabri® (IV Natalizumab)	300 mg q4w	ASCEND	RR	**0.453 (0.323 to 0.634)**		0.99 (0.64 to 1.54)	0.99 (0.64 to 1.53)	1.11 (0.69 to 1.78)	1.43 (0.78 to 2.61)	0.65 (0.39 to 1.06)
Avonex® (IM IFNβ-1a)	60 µg qw	IMPACT	RR	**0.67 (0.49 to 0.90)** [c]		0.68 (0.45 to 1.01)	0.67 (0.45 to 1.01)	0.93 (0.52 to 1.66)	0.997 (0.46 to 2.18)	0.67 (0.33 to 1.37)
Rebif® (SC IFNβ-1a)	22 µg tiw	SPECTRIMS	RR	**0.69 (0.56 to 0.84)**		**0.65 (0.46 to 0.92)**	**0.65 (0.46 to 0.92)**	0.83 (0.49 to 1.40)	0.73 (0.40 to 1.31)	0.50 (0.29 to 0.87)
Rebif® (SC IFNβ-1a)	44 µg tiw	SPECTRIMS	RR	**0.69 (0.56 to 0.85)**		**0.65 (0.46 to 0.92)**	**0.65 (0.46 to 0.92)**	0.83 (0.49 to 1.40)	0.73 (0.40 to 1.32)	0.50 (0.29 to 0.87)

Note: An effect size of <1 indicates that the intervention has a favourable outcome relative to the comparator or placebo. Statistically significant values are bolded.
[a]Extracted or derived from the EXPAND or comparator publication(s); [b]The target population is that of the comparator trial; [c]Error was calculated from the reported RR and p-value; [d]Error has been estimated using the CI from the North American Study 160 µg/m^2 treatment arm which has a similar effect size and sample size. The Handling Continuous Outcomes in Quantitative Synthesis (Fu et al., 2013) guide recommends that studies only missing error should not be excluded as this can lead to a biased combined estimate; [e]Matched only (could not adjust); [f]Prior interferon beta is modelled as an effect modifier.
ARR, annualised relapse rate; CI = confidence interval; HR, hazard ratio; IFNβ, interferon beta; IM, intramuscular; IPD, individual patient data; ITC, indirect treatment comparison; IV, intravenous; MAIC, matching-adjusted indirect comparison; mg, milligram; n/a, not applicable; OR, odds ratio; PBO, placebo; PO, oral; qd, once daily; q2d, once every other day; qw,once weekly; q4w, once every four weeks; RR, rate ratio; SC, subcutaneous; tiw, three times weekly; µg, microgram.

Conclusions of the MAICs

Given the imbalance observed and presence of effect modifiers between EXPAND and the comparator trials, MAICs allow for the best use of all the efficacy data available in SPMS, in a fair and adjusted comparison.

Matching the EXPAND IPD to comparator trials reduced the effective sample size, depending on criteria of the trial(s) available for each DMT. This illustrates the magnitude of dissimilarity between the included/excluded patients of each trial relative to EXPAND, which underscores the inadequacy of an unadjusted summary-level ITC methods for comparing these heterogeneous trials.

Despite the reduction in sample size, siponimod demonstrated numerical or statistical superiority for all CDP-related outcomes. In particular, siponimod was determined to be more effective for the outcome of time to 6-month CDP, which is seen as the more relevant measure of CDP, compared with Betaferon®, and this result was statistically significant. Siponimod was numerically superior regarding the proportion of patients with 6-month CDP at 96 weeks compared with natalizumab, and the outcome of time to 3-month CDP compared with Betaferon®, Avonex®, and both regimens of Rebif® (22 or 44 µg TIW); the result for Avonex® was statistically significant.

For the outcome of ARR, siponimod was numerically but not statistically superior to Avonex®, Rebif® or Betaferon®; siponimod was numerically inferior with regards to ARR in the comparison with natalizumab, although the result was not statistically significant.

The STC method validates the MAICs by producing comparable results. Similar to the MAIC results, the STCs showed siponimod to be numerically superior for all CDP-related outcomes. Unlike the MAIC results, the STC did not reach statistical significance for comparisons of siponimod with Betaferon® for 6-month CDP, or Avonex® for 3-month CDP. The STC results for the outcome of ARR are similar in that, siponimod was numerically but not statistically superior to Avonex®, Betaferon® and Rebif®, and numerically but not statistically inferior to natalizumab. Although MAICs and STCs are often presented as equivalent methods of estimating population-adjusted relative treatment effects, MAICs are more commonly used for health technology assessments, may be more intuitive to clinicians, and are considered more flexible for non-linear outcomes (such as ARR) and time-to-event outcomes (such as CDP).[120] For these reasons, MAICs are considered the preferred and primary method for deriving ITCs between siponimod and comparator treatments

Generalisability of the MAIC results to active SPMS subgroup

Although a separate MAIC in the active SPMS subgroup itself is infeasible (see Section 5.3.4), the results of the matching and adjusting process show that the base case comparison to interferon β-1b is selective for a more active subset of the EXPAND trial: average age and baseline EDSS are lowered, the proportion of patients experiencing relapses in the two years prior to the trial is increased, as is the average number of relapses per patients in the two years prior to the trial. Therefore, although the extrapolation of the MAIC results to the active SPMS subgroup has inherent limitations, it remains preferable to an unadjusted naïve comparison of subgroup data between two trials which are known to differ in many respects.

5.4 Individual study results (safety outcomes)

1. Describe the relevant endpoints, including the definition of the endpoint and methods of analysis (Table 60).

The relevant endpoints for safety outcomes considered in this submission are presented in Table 60, Table 61, Table 62 and Table 63.

Table 60: Methods of data collection and analysis of adverse events

Study reference/ID	Endpoint definition	Method of analysis
EXPAND	Any AE that started on or after the first dose of study medication.	Graded using the Common Terminology Criteria for Adverse Events (CTCAE). The frequency of TEAEs was summarised by primary system organ class and preferred term. TEAEs were also summarised by Standardised MedDRA Query (SMQ) Level 1 and preferred term.
SPECTRIMS	NR	NR
North American	NR	NR
European	NR	NR
ASCEND	NR	NR
IMPACT	NR	NR

Table 61: Methods of data collection and analysis of serious adverse events

Study reference/ID	Endpoint definition	Method of analysis
EXPAND	Any Grade 3 or above AE that started on or after the first dose of study medication.	Graded using the Common Terminology Criteria for Adverse Events (CTCAE). The frequency of SAEs was summarised by primary system organ class and preferred term. SAEs were also summarised by Standardised MedDRA Query (SMQ) Level 1 and preferred term.
SPECTRIMS	NR	NR
North American	NR	NR
European	NR	NR
ASCEND	NR	NR
IMPACT	NR	NR

Table 62: Methods of data collection and analysis of adverse events leading to treatment discontinuation

Study reference/ID	Endpoint definition	Method of analysis
EXPAND	Discontinuation of study medication due to emergence of certain adverse events, such as malignancy (except successfully treated basal	For patients who discontinued study medication, remained in the study, and either switched to open-label siponimod or continued according to the abbreviated visit schedule, an EOT visit was conducted when they stopped taking double-blind study medication. These patients also completed

	cell carcinoma), liver failure or, serious chronic infection (such as HIV).	the EOS visit either when they completed the Core Part or if they withdrew prematurely. A follow-up visit, 1 month after the EOS visit, was completed for patients who received open-label siponimod treatment. No follow-up visit was required after the EOS visit for patients on the abbreviated visit schedule. Patients who discontinued study medication prematurely and did not either begin open-label siponimod treatment or continue participation per the abbreviated schedule were to complete an EOS visit and a follow-up visit 1 month after their EOS visit, otherwise, these patients were considered lost to follow-up. Patients who did not return for a required follow-up visit were also considered lost to follow-up. Patients who prematurely withdrew from the study were not replaced by an equal number of newly enrolled patients.
SPECTRIMS	NR	NR
North American	NR	NR
European	NR	NR
ASCEND	NR	NR
IMPACT	NR	NR

Table 63: Methods of data collection and analysis of treatment-related mortality

Study reference/ID	**Endpoint definition**	**Method of analysis**
EXPAND	Deaths deemed to be treatment-related.	Summary data were provided for deaths. Two different analyses were performed: the main one included all events, regardless of safety cut off, and the secondary one only included and deaths up to and including safety cut off.
SPECTRIMS	NR	NR
North American	NR	NR
European	NR	NR
ASCEND	NR	NR
IMPACT	NR	NR

2. For the technology, and the comparator, tabulate the total number of adverse events, frequency of occurrence (as a %), absolute and relative risk and 95% CI reported in each of the clinical studies. Categorise the adverse events by frequency, severity and system organ class.

An overview of the data available for adverse events is presented in Table 64, with more detailed adverse events presented in Table 65. Due to limitations in the extent of safety data reported for each study, the absolute and relative risk are unable to be presented, and there is insufficient data to present adverse events by severity, system class and frequency of adverse events.

Additional safety data that is available for the EXPAND ITT is presented in Appendix B (Section 6.2.3).

Table 64: Overview of adverse events

	EXPAND		SPECTRIMS			European Study		North American Study		ASCEND		IMPACT	
	Siponimod (n = 1099) n (%)	Placebo (n = 546) n (%)	Interferon β-1a 22 µg (n = 209) n (%)	Interferon β-1a 44 µg (n = 204) n (%)	Placebo (n = 205) n (%)	Interferon β-1b (250 µg) (n = 360) n (%)	Placebo (n = 358) n (%)	Interferon β-1b 250 µg/m2 (n = 317) n (%)	Placebo (n = 308) n (%)	Natalizumab (n = 439) n (%)	Placebo (n = 440) n (%)	IFN β-1a 60 µg (n = 217) n (%)	Placebo (n = 218) n (%)
Total number of adverse events	975 (88.7)	445 (81.5)	NR	NR	NR	NR	NR	NR	NR	401 (91.3)	410 (93.2)	215 (99.1)	215 (98.6)
Total number of serious adverse events	197 (17.9)	83 (15.2)	NR	NR	NR	NR	NR	NR	NR	90 (20.5)	100 (22.3)	NR	NR
Total number of deaths	4 (0.4)	4 (0.7)	1 (0.5)	2 (1.0)	2 (1.0)	3 (0.8)	1 (0.3)	4 (1.3)	1 (0.3)	2 (0.5)	0 (0)	2 (0.9)	0 (0)
Total number of adverse events leading to temporary or permanent treatment withdrawal	160 (14.5)	44 (8.1)	NR	NR	NR	5 (1.4)	4 (1.1)	30 (9.5)	12 (3.9)	NR	NR	NR	NR
Total number of withdrawals from the study because of adverse events	84 (7.6)	28 (5.1)	NR	NR	NR	NR	NR	NR	NR	21 (4.8)	21 (4.8)	13 (6.0)	8 (3.6)

Source: Kappos et al., 2018;[24] SPECTRIMS study group, 2001;[103] Panitch et al., 2004;[118] European Study Group, 1998;[113] Kapoor et al, 2018;[42] Cohen et al., 2002.[104]

Table 65: Detailed adverse events

	EXPAND		SPECTRIMS			European Study		North American Study		ASCEND		IMPACT	
	Siponimod (n = 1099) n (%)	Placebo (n = 546) n (%)	Interferon β-1a 22 µg (n = 209) n (%)	Interferon β-1a 44 µg (n = 204) n (%)	Placebo (n = 205) n (%)	Interferon β-1b (250 µg) (n = 360) n (%)	Placebo (n = 358) n (%)	Interferon β-1b 250 µg/m2 (n = 317) n (%)	Placebo (n = 308) n (%)	Natalizumab (n = 439) n (%)	Placebo (n = 440) n (%)	Interferon β-1a 60 µg (n = 217) n (%)	Placebo (n = 218) n (%)
Arthralgia, %	4.5	6.4	NR	NR	NR	NR	NR	NR	NR	9.8	9.1	24.0	19.7
Back pain, %	6.1	7.9	NR	NR	NR	NR	NR	NR	NR	10.5	11.6	19.4	24.3
Chills, %	4.5	5.5	NR	NR	NR	21.9	7.3	22.1	11.7	NR	NR	NR	NR
Depression, %	11.6	10.8	32.0	35.0	29.0	NR	NR	NR	NR	19.8	19.5	NR	NR
Fever, %	9.1	9.3	NR	NR	NR	NR	NR	NR	NR	13.4	12.0	NR	NR
Flu-like symptoms, %	NR	NR	51.0	50.0	52.0	NR	NR	13.6	10.7	NR	NR	NR	NR
Flu syndrome, %	14.5	13.0	NR	NR	NR	59.2	37.2	NR	NR	15.0	11.4	69.6	33.0
Headache, %	10.5	7.5	NR	NR	NR	NR	NR	17.4	14.9	NR	NR	48.8	49.1
Hypertension, %	0.2	1.3	NR	NR	NR	3.9	0.8	NR	NR	16.6	27.7	NR	NR
Injection site inflammation, %	NR	NR	NR	NR	NR	50.0	4.2	15.8	1.9	6.4	8.9	NR	NR
Injection site reaction, %	5.5	3.8	NR	NR	NR	43.61	10.34	16.40	4.55	9.6	9.5	NR	NR
Injection site necrosis, %	6.7	3.5	3.3	8.8	0.0	4.7	0.0	NR	NR	NR	NR	NR	NR
MS relapse, %	13.6	14.5	NR	NR	NR	NR	NR	NR	NR	22.3	16.6	28.1	38.1
Muscular weakness, %	0.8	0.0	NR	NR	NR	NR	NR	NR	NR	NR	NR	50.2	44.0
Lymphopenia, %	8.3	7.5	22.0	26.0	15.0	NR	NR	NR	NR	10.9	6.8	NR	NR

	EXPAND		SPECTRIMS			European Study		North American Study		ASCEND		IMPACT	
	Siponimod (n = 1099) n (%)	**Placebo (n = 546) n (%)**	**Interferon β-1a 22 µg (n = 209) n (%)**	**Interferon β-1a 44 µg (n = 204) n (%)**	**Placebo (n = 205) n (%)**	**Interferon β-1b (250 µg) (n = 360) n (%)**	**Placebo (n = 358) n (%)**	**Interferon β-1b 250 µg/m2 (n = 317) n (%)**	**Placebo (n = 308) n (%)**	**Natalizumab (n = 439) n (%)**	**Placebo (n = 440) n (%)**	**Interferon β-1a 60 µg (n = 217) n (%)**	**Placebo (n = 218) n (%)**
Urinary tract infection, %	12.1	14.7	NR	NR	NR	NR	NR	NR	NR	23.2	24.3	24.9	20.6

Source: Kappos et al., 2018;[24] SPECTRIMS study group, 2001;[103] Panitch et al., 2004;[118] European Study Group, 1998;[113] Kapoor et al, 2018;[42] Cohen et al., 2002.[104]

5.5 Conclusions

1. Provide a general interpretation of the evidence base considering the benefits associated with the technology relative to those of the comparators.

In comparison to placebo, siponimod provided clinically meaningful improvements in delaying the time to 3-month and 6-month CDP in patients with SPMS, with greater efficacy observed in the active SPMS subgroup.

Results from EXPAND, the largest RCT in a representative population of participants with SPMS, showed that siponimod delayed disability progression and improved both relapse and MRI outcomes versus placebo; in a *post hoc* subgroup analysis in patients with active SPMS the benefit in delayed disability progression was found to be even greater. Based on these results it is hypothesised that siponimod has an effect on both the inflammatory and the neurodegenerative components of SPMS.

Importantly, siponimod significantly reduced the risk of 3-month CDP versus placebo by 32% in patients with active SPMS, and alsofor 6-month CDP (35.8% risk reduction), which is a more robust measure of disability progression. In patients with SPMS who have moderate-to-high levels of disability, as was the case in EXPAND, even small changes in EDSS score can correspond to substantial changes in physical and neurological functioning and daily activities and results in fewer patients who require assistance to walking or wheelchairs.

Across the whole EXPAND population, significant improvements in relapse outcomes and MRI outcomes, including brain volume loss, and patient-reported cognitive processing speed (as measured by SDMT) were also observed with siponimod versus placebo. Statistical analyses in EXPAND showed that siponimod had a positive effect across patient subgroups, although the study was not powered to measure statistical significance in the subgroups and therefore sample sizes were not always large enough for trends to reach statistical significance.

Ultimately, siponimod will be the first treatment to combine convenient oral administration with proven efficacy in reducing disability progression in the overall population of patients with active SPMS, for whom there are currently no effective treatment options that can slow progression of irreversible disability.

The results of the matched adjusted indirect treatment comparison support that siponimod is of benefit in treating patients with SPMS in comparison to interferons and natalizumab

An exploratory unadjusted pairwise Bucher ITC was conducted in the relapsing SPMS population, which demonstrated that siponimod achieves numerically superior 3-month CDP. However, this analysis is subject to a number of limitations due to substantial between-trial heterogeneity in patient populations that confer measurable differences in baseline risk. This heterogeneity undermines and potentially biases the clinical validity of the results. As a result, it is recommended that the assessment of relative effectiveness in the active SPMS population is informed by the MAICs conducted in the overall SPMS population. This is not anticipated to bias the results in favour of siponimod, because the efficacy of siponimod in the active subgroup has been shown to be stronger compared to the ITT population in the EXPAND study, ergo an ITC based on the ITT population of EXPAND is in fact conservative regarding the benefits of siponimod. As described above, the results from the MAICs are thought to be generalisable to

the active SPMS sub-population because the matching and adjustment process results in a population more similar to the more highly relapsing comparator population.

Pairwise MAICs were conducted to evaluate the efficacy of siponimod in disability and relapse outcomes compared to several relevant comparators. This included IFNβ-1b (Extavia/Betaferon®), which is the only DMT indicated for the treatment of people with active SPMS, evidenced by relapses (in the EU/EEA). Compared with IFNβ-1b (Extavia®/Betaferon®), siponimod was statistically significantly more efficacious in increasing the time to 6-month CDP and also numerically increased the time to 3-month CDP and reduced relapse rates.

Compared with the other IFNs, IM IFNβ-1a (Avonex®) or SC IFNβ-1a (Rebif®), siponimod numerically increased the time to 3-month CDP and numerically reduced relapse rates. These results were statistically significant for the comparison of 3-month CDP with Avonex®, and for the comparison of ARR with Rebif®. Siponimod also demonstrated numerical superiority compared with natalizumab for 6-month CDP but was not superior for ARR. It is important to note that the consistent superiority of siponimod versus relevant therapies compares favourably to previous assessments of relative effectiveness of DMTs in patients with RRMS or mixed patient populations, where inconsistent results have been observed.[123-125] A lack of appropriate comparator data, possibly due to temporal differences influencing trial design and outcomes considered in the ITT population, prevented demonstration of the comparative superiority of siponimod on other endpoints beyond 6-month CDP and ARR. However, CDP and ARR are highly clinically relevant for patients, as well as representing the most relevant outcomes for economic modelling; the lack of comparative data should therefore not detract from the evident added therapeutic value of siponimod.

The greater comparative effectiveness of siponimod on disability progression compared to that with relevant comparators is a significant finding. This is due to the fact that SPMS is a progressive disease, in which patients experience irreversible worsening of disability, irrespective of relapses. In particular, 6-month CDP is a robust measure of sustained disability progression that is endorsed by the EMA.[119, 126] However, to date, no approved treatments have safely slowed disability progression in patients with SPMS, which represents a clear unmet need. Siponimod addresses this unmet need owing to its superior effectiveness in slowing disability progression compared with IFNβ-1b (Extavia®/Betaferon®), and the numerically superior results compared with other relevant comparators; these are important findings in a progressive disease such as SPMS.

2. Provide a general interpretation of the evidence base considering the harms associated with the technology relative to those of the comparators.

EXPAND demonstrated that siponimod is associated with a manageable safety profile

In EXPAND, siponimod was generally well tolerated for up to 3 years and had a safety profile that was generally consistent with those of other S1P receptor modulators with no unexpected safety signals. Rates of herpes zoster infections, macular oedema, hypertension, convulsions and elevated liver enzyme levels, which have been reported in the patients with MS in the context of S1P receptor modulation, all occurred at a slightly higher frequency in the siponimod group versus the placebo group. Cardiac disorders during treatment initiation (days 1–15) also occurred at a slightly higher frequency in the siponimod group versus the placebo group, but were largely mitigated by titration of initial doses as compared with experience in the phase 2 trial in which siponimod was not titrated. The proportions of participants experiencing other AEs that occurred with a high frequency were similar between the groups. The results from EXPAND are

supported by a recent pooled analysis of data from the EXPAND and BOLD, a Phase 2 study of siponimod in RRMS, which revealed that there was no increase in incidence of AEs during long-term follow up and no new safety concerns were identified.[127]

5.6 Strengths and limitations

1. Summarise the internal validity of the evidence base, taking into account the study quality, the validity of the endpoints used as well as the overall level of evidence. Include a statement about the consistency of the results in the evidence base.

Internal validity of EXPAND

The EXPAND trial was methodologically robust and well reported. The results were considered to be at low risk of bias:

- EXPAND was a large, well designed, Phase 3 RCT, the preferred standard for clinical evidence.
- Participants were appropriately randomised using an IWRS, treatment allocation was concealed, and participants and care providers were blinded
- The sample size was sufficient to detect a difference in the primary objective of time to three-month CDP between the two treatment groups
- Participant flow through the study was well reported, and there were no meaningful differences in the rates of treatment discontinuation between treatment arms
- All randomised patients were included in the efficacy analyses, thereby maintaining the principle of ITT analysis and preserving randomisation
- CDP is the preferred endpoint for disability progression by the Committee for Medicinal Products for Human Use;[119, 126] EXPAND measured and reported both 3- and 6-month CDP.
- EDSS was measured by an Independent Rater every 3 months, to reduce potential bias of an investigator assessment

Strengths and limitations of the indirect treatment comparison

There has been no direct comparison of efficacy and safety between siponimod and the relevant comparators in a clinical trial setting, necessitating an indirect comparison to be performed. Due to population differences, high levels of heterogeneity, and an imbalance in treatment effect modifiers between trial populations, results from summary-level ITCs were deemed unreliable and biased, and MAICs were therefore performed instead.

A strength of the present MAIC analyses is that it leveraged IPD from EXPAND in order to adjust for clinically important differences with comparator trials. Of note, there was a large reduction in the effective sample size when aligning EXPAND with comparator trials according to characteristics that were important effect modifiers. This demonstrates the magnitude of heterogeneity in patient characteristics between the trials and highlights the unsuitability of an unadjusted ITC (such as the Bucher method) or an unadjusted network meta-analysis (NMA).

MAICs therefore ensured that a more robust comparison of the relative effectiveness of therapies in patients with SPMS could be made and resulted in more clinically valid estimates of comparative effectiveness than would have been possible with unadjusted ITCs or NMAs. Limitations of the present analyses include the fact that variables reported by only one study and unobserved in other studies could not be controlled via MAICs. The was validated through an STC sensitivity analysis, which produced comparable results.

Whilst a MAIC was not possible in the active SPMS subgroup, the results of the MAICs in the ITT population were determined to be generalisable to active SPMS.

2. Provide a brief statement of the relevance of the evidence base to the scope of the assessment.

Population

Adult patients with SPMS, classified as active, evidenced by clinical and imaging features characteristic of inflammatory activity

Whilst baseline characteristics reported for EXPAND facilitate division of the overall SPMS population into ‘active’ and ‘non-active’ at baseline, no data were not available for the comparator treatments considered in the submission to permit a robust treatment comparison in this sub-population. However, results from EXPAND showed that siponimod is more efficacious versus placebo in the active SPMS subgroup than in the ITT population, therefore MAICs concerning the ITT population of EXPAND should be an appropriate measure of relative effectiveness in the active SPMS population; importantly, this result would be a conservative estimate of the relative effectiveness of siponimod in the active SPMS population.

Intervention

Siponimod was directly evaluated as a treatment option for patients with active SPMS, by comparing siponimod to placebo.

Comparators

No direct evidence is available for siponimod versus any of the active comparators specified in the scope of the submission, and clinical trial evidence for the efficacy in an SPMS population is not available for all treatments specified. The current submission has presented an indirect comparison, in the form of a MAIC, for those treatments with sufficient data available; this included interferon β-1b and -1a and natalizumab. As a MAIC was not considered feasible in the active SPMS population, an exploratory unadjusted Bucher ITC was performed; however, the limitations of this analysis undermine the clinical validity of the results and the MAIC conducted in the ITT population should be the principal analysis considered when evaluating the relative effectiveness of siponimod in active SPMS patients.

Outcomes

The Project Plan for this submission specified a broad range of outcomes and, where available, detailed data for these outcomes have been presented for EXPAND. However, some outcomes were not reported in EXPAND. For example, long term mortality benefit was not reported by EXPAND, as short-term clinical trials are not designed to demonstrate mortality differences in a life-long disease.

For trials of the comparators, and in the MAIC, three outcomes were presented (time to both 3-month and 6-month CDP, and ARR). These are the most relevant to economic analyses, in addition to providing valuable clinical insights. In particular, time to 3- and 6-month CDP are particularly valuable endpoints for SPMS as there are currently no treatment options available to SPMS patients that slow down disability progression. Furthermore, given the heterogeneity in the trial outcomes reported, it would not have been possible to perform comparisons for some of the outcomes specified.

Conclusions

The quality of the evidence provided by the EXPAND study is supported by robust and well-reported methodology, and the evidence presented is both highly relevant to the submission and directly relevant to the treatment of patients with active SPMS.

Siponimod has been shown to significantly improve the time to both 3-month and 6-month CDP compared with placebo in patients with active SPMS, with a tolerable safety profile allowing for continued treatment. Combined with additional improvements in MRI measures and reductions in relapse rates, siponimod provides patients with a significant improvement in both disease and disability progression, particularly as there are currently no treatment options for these patients that have been demonstrated to significantly slow disability progression in a typical SPMS population. Furthermore, the relative effectiveness of siponimod has been demonstrated, with the results of the MAICs consistently favouring siponimod to comparators in terms of disability progression outcomes in their respective SPMS trial populations. Only one comparator study (of interferon β-1b), which considered a very different study population, showed any statistically significant effect on the primary endpoint of disability progression, and this effect was not replicated in other trials in SPMS populations of the same compound.

Patients with active SPMS currently have no effective treatment options available and suffer high disease burden; whilst interferon β-1b is licensed to patients with SPMS which active disease (evidenced by relapses), this therapy has not demonstrated a consistent treatment effect on disability.[102, 103] Siponimod offers a significant therapeutic advance that can slow disease progression in active SPMS.

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6 Appendices

6.1 Appendix A: SLR search strategy

Table 66: Original SLR search strategy for MEDLINE Daily, MEDINE Epub Ahead of Print and Embase (via the Embase.com platform)

#	Search terms	Results (17 Oct 2018)
1	'clinical trial'/exp	1345882
2	'randomized controlled trial'/de	517372
3	'controlled clinical trial'/de	425520
4	'phase 3 clinical trial'/de OR 'phase 2 clinical trial'/de OR 'phase 4 clinical trial'/de	100668
5	'randomization'/de	79396
6	'controlled study'/de	6218674
7	'comparative study'/de	798287
8	'single blind procedure'/de	32716
9	'double blind procedure'/de	153716
10	'crossover procedure'/de	56647
11	'placebo'/de OR placebo*	425712
12	'clinical trial' OR 'clinical trials'	1602219
13	'controlled clinical trial' OR 'controlled clinical trials'	455473
14	'randomised controlled trial' OR 'randomized controlled trial' OR 'randomised controlled trials' OR 'randomized controlled trials'	712824
15	'randomisation' OR 'randomization'	108016
16	rct	33678
17	'random allocation' OR 'randomly allocated' OR 'allocated randomly'	34969
18	(allocated NEAR/2 random) OR (random* NEAR/1 assign*) OR random*	1537665
19	'prospective study'/exp	474810
20	(single OR double OR triple OR treble) NEAR/1 (blind* OR mask*)	278882
21	'cohort analysis'/exp OR cohort*:ab,ti	867753
22	'longitudinal study'/exp	116645
23	'multicenter study'/exp	195181
24	'follow up'/exp	1329917
25	'major clinical study'/exp	3226481
26	'case control study'/exp OR ((case* NEXT/1 control*):ab,ti)	203902
27	'clinical article'/exp	1992135
28	'survival'/exp	959174
29	(('follow up' OR followup) NEXT/1 (study OR studies)):ab,ti	61254
30	(clinical NEXT/1 trial*):ab,ti	445389
31	'retrospective study'/exp	696404
32	'case control study'/exp	147938
33	((observational OR cohort) NEXT/1 (study OR studies)):ab,ti	357510
34	'intervention study'/exp	37569
35	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34	12418906
36	'case study'/de	56388
37	'case report'	2397493
38	'abstract report'/de	89742
39	'letter'/de	979638
40	#36 OR #37 OR #38 OR #39	3316731
41	#35 NOT #40	11835569
42	((((disseminated OR insular OR multiple) NEAR/4 sclerosis):ab,ti) OR ms:ab,ti) AND ('secondary progressive':ab,ti OR progressive:ab,ti OR 'non-relapsing':ab,ti)	16343

#	Search terms	Results (17 Oct 2018)
43	('secondary progressive' OR 'secondary-progressive' OR progressive OR secondary OR deteriorat* OR 'non relapsing' OR 'non relapsing') NEAR/3 (ms OR 'multiple sclerosis' OR 'disseminated sclerosis' OR 'encephalomyelitis disseminata' OR 'chariot disease' OR 'insular sclerosis')	8713
44	spms OR cpms	3148
45	'progressive secondary multiple sclerosis' OR 'secondary progressive multiple sclerosis'	1082
46	#42 OR #43 OR #44 OR #45	18747
47	'disease modifying therapies':ab,ti OR dmt*:ab,ti OR 'disease modifying therapy':ab,ti OR 'disease modifying drugs':ab,ti OR 'disease modifying drug':ab,ti OR dmd*:ab,ti	24552
48	'glatiramer'/syn OR glatiramer OR 'cop 1' OR copaxone OR 'copolymer 1' OR 'copolymer cop 1' OR 'copolymer i' OR (glatiramer NEAR/1 (acetate OR sodium)) OR glatopa OR 'tv 5010' OR tv5010	8098
49	'alemtuzumab'/syn OR alemtuzumab OR 'campath 1' OR 'campath 1h' OR (cd52 NEAR/1 'monoclonal antibody') OR 'ldp 103' OR ldp103 OR lemtrada OR mabcampath	14824
50	'mitoxantrone'/syn OR mitoxantrone OR 'cl 232, 315' OR 'cl 232315' OR 'cl232, 315' OR cl232315 OR dhad OR dhaq OR domitrone OR elsep OR formyxan OR genefadrone OR misostol OR mitoxanthrone OR mitoxantron OR mitoxantrona OR mitoxgen OR mitozantrone OR mitroxantrone OR mitroxone OR neotalem OR norexan OR novanthron OR novantron OR novantrone OR 'now 85 34' OR 'now 8534' OR now8534 OR 'nsc 279836' OR 'nsc 301739' OR 'nsc 301739d' OR nsc279836 OR nsc301739 OR nsc301739d OR oncotron OR onkotrone OR ralenova	22787
51	'rituximab'/syn OR rituximab OR blitzima OR 'ct p10' OR 'ctp10' OR 'idec 102' OR 'idec c2b8' OR 'idec102' OR idecc2b8 OR mabthera OR 'r 105' OR r105 OR reditux OR 'rg 105' OR rg105 OR ritemvia OR rituxan OR rituxin OR rituzena OR rixathon OR riximyo OR 'ro 452294' OR ro452294 OR truxima OR tuxella	70012
52	'fingolimod'/syn OR fingolimod OR 'fty 720' OR fty720 OR gilenia OR gilenya	8223
53	'natalizumab'/syn OR natalizumab OR 'an 100226' OR an100226 OR antegren OR tysabri	9157
54	'fumaric acid dimethyl ester'/syn OR 'bg 12' OR bg12 OR 'dimethyl fumarate' OR dimethylfumarate OR 'fag 201' OR fag201 OR panaclar OR psorinovo OR skilarence OR tecfidera OR dmf	12157
55	'teriflunomide'/syn OR teriflunomide OR 'a 771726' OR 'a77 1726' OR 'a77-1726' OR a771726 OR aubagio OR 'hmr 1726' OR hmr1726 OR 'rs 61980' OR rs61980 OR 'su 0020' OR su0020	2270
56	'cladribine'/syn OR cladribine OR intocel OR leustat OR leustatin OR leustatine OR litak OR litax OR mavenclad OR movectro OR mylinax OR 'rwj 26251' OR rwj26251020	6402
57	'beta interferon'/syn OR 'recombinant beta interferon'/exp OR ((interferon OR ifn) NEAR/2 beta) OR belerofon OR ifn?beta OR (beta1* NEAR/2 interferon) OR 'interferon beta1' OR 'beta-1 interferon' OR 'beta 1 interferon'	35607
58	'beta1a interferon'/syn OR 'beta interferon 1a'/exp OR avonex OR ((interferon OR ifn) NEAR/1 ('beta 1a' OR 'beta-1a' OR beta1a OR 'beta 1b' OR beta1b OR 'beta 1b')) OR rebif OR 'rifn beta'	8043
59	'interferon beta serine'/syn OR 'beta interferon 1b'/exp OR beneseron OR betaferon OR betaseron OR extavia OR 'rifn beta-1b' OR 'sh 579' OR sh579 OR 'zk 157046' OR zk157046	5022
60	'masitinib'/syn OR masitinib OR 'ab 1010' OR ab1010 OR kinaction OR masatinib OR masican OR masipro OR masivet OR masiviera	473

#	Search terms	Results (17 Oct 2018)
61	'siponimod'/syn OR siponimod OR 'baf 312' OR baf312 OR mayzent	242
62	mis416	29
63	'imilecleucel t'/syn OR 'imilecleucel t' OR tcelna OR tovaxin	30
64	'biotin'/exp OR biotin OR biotine OR md1003	36072
65	'ibudilast'/syn OR ibudilast OR 'av 411' OR av411 OR 'kc 404' OR kc404 OR ketas OR 'mn-166'	619
66	'ocrelizumab'/syn OR ocrelizumab OR ocrevus OR 'pro 70769' OR pro70769 OR 'rhumab 2h7'	1174
67	'peginterferon'/exp OR 'peginterferon beta1a'/exp OR peginterferon OR 'beta 1a peginterferon' OR 'beta1a peginterferon' OR 'biib 017' OR 'biib017' OR 'peginterferon beta 1a' OR 'peginterferon beta-1a' OR 'pegylated human interferon beta 1a' OR 'pegylated interferon beta 1a' OR 'pegylated interferon beta-1a' OR 'pegylated interferon beta1a' OR plegridy	24523
68	'idebenone'/syn OR idebenone OR avan OR cerestabon OR 'cv 2619' OR cv2619 OR mnesis OR 'qsa 10' OR qsa10 OR raxone OR 'snt mc17' OR sovrima	2298
69	'opicinumab'/syn OR opicinumab OR 'biib 033' OR biib033	93
70	'stem cell transplantation'/exp OR 'hematopoietic stem cell transplantation'/syn OR ('stem cell' NEAR/2 (therap* OR transplant*)) OR hsct	165827
71	'simvastatin'/syn OR simvastatin OR avastinee OR belmalip OR cholestat OR clinfar OR colastatina OR colemin OR colestricon OR covastin OR denan OR epistatin OR esvat OR ethicol OR eucor OR ifistatin OR jabastatina OR kavelor OR klonastin OR kolestevan OR 'l 644128' OR l644128 OR lipcut OR lipecor OR lipex OR lipinorm OR liponorm OR lipovas OR lodales OR medipo OR mersivas OR 'mk 733' OR mk733 OR 'nor vastina' OR normofat OR orovas OR pantok OR rechol OR simbado OR simcard OR simchol OR simovil OR simtin OR simva OR simvacor OR simvahex OR simvalord OR simvastar OR simvastatina OR simvastatine OR simvata OR simvatin OR simvor OR simvotin OR sinvacor OR sinvastatin OR sinvinolin OR sivastin OR starzoco OR synvinolin OR torio OR valemia OR vasilip OR vasotenal OR vazim OR vidastat OR zimmex OR zocor OR zocord OR zovast	36641
72	'riluzole'/syn OR riluzole OR 'pk 26124' OR pk26124 OR rilutek OR 'rp 54274' OR rp54274	4284
73	'fluoxetine'/syn OR fluoxetine OR actan OR adofen OR 'alzac 20' OR andep OR ansilan OR 'atd 20' OR auroken OR auscap OR captaton OR 'compound 110140' OR daforin OR depren OR deprexin OR deprizac OR deproxin OR elizac OR floxet OR fluctin OR fluctine OR fludac OR flufran OR fluketin OR flunil OR flunirin OR fluohexal OR fluox OR 'fluox puren' OR fluoxac OR fluoxeren OR fluoxifar OR fluoxil OR fluronin OR flusac OR flutin OR flutine OR fluxen OR fluxet OR fluxetil OR fluxetin OR fontex OR foxetin OR foxtin OR fropine OR fuloren OR lanclic OR 'lilly 110140' OR lilly110140 OR lorien OR lovan OR 'ly 110140' OR ly110140 OR magrilan OR margrilan OR modipran OR nopres OR nuzak OR oxedep OR plinzene OR pragmaten OR prizma OR proctin OR prodep OR prosac OR prozac OR prozamin OR qualisac OR rapiflux OR rowexetina OR salipax OR sanzur OR sarafem OR selfemra OR sinzac OR zactin OR zepax	47704
74	'amiloride'/syn OR amiloride OR amiclaran OR amikal OR 'amilo 5' OR amilorid OR amiloridehydrochlorhydrate OR amiloridine OR amipramidine OR amyloride OR arumil OR berkamil OR colectril OR guanamprazine OR kaluril OR medamor OR midamor OR 'mk 870' OR modamide OR nirulid OR pandiuren	19855
75	#47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR	496801

#	Search terms	Results (17 Oct 2018)
	#64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74	
76	#41 AND #46 AND #75	3376
77	#76 AND ([conference review]/lim OR [editorial]/lim OR [letter]/lim OR [review]/lim)	536
78	#76 AND [animals]/lim NOT ([animals]/lim AND [humans]/lim)	83
79	#77 OR #78	617
80	#76 NOT #79	2756
81	#80 AND [english]/lim	2655

Table 67: Original SLR search strategy for MEDLINE® InProcess (via the PubMed.com platform)

#	Search terms	Results (17 Oct 2018)
1	Search "Multiple Sclerosis, Chronic Progressive" OR "chronic progressive multiple sclerosis"	1984
2	Search (((disseminated[Title/Abstract] or insular[Title/Abstract] or multiple[Title/Abstract])) AND (sclerosis[Title/Abstract])) AND ("secondary progressive" OR progressive OR secondary or non-relapsing)	10372
3	Search ("secondary progressive" OR "secondary-progressive" OR progressive OR secondary OR deteriorat* OR "non relapsing" OR non-relapsing) AND (ms OR "multiple sclerosis" OR "disseminated sclerosis" OR "encephalomyelitis disseminate" OR "chariot disease" OR "insular sclerosis")	23154
4	Search spms or cpms	1490
5	Search "progressive secondary multiple sclerosis" or "secondary progressive multiple sclerosis"	2598
6	Search #1 OR #2 OR #3 OR #4 OR #5	24626
7	Search "clinical trial" OR "clinical trials"	953606
8	Search "randomized controlled trial"	490277
9	Search "Random Allocation"	97602
10	Search "Double Blind"	183093
11	Search "Single Blind"	31388
12	Search "phase i" OR phasei OR "Phase 1" OR phase1	60296
13	Search "phase ii" OR phaseii OR "Phase 2" OR phase2	80260
14	Search "phase iii" OR phaseiii OR "Phase 3" OR phase3	51418
15	Search "phase iv" OR phaseiv OR "Phase 4" OR phase4	4861
16	Search "controlled clinical trial" OR "controlled clinical trials"	121254
17	Search "multicenter study"	247083
18	Search "Observational Study" OR "Comparative Study" OR "Cross-Over Studies" OR "Cross-Over Study" OR "Prospective Studies" OR "Prospective Study"	2376117
19	Search "Cohort Studies" OR "Cohort Study" OR "Longitudinal Studies" OR "Longitudinal Study" OR "Follow-Up Studies" Or "Follow-Up Study"	1019156
20	Search "Clinical Study" OR "Historically Controlled Study" OR "Retrospective Study" OR "Retrospective Studies"	799515
21	Search Survival	1783408
22	Search placebo*	212733
23	Search "clinical trial"[Title/Abstract]	124445
24	Search ((singl*[Title/Abstract] or doubl*[Title/Abstract] or treb*[Title/Abstract] or tripl*[Title/Abstract])) AND (blind* or mask*[Title/Abstract])	184215
25	Search "randomly allocated"[Title/Abstract]	25009
26	Search (allocated AND random*)	38800

#	Search terms	Results (17 Oct 2018)
27	Search "randomised controlled trial" OR "randomized controlled trial" OR "randomised controlled trials" OR "randomized controlled trials"	638715
28	Search "randomisation" OR "randomization" OR random*	1224356
29	Search rct	18085
30	Search ((case*[Title/Abstract])) AND (control*[Title/Abstract])	448808
31	Search (("follow up"[Title/Abstract] or followup[Title/Abstract])) AND (study[Title/Abstract] or studies[Title/Abstract])	529828
32	Search ((clinical[Title/Abstract])) AND (trial*[Title/Abstract])	462773
33	Search ((observational[Title/Abstract] or cohort[Title/Abstract])) AND (study[Title/Abstract] or studies[Title/Abstract])	460649
34	Search #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #33 OR #33	6454526
35	Search case report[Title/Abstract]	278733
36	Search letter	1064783
37	Search #35 OR #36	1336352
38	Search #34 NOT #37	6298339
39	Search “disease modifying therapies” [Title/Abstract] OR dmt*[Title/Abstract] OR "disease modifying therapy"[Title/Abstract] OR "disease modifying drugs"[Title/Abstract] OR "disease modifying drug"[Title/Abstract] OR dmd*[Title/Abstract]	15828
40	Search "Glatiramer Acetate" OR “cop 1” or copaxone or “copolymer 1” or “copolymer cop 1” or “copolymer i” or glatiramer or glatopa or “tv 5010” or tv5010	2107
41	Search "Alemtuzumab" OR “campath 1” or “campath 1h” or (cd52 AND “monoclonal antibody”) or “ldp 103” or ldp103 or lemtrada or mabcampath	3048
42	Search "Mitoxantrone" OR “cl 232, 315” or “cl 232315” or “cl232, 315” or cl232315 or dhad or dhaq or domitrone or elsep or formyxan or genefadrone or misostol or mitoxanthrone or mitoxantron or mitoxantrona or mitoxgen or mitozantrone or mitroxantrone or mitroxone or neotalem or norexan or novanthron or novantron or novantrone or “now 85 34” or “now 8534” or now8534 or “nsc 279836” or “nsc 301739” or “nsc 301739d” or nsc279836 or nsc301739 or nsc301739d or oncotron or onkotrone or ralenova	6496
43	Search "Rituximab" OR blitzima or “ct p10” or “ctp10” or “idec 102” or “idec c2b8” or “idec102” or idecc2b8 or mabthera or “r 105” or r105 or reditux or “rg 105” or rg105 or ritemvia or rituxan or rituxin or rituzena or rixathon or riximyo or “ro 452294” or ro452294 or truxima or tuxella	20319
44	Search Fingolimod OR “fty 720” or fty720 or gilenia or gilenya	2858
45	Search Natalizumab OR “an 100226” or an100226 or antegren or tysabri	2264
46	Search "Dimethyl Fumarate" OR dimethylfumarate or “fag 201” or fag201 or panaclar or psorinovo or skilarence or tecfidera or dmf	16441
47	Search Cladribine OR intocel or leustat or leustatin or leustatine or litak or litax or mavenclad or movectro or mylinax or “rwj 26251” or rwj26251	1910
48	Search teriflunomide or “a 771726” or “a77 1726” or a771726 or aubagio or “hmr 1726” or hmr1726 or “rs 61980” or rs61980 or “su 0020” or su0020	601
49	Search "Interferon-beta" OR “recombinant beta interferon” or ((interferon or ifn) AND beta) or belerofon or ifn?beta or (beta1* AND interferon) or “interferon beta1” or “beta-1 interferon” or “beta 1 interferon”	37984
50	Search "Interferon beta-1a" OR “beta1a interferon” or “beta interferon 1a” or avonex or ((interferon or ifn) AND (“beta 1a” or “beta-1a” or beta1a or “beta 1b” or beta1b or “beta 1b”)) or rebif or “rifn beta”	2828
51	Search "Interferon beta-1b" OR “interferon beta serine” or “beta interferon 1b” or beneseron or betaferon or betaseron or extavia or “rifn beta-1b” or “sh 579” or sh579 or “zk 157046” or zk157046	1393

#	Search terms	Results (17 Oct 2018)
52	Search masitinib or “ab 1010” or ab1010 or kinaction or masatinib or masican or masipro or masivet or masiviera	122
53	Search siponimod or “baf 312” or baf312 or mayzent	59
54	Search mis416	10
55	Search “imilecleucel t” or tcelna or tovaxin	40
56	Search biotin OR biotine OR md1003	31417
57	Search “ibudilast” or “av 411” or av411 or “kc 404” or kc404 or ketas OR mn-166	240
58	Search ocrelizumab or ocrevus or “pro 70769” or pro70769 or “rhumab 2h7”	222
59	Search "peginterferon beta-1a" OR peginterferon or “peginterferon beta1a” or “beta 1a peginterferon” or “beta1a peginterferon” or “biib 017” or “biib017” or “peginterferon beta 1a” or “peginterferon beta-1a” or “pegylated human interferon beta 1a” or “pegylated interferon beta 1a” or “pegylated interferon beta-1a” or “pegylated interferon beta1a” or plegridy	6397
60	Search idebenone OR avan OR cerestabon OR "cv 2619" OR cv2619 OR mnesis OR "qsa 10" OR qsa10 OR raxone OR "snt mc17" OR sovrima	963
61	Search opicinumab OR "biib 033" OR biib033	13
62	Search “Stem Cell Transplantation” OR “Hematopoietic Stem Cell Transplantation” OR “Haematopoietic Stem Cell Transplantation”	87322
63	Search ("stem cell" AND (therap* OR transplant*)) OR hsct	126888
64	Search simvastatin OR avastinee OR belmalip OR cholestat OR clinfar OR colastatina OR colemin OR colestricon OR covastin OR denan OR epistatin OR esvat OR ethicol OR eucor OR ifistatin OR jabastatina OR kavelor OR klonastin OR kolestevan OR "l 644128" OR l644128 OR lipcut OR lipecor OR lipex OR lipinorm OR liponorm OR lipovas OR lodales OR medipo OR mersivas OR "mk 733" OR mk733 OR "nor vastina" OR normofat OR orovas OR pantok OR rechol OR simbado OR simcard OR simchol OR simovil OR simtin OR simva OR simvacor OR simvahex OR simvalord OR simvastar OR simvastatina OR simvastatine OR simvata OR simvatin OR simvor OR simvotin OR sinvacor OR sinvastatin OR sinvinolin OR sivastin OR starzoco OR synvinolin OR torio OR valemia OR vasilip OR vasotenal OR vazim OR vidastat OR zimmex OR zocor OR zocord OR zovast	10253
65	Search riluzole OR "pk 26124" OR pk26124 OR rilutek OR "rp 54274" OR rp54274	1529
66	Search fluoxetine OR actan OR adofen OR "alzac 20" OR andep OR ansilan OR "atd 20" OR auroken OR auscap OR captaton OR "compound 110140" OR daforin OR depren OR deprexin OR deprizac OR deproxin OR elizac OR floxet OR fluctin OR fluctine OR fludac OR flufran OR fluketin OR flunil OR flunirin OR fluohexal OR fluox OR 'fluox puren' OR fluoxac OR fluoxeren OR fluoxifar OR fluoxil OR fluronin OR flusac OR flutin OR flutine OR fluxen OR fluxet OR fluxetil OR fluxetin OR fontex OR foxetin OR foxtin OR fropine OR fuloren OR lanclic OR "lilly 110140" OR lilly110140 OR lorien OR lovan OR "ly 110140" OR ly110140 OR magrilan OR margrilan OR modipran OR nopres OR nuzak OR oxedep OR plinzene OR pragmaten OR prizma OR proctin OR prodep OR prosac OR prozac OR prozamin OR qualisac OR rapiflux OR rowexetina OR salipax OR sanzur OR sarafem OR selfemra OR sinzac OR zactin OR zepax	13362
67	Search amiloride OR amiclaran OR amikal OR "amilo 5" OR amilorid OR amiloridehydrochlorhydrate OR amiloridine OR amipramidine OR amyloride OR arumil OR berkamil OR colectril OR guanamprazine OR kaluril OR medamor OR midamor OR "mk 870" OR modamide OR nirulid OR pandiuren	11755
68	Search #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR	302634

#	Search terms	Results (17 Oct 2018)
	#55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67	
69	Search #6 AND #38 AND #68	1665
70	Search #69 AND (inprocess[sb] OR pubstatusaheadofprint)	71

Table 68: Update SLR search terms for MEDLINE Daily, MEDLINE In-Process and Epub Ahead of Print (searched via Ovid SP)

#	Search terms	Results (21 Mar 2019)
1	exp clinical trial/	820853
2	randomized controlled trial/	478170
3	controlled clinical trial/	92974
4	random allocation/	98069
5	comparative study/	1824398
6	single-blind method/	26436
7	double blind method/	150163
8	crossover studies/	44815
9	Placebo/ or placebo$.mp.	216743
10	(clinical trial or clinical trials).mp.	958491
11	(controlled clinical trial or controlled clinical trials).mp.	121643
12	(randomised controlled trial or randomized controlled trial or randomised controlled trials or randomized controlled trials).mp.	657013
13	(randomisation or randomization).mp.	33156
14	rct.mp.	19136
15	(random allocation or randomly allocated or allocated randomly).mp.	125012
16	((allocated adj2 random) or (random$ adj1 assign) or random$).mp.	1258681
17	exp prospective studies/	496880
18	((single or double or triple or treble) adj1 (blind$ or mask$)).mp.	223337
19	exp cohort studies/ or cohort$.ti,ab.	2062771
20	exp longitudinal studies/	121753
21	exp multicenter study/	247082
22	exp follow up studies/	609671
23	exp case control studies/ or (case$ adj control$).ti,ab.	1017578
24	exp survival/	4564
25	((follow up or followup) adj (study or studies)).ti,ab.	47222
26	(clinical adj trial$).ti,ab.	328014
27	exp retrospective studies/	737077
28	exp case control studies/	978377
29	((observational or cohort) adj (study or studies)).ti,ab.	257787
30	or/1-29	5188857
31	case reports/	1963106
32	case report.mp.	274496
33	letter/	1019712
34	or/31-33	2833462
35	30 not 34	4981098
36	((((disseminated or insular or multiple) adj4 sclerosis) or ms) and (secondary progressive or progressive or non-relapsing)).ti,ab.	9025
37	(Secondary progressive or secondary-progressive or progressive or secondary or deteriorat$ or non relapsing or non-relapsing) adj3 (ms or multiple sclerosis or disseminated sclerosis or encephalomyelitis disseminata or chariot disease or insular sclerosis).ti,ab,kf.	4643
38	(spms or cpms).mp.	1534
39	(progressive secondary multiple sclerosis or secondary progressive multiple sclerosis).mp.	620
40	or/36-39	10370

#	Search terms	Results (21 Mar 2019)
41	disease modifying therapies.ti,ab. or dmt$.ti,ab. or disease modifying therapy.ti,ab. or disease modifying drugs.ti,ab. or disease modifying drug.ti,ab. or dmd$.ti,ab.	16218
42	glatiramer acetate/ or (cop 1 or copaxone or copolymer 1 or copolymer cop 1 or copolymer i OR (glatiramer adj1 (acetate or sodium)) or glatopa or 'tv 5010' or tv5010).ti,ab,kf.	2111
43	alemtuzumab/ or (alemtuzumab or campath 1 or campath 1h or (cd52 adj1 monoclonal antibody) or ldp 103 or ldp103 or lemtrada or mabcampath).ti,ab,kf.	3071
44	mitoxantrone/ or (mitoxantrone or 'cl 232, 315' or 'cl 232315' or 'cl232, 315' or cl232315 or dhad or dhaq or domitrone or elsep or formyxan or genefadrone or misostol or mitoxanthrone or mitoxantron or mitoxantrona or mitoxgen or mitozantrone or mitroxantrone or mitroxone or neotalem or norexan or novanthron or novantron or novantrone or 'now 85 34' or 'now 8534' or now8534 or 'nsc 279836' or 'nsc 301739' or 'nsc 301739d' or nsc279836 or nsc301739 or nsc301739d or oncotron or onkotrone or ralenova).ti,ab,kf.	6212
45	rituximab/ or (rituximab or blitzima or ct p10 or ctp10 or 'idec 102' or idec c2b8 or idec102 or idecc2b8 or mabthera or r 105 or r105 or reditux or 'rg 105' or rg105 or ritemvia or rituxan or rituxin or rituzena or rixathon or riximyo or 'ro 452294' or ro452294 or truxima or tuxella).ti,ab,kf.	20693
46	fingolimod/ or (fingolimod or 'fty 720' or fty720 or gilenia or gilenya).ti,ab,kf.	2972
47	natalizumab/ or (natalizumab or 'an 100226' or an100226 or antegren or Tysabri).ti,ab,kf.	2331
48	dimethyl fumarate/ or (bg 12 or bg12 or dimethyl fumarate or dimethylfumarate or fag 201 or fag201 or panaclar or psorinovo or skilarence or tecfidera or dmf).ti,ab,kf.	8074
49	(teriflunomide or a 771726 or a77 1726 or a77-1726 or a771726 or aubagio or hmr 1726 or hmr1726 or rs 61980 or rs61980 or su 0020 or su0020).ti,ab,kf.	581
50	cladribine/ or (cladribine or intocel or leustat or leustatin or leustatine or litak or litax or mavenclad or movectro or mylinax or rwj 26251 or rwj26251020).ti,ab,kf.	1908
51	interferon-beta/ or (recombinant beta interferon or ((interferon or ifn) adj2 beta) or belerofon or ifn?beta or (beta1$ adj2 interferon) or interferon beta1 or beta-1 interferon or 'beta 1 interferon).ti,ab,kf.	19051
52	(beta1a interferon or beta interferon 1a or avonex or (((interferon or ifn) adj1 beta 1a or beta-1a or beta1a or beta 1b or beta1b or beta 1b)) or rebif or rifn beta).ti,ab,kf.	2805
53	(interferon beta serine or beta interferon 1b or beneseron or betaferon or betaseron or extavia or rifn beta-1b or sh 579 or sh579 or zk 157046 or zk157046).ti,ab,kf.	319
54	(masitinib or ab 1010 or ab1010 or kinaction or masatinib or masican or masipro or masivet or masiviera).ti,ab,kf.	111
55	siponimod/ or (siponimod or 'baf 312' or baf312 or mayzent).ti,ab,kf.	60
56	mis416.ti,ab,kf.	10
57	(imilecleucel t or tcelna or tovaxin).ti,ab,kf.	5
58	exp biotin/ or (biotin or biotine or md1003).ti,ab,kf.	31765
59	(ibudilast or av 411 or av411 or kc 404 or kc404 or ketas or mn-166).ti,ab,kf.	172
60	(ocrelizumab or ocrevus or pro 70769 or pro70769 or rhumab 2h7).ti,ab,kf.	225
61	(peginterferon or peginterferon beta1a or peginterferon or beta 1a peginterferon or beta1a peginterferon or biib 017 or biib017 or peginterferon beta 1a or peginterferon beta-1a or 'pegylated human interferon beta 1a or pegylated interferon beta 1a or pegylated interferon beta-1a or pegylated interferon beta1a or plegridy).ti,ab,kf.	2601

#	Search terms	Results (21 Mar 2019)
62	(idebenone or avan or cerestabon or cv 2619 or cv2619 or mnesis or qsa 10 or qsa10 or raxone or snt mc17 or sovrima).ti,ab,kf.	514
63	(opicinumab or biib 033 or biib033).ti,ab,kf.	15
64	exp stem cell transplantation/ or hematopoietic stem cell transplantation/ or ((stem cell adj2 (therap$ or transplant$)) or hsct).ti,ab,kf.	94109
65	simvastatin/ or (simvastatin or avastinee or belmalip or cholestat or clinfar or colastatina or colemin or colestricon or covastin or denan or epistatin or esvat or ethicol or eucor or ifistatin or jabastatina or kavelor or klonastin or kolestevan or 'l 644128' or l644128 or lipcut or lipecor or lipex or lipinorm or liponorm or lipovas or lodales or medipo or mersivas or 'mk 733' or mk733 or 'nor vastina' or normofat or orovas or pantok or rechol or simbado or simcard or simchol or simovil or simtin or simva or simvacor or simvahex or simvalord or simvastar or simvastatina or simvastatine or simvata or simvatin or simvor or simvotin or sinvacor or sinvastatin or sinvinolin or sivastin or starzoco or synvinolin or torio or valemia or vasilip or vasotenal or vazim or vidastat or zimmex or zocor or zocord or zovast).ti,ab,kf.	10323
66	riluzole/ or (riluzole or pk 26124 or pk26124 or rilutek or rp 54274 or rp54274).ti,ab,kf.	1567
67	fluoxetine/ or (fluoxetine or actan or adofen or 'alzac 20' or andep or ansilan or 'atd 20' or auroken or auscap or captaton or 'compound 110140' or daforin or depren or deprexin or deprizac or deproxin or elizac or floxet or fluctin or fluctine or fludac or flufran or fluketin or flunil or flunirin or fluohexal or fluox or 'fluox puren' or fluoxac or fluoxeren or fluoxifar or fluoxil or fluronin or flusac or flutin or flutine or fluxen or fluxet or fluxetil or fluxetin or fontex or foxetin or foxtin or fropine or fuloren or lanclic or 'lilly 110140' or lilly110140 or lorien or lovan or 'ly 110140' or ly110140 or magrilan or margrilan or modipran or nopres or nuzak or oxedep or plinzene or pragmaten or prizma or proctin or prodep or prosac or prozac or prozamin or qualisac or rapiflux or rowexetina or salipax or sanzur or sarafem or selfemra or sinzac or zactin or zepax).ti,ab,kf.	13484
68	amiloride/ or (amiloride or amiclaran or amikal or 'amilo 5' or amilorid or amiloridehydrochlorhydrate or amiloridine or amipramidine or amyloride or arumil or berkamil or colectril or guanamprazine or kaluril or medamor or midamor or 'mk 870' or modamide or nirulid or pandiuren).ti,ab,kf.	11783
69	or/41-68	240936
70	35 and 40 and 69	1014
71	("conference review" or "editorial" or "letter" or "review").pt.	3972101
72	exp animals/ not (exp animals/ and exp humans/)	4559068
73	71 or 72	8340958
74	70 not 73	701
75	Limit 74 to english	655

Table 69: Update SLR search terms for Embase (searched via Ovid SP)

#	Search terms	Results (21 Mar 2019)
1	exp clinical trial/	1368100
2	randomized controlled trial/	537004
3	controlled clinical trial/	458788
4	phase 3 clinical trial/ or phase 2 clinical trial/ or phase 4 clinical trial/	106154
5	randomization/	81329
6	controlled study/	6491532
7	comparative study/	792896
8	single blind procedure/	33981
9	double blind procedure/	158029
10	crossover procedure/	58296
11	Placebo/ or placebo$.mp.	426804

#	Search terms	Results (21 Mar 2019)
12	(clinical trial or clinical trials).mp.	1592977
13	(controlled clinical trial or controlled clinical trials).mp.	488571
14	(randomised controlled trial or randomized controlled trial or randomised controlled trials or randomized controlled trials).mp.	742384
15	(randomisation or randomization).mp.	111139
16	rct.mp.	32931
17	(random allocation or randomly allocated or allocated randomly).mp.	36307
18	((allocated adj2 random) or (random$ adj1 assign) or random$).mp.	1589951
19	exp prospective study/	502659
20	(single or double or triple or treble) adj1 (blind$ or mask$).mp.	283689
21	exp cohort analysis/ or cohort$.ti,ab.	920921
22	exp longitudinal study/	122552
23	exp multicentre study/	208366
24	exp follow up/	1365498
25	major clinical study/	3304524
26	exp case control study/ or (case$ adj control$).ti,ab.	211685
27	exp clinical article/	2081462
28	exp survival/	994440
29	((follow up or followup) adj (study or studies)).ti,ab.	60283
30	(clinical adj trial$).ti,ab.	461102
31	exp retrospective study/	743529
32	exp case control study/	154610
33	((observational or cohort) adj (study or studies)).ti,ab.	379773
34	exp intervention study/	39519
35	or/1-34	12747893
36	case study/	59544
37	case report.mp.	2351831
38	abstract report/	89743
39	letter/	998135
40	or/36-39	3289039
41	35 not 40	12120317
42	((((disseminated or insular or multiple) adj4 sclerosis).ti,ab.) or ms.ti,ab.) and (secondary progressive.ti,ab. or progressive.ti,ab. or non-relapsing.ti,ab.)	16894
43	(Secondary progressive or secondary-progressive or progressive or secondary or deteriorat$ or non relapsing or non-relapsing) adj3 (ms or multiple sclerosis or disseminated sclerosis or encephalomyelitis disseminata or chariot disease or insular sclerosis).mp.	8533
44	(spms or cpms).mp.	3236
45	(progressive secondary multiple sclerosis or secondary progressive multiple sclerosis).mp.	1135
46	or/42-45	19108
47	disease modifying therapies.ti,ab. or dmt$.ti,ab. or disease modifying therapy.ti,ab. or disease modifying drugs.ti,ab. or disease modifying drug.ti,ab. or dmd$.ti,ab.	25696
48	glatiramer acetate/ or (cop 1 or copaxone or copolymer 1 or copolymer cop 1 or copolymer i or (glatiramer adj1 (acetate or sodium)) or glatopa or 'tv 5010' or tv5010).ti,ab,kw.	8258
49	alemtuzumab/ or (alemtuzumab or campath 1 or campath 1h or (cd52 adj1 monoclonal antibody) or ldp 103 or ldp103 or lemtrada or mabcampath).ti,ab,kw.	15062
50	mitoxantrone/ or (mitoxantrone or 'cl 232, 315' or 'cl 232315' or 'cl232, 315' or cl232315 or dhad or dhaq or domitrone or elsep or formyxan or genefadrone or misostol or mitoxanthrone or mitoxantron or mitoxantrona or mitoxgen or mitozantrone or mitroxantrone or mitroxone or neotalem or norexan or novanthron or novantron or novantrone or 'now 85 34' or 'now	23094

#	Search terms	Results (21 Mar 2019)
	8534' or now8534 or 'nsc 279836' or 'nsc 301739' or 'nsc 301739d' or nsc279836 or nsc301739 or nsc301739d or oncotron or onkotrone or ralenova).ti,ab,kw.	
51	rituximab/ or (rituximab or blitzima or ct p10 or ctp10 or 'idec 102' or idec c2b8 or idec102 or idecc2b8 or mabthera or r 105 or r105 or reditux or 'rg 105' or rg105 or ritemvia or rituxan or rituxin or rituzena or rixathon or riximyo or 'ro 452294' or ro452294 or truxima or tuxella).ti,ab,kw.	72375
52	fingolimod/ or (fingolimod or 'fty 720' or fty720 or gilenia or gilenya).ti,ab,kw.	8604
53	natalizumab/ or (natalizumab or 'an 100226' or an100226 or antegren or Tysabri).ti,ab,kw.	9448
54	dimethyl fumarate/ or (bg 12 or bg12 or dimethyl fumarate or dimethylfumarate or fag 201 or fag201 or panaclar or psorinovo or skilarence or tecfidera or dmf).ti,ab,kw.	12006
55	(teriflunomide or a 771726 or a77 1726 or a77-1726 or a771726 or aubagio or hmr 1726 or hmr1726 or rs 61980 or rs61980 or su 0020 or su0020).ti,ab,kw.	1296
56	cladribine/ or (cladribine or intocel or leustat or leustatin or leustatine or litak or litax or mavenclad or movectro or mylinax or rwj 26251 or rwj26251020).ti,ab,kw.	6474
57	interferon-beta/ or (recombinant beta interferon or ((interferon or ifn) adj2 beta) or belerofon or ifn?beta or (beta1$ adj2 interferon) or interferon beta1 or beta-1 interferon or 'beta 1 interferon).ti,ab,kw.	32734
58	beta1a interferon/ or (avonex or ((interferon or ifn) adj1 (beta 1a or beta-1a or beta1a or beta 1b or beta1b or beta 1b)) or rebif or rifn beta).ti,ab,kw.	8864
59	interferon beta serine/ or (interferon beta serine or beneseron or betaferon or betaseron or extavia or rifn beta-1b or sh 579 or sh579 or zk 157046 or zk157046).ti,ab,kw.	5003
60	(masitinib or ab 1010 or ab1010 or kinaction or masatinib or masican or masipro or masivet or masiviera).ti,ab,kw.	189
61	siponimod/ or (siponimod or 'baf 312' or baf312 or mayzent).ti,ab,kw.	252
62	mis416.ti,ab,kw.	31
63	(imilecleucel t or tcelna or tovaxin).ti,ab,kw.	7
64	exp biotin/ or (biotin or biotine or md1003).ti,ab,kw.	35110
65	(ibudilast or av 411 or av411 or kc 404 or kc404 or ketas or mn-166).ti,ab,kw.	297
66	(ocrelizumab or ocrevus or pro 70769 or pro70769 or rhumab 2h7).ti,ab,kw.	489
67	peginterferon/ or peginterferon beta1a/ or (peginterferon or peginterferon beta1a or peginterferon or beta 1a peginterferon or beta1a peginterferon or biib 017 or biib017 or peginterferon beta 1a or peginterferon beta-1a or 'pegylated human interferon beta 1a or pegylated interferon beta 1a or pegylated interferon beta-1a or pegylated interferon beta1a or plegridy).ti,ab,kw.	15572
68	idebenone/ or (idebenone or avan or cerestabon or cv 2619 or cv2619 or mnesis or qsa 10 or qsa10 or raxone or snt mc17 or sovrima).ti,ab,kw.	1472
69	opicinumab/ or (opicinumab or biib 033 or biib033).ti,ab,kw.	88
70	exp stem cell transplantation/ or hematopoietic stem cell transplantation/ or ((stem cell adj2 (therap$ or transplant$)) or hsct).ti,ab,kw.	158637
71	simvastatin/ or (simvastatin or avastinee or belmalip or cholestat or clinfar or colastatina or colemin or colestricon or covastin or denan or epistatin or esvat or ethicol or eucor or ifistatin or jabastatina or kavelor or klonastin or kolestevan or 'l 644128' or l644128 or lipcut or lipecor or lipex or lipinorm or liponorm or lipovas or lodales or medipo or mersivas or 'mk 733' or mk733 or 'nor vastina' or normofat or orovas or pantok or rechol or simbado or simcard or simchol or simovil or simtin or simva or simvacor or	36532

#	Search terms	Results (21 Mar 2019)
	simvahex or simvalord or simvastar or simvastatina or simvastatine or simvata or simvatin or simvor or simvotin or sinvacor or sinvastatin or sinvinolin or sivastin or starzoco or synvinolin or torio or valemia or vasilip or vasotenal or vazim or vidastat or zimmex or zocor or zocord or zovast).ti,ab,kw.	
72	riluzole/ or (riluzole or pk 26124 or pk26124 or rilutek or rp 54274 or rp54274).ti,ab,kw.	4396
73	fluoxetine/ or (fluoxetine or actan or adofen or 'alzac 20' or andep or ansilan or 'atd 20' or auroken or auscap or captaton or 'compound 110140' or daforin or depren or deprexin or deprizac or deproxin or elizac or floxet or fluctin or fluctine or fludac or flufran or fluketin or flunil or flunirin or fluohexal or fluox or 'fluox puren' or fluoxac or fluoxeren or fluoxifar or fluoxil or fluronin or flusac or flutin or flutine or fluxen or fluxet or fluxetil or fluxetin or fontex or foxetin or foxtin or fropine or fuloren or lanclic or 'lilly 110140' or lilly110140 or lorien or lovan or 'ly 110140' or ly110140 or magrilan or margrilan or modipran or nopres or nuzak or oxedep or plinzene or pragmaten or prizma or proctin or prodep or prosac or prozac or prozamin or qualisac or rapiflux or rowexetina or salipax or sanzur or sarafem or selfemra or sinzac or zactin or zepax).ti,ab,kw.	45564
74	amiloride/ or (amiloride or amiclaran or amikal or 'amilo 5' or amilorid or amiloridehydrochlorhydrate or amiloridine or amipramidine or amyloride or arumil or berkamil or colectril or guanamprazine or kaluril or medamor or midamor or 'mk 870' or modamide or nirulid or pandiuren).ti,ab,kw.	18590
75	or/47-74	480889
76	41 and 46 and 75	3441
77	("conference review" or "editorial" or "letter" or "review").pt.	4058172
78	exp animals/ not (exp animals/ and exp humans/)	4394474
79	77 or 78	8308237
80	76 not 79	2851
81	Limit 80 to english	2751

Table 70: Original and Update SLR search strategy for CENTRAL and CDSR (via the Wiley Online Platform)

#	Search terms	Results (17 Oct 2018)	Results (21 Mar 2019)
1	MeSH descriptor: [Multiple Sclerosis, Chronic Progressive] explode all trees	207	214
2	((((disseminated OR insular OR multiple) NEAR/4 sclerosis):ab,ti,kw) OR ms:ab,ti,kw) AND (“secondary progressive”:ab,ti,kw OR progressive:ab,ti,kw OR non-relapsing:ab,ti,kw)	1315	1232
3	("secondary progressive" OR "secondary-progressive" OR progressive OR secondary OR deteriorat* OR "non relapsing" OR non-relapsing) NEAR/3 (ms OR "multiple sclerosis" OR "disseminated sclerosis" OR "encephalomyelitis disseminate" OR "chariot disease" OR "insular sclerosis")	1051	1004
4	spms OR cpms	307	261
5	progressive secondary multiple sclerosis OR "secondary progressive multiple sclerosis"	215	663
6	#1 OR #2 OR #3 OR #4 OR #5	1546	1546
7	disease modifying therapies:ab,ti,kw OR dmt*:ab,ti,kw OR "disease modifying therapy":ab,ti,kw OR "disease modifying drugs":ab,ti,kw OR "disease modifying drug":ab,ti,kw OR dmd*:ab,ti,kw	1210	1280
8	MeSH descriptor: [Glatiramer Acetate] explode all trees	153	156

#	Search terms	Results (17 Oct 2018)	Results (21 Mar 2019)
9	glatiramer OR “cop 1” or copaxone or “copolymer 1” or “copolymer cop 1” or “copolymer i” or (glatiramer near/1 (acetate or sodium)) or glatopa or “tv 5010” or tv5010	617	577
10	MeSH descriptor: [Alemtuzumab] explode all trees	122	124
11	Alemtuzumab OR “campath 1” or “campath 1h” or (cd52 near/1 “monoclonal antibody”) or “ldp 103” or ldp103 or lemtrada or mabcampath	571	531
12	MeSH descriptor: [Mitoxantrone] explode all trees	469	473
13	Mitoxantrone or “cl 232, 315” or “cl 232315” or “cl232, 315” or cl232315 or dhad or dhaq or domitrone or elsep or formyxan or genefadrone or misostol or mitoxanthrone or mitoxantron or mitoxantrona or mitoxgen or mitozantrone or mitroxantrone or mitroxone or neotalem or norexan or novanthron or novantron or novantrone or “now 85 34” or “now 8534” or now8534 or “nsc 279836” or “nsc 301739” or “nsc 301739d” or nsc279836 or nsc301739 or nsc301739d or oncotron or onkotrone or ralenova	1377	1320
14	MeSH descriptor: [Rituximab] explode all trees	906	933
15	Rituximab or blitzima or “ct p10” or “ctp10” or “idec 102” or “idec c2b8” or “idec102” or idecc2b8 or mabthera or “r 105” or r105 or reditux or “rg 105” or rg105 or ritemvia or rituxan or rituxin or rituzena or rixathon or riximyo or “ro 452294” or ro452294 or truxima or tuxella	3355	3123
16	MeSH descriptor: [Fingolimod Hydrochloride] explode all trees	119	122
17	Fingolimod or “fty 720” or fty720 or gilenia or gilenya	508	483
18	MeSH descriptor: [Natalizumab] explode all trees	78	80
19	Natalizumab or “an 100226” or an100226 or antegren or tysabri	391	374
20	MeSH descriptor: [Dimethyl Fumarate] explode all trees	67	70
21	“Dimethyl Fumarate” or dimethylfumarate or “fag 201” or fag201 or panaclar or psorinovo or skilarence or tecfidera or dmf	963	943
22	teriflunomide or “a 771726” or “a77 1726” or a771726 or aubagio or “hmr 1726” or hmr1726 or “rs 61980” or rs61980 or “su 0020” or su0020	2502	2525
23	MeSH descriptor: [Cladribine] explode all trees	85	85
24	Cladribine or intocel or leustat or leustatin or leustatine or litak or litax or mavenclad or movectro or mylinax or “rwj 26251” or rwj26251	282	273
25	MeSH descriptor: [Interferon-beta] explode all trees	636	649
26	“recombinant beta interferon” or ((interferon or ifn) near/2 beta) or belerofon or ifn?beta or (beta1* near/2 interferon) or “interferon beta1” or “beta-1 interferon” or “beta 1 interferon”	1847	1785
27	MeSH descriptor: [Interferon beta-1a] explode all trees	340	347
28	“beta1a interferon” or “beta interferon 1a” or avonex or ((interferon or ifn) near/1 (“beta 1a” or “beta-1a” or beta1a or “beta 1b” or beta1b or “beta 1b”)) or rebif or “rifn beta”	1294	1251
29	MeSH descriptor: [Interferon beta-1b] explode all trees	158	160
30	“interferon beta serine” or “beta interferon 1b” or beneseron or betaferon or betaseron or extavia or “rifn beta-1b” or “sh 579” or sh579 or “zk 157046” or zk157046	224	206
31	masitinib or “ab 1010” or ab1010 or kinaction or masatinib or masican or masipro or masivet or masiviera	40	40
32	siponimod or “baf 312” or baf312 or mayzent	55	56
33	mis416	1	1
34	imilecleucel-t OR tcelna OR tovaxin	2	2
35	MeSH descriptor: [Biotin] explode all trees	38	39
36	biotin OR biotine OR md1003	254	242

#	Search terms	Results (17 Oct 2018)	Results (21 Mar 2019)
37	ibudilast OR "av 411" OR av411 OR "kc 404" OR kc404 OR ketas OR mn-166	72	72
38	ocrelizumab OR ocrevus OR "pro 70769" OR pro70769 OR "rhumab 2h7"	113	104
39	peginterferon or “peginterferon beta1a” or “beta 1a peginterferon” or “beta1a peginterferon” or “biib 017” or “biib017” or “peginterferon beta 1a” or “peginterferon beta-1a” or “pegylated human interferon beta 1a” or “pegylated interferon beta 1a” or “pegylated interferon beta-1a” or “pegylated interferon beta1a” or plegridy	2466	2351
40	idebenone OR avan OR cerestabon OR "cv 2619" OR cv2619 OR mnesis OR "qsa 10" OR qsa10 OR raxone OR "snt mc17" OR sovrima	129	135
41	opicinumab OR "biib 033" OR biib033	23	22
42	MeSH descriptor: [Stem Cell Transplantation] explode all trees	1829	1844
43	MeSH descriptor: [Hematopoietic Stem Cell Transplantation] explode all trees	1262	1271
44	("stem cell" NEAR/2 (therap* OR transplant*)) OR hsct	6644	6653
45	MeSH descriptor: [Simvastatin] explode all trees	1608	1625
46	simvastatin OR avastinee OR belmalip OR cholestat OR clinfar OR colastatina OR colemin OR colestricon OR covastin OR denan OR epistatin OR esvat OR ethicol OR eucor OR ifistatin OR jabastatina OR kavelor OR klonastin OR kolestevan OR "l 644128" OR l644128 OR lipcut OR lipecor OR lipex OR lipinorm OR liponorm OR lipovas OR lodales OR medipo OR mersivas OR "mk 733" OR mk733 OR "nor vastina" OR normofat OR orovas OR pantok OR rechol OR simbado OR simcard OR simchol OR simovil OR simtin OR simva OR simvacor OR simvahex OR simvalord OR simvastar OR simvastatina OR simvastatine OR simvata OR simvatin OR simvor OR simvotin OR sinvacor OR sinvastatin OR sinvinolin OR sivastin OR starzoco OR synvinolin OR torio OR valemia OR vasilip OR vasotenal OR vazim OR vidastat OR zimmex OR zocor OR zocord OR zovast	3261	3148
47	MeSH descriptor: [Riluzole] explode all trees	117	122
48	riluzole OR "pk 26124" OR pk26124 OR rilutek OR "rp 54274" OR rp54274	337	330
49	MeSH descriptor: [Fluoxetine] explode all trees	1354	1358
50	fluoxetine OR actan OR adofen OR "alzac 20" OR andep OR ansilan OR "atd 20" OR auroken OR auscap OR captaton OR "compound 110140" OR daforin OR depren OR deprexin OR deprizac OR deproxin OR elizac OR floxet OR fluctin OR fluctine OR fludac OR flufran OR fluketin OR flunil OR flunirin OR fluohexal OR fluox OR 'fluox puren' OR fluoxac OR fluoxeren OR fluoxifar OR fluoxil OR fluronin OR flusac OR flutin OR flutine OR fluxen OR fluxet OR fluxetil OR fluxetin OR fontex OR foxetin OR foxtin OR fropine OR fuloren OR lanclic OR "lilly 110140" OR lilly110140 OR lorien OR lovan OR "ly 110140" OR ly110140 OR magrilan OR margrilan OR modipran OR nopres OR nuzak OR oxedep OR plinzene OR pragmaten OR prizma OR proctin OR prodep OR prosac OR prozac OR prozamin OR qualisac OR rapiflux OR rowexetina OR salipax OR sanzur OR sarafem OR selfemra OR sinzac OR zactin OR zepax	3242	3136
51	MeSH descriptor: [Amiloride] explode all trees	290	291
52	amiloride OR amiclaran OR amikal OR "amilo 5" OR amilorid OR amiloridehydrochlorhydrate OR amiloridine OR amipramidine OR amyloride OR arumil OR berkamil OR colectril OR guanamprazine OR kaluril OR medamor OR midamor OR "mk 870" OR modamide OR nirulid OR pandiuren	642	621

#	Search terms	Results (17 Oct 2018)	Results (21 Mar 2019)
53	#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52	28146	27625
54	#6 and #53 (Word variations have been searched)	657	772
55	#54 in Trials (Word variations have been searched)	610	646
56	#54 in Cochrane Reviews, Cochrane Protocols (Word variations have been searched)	47	125

Table 71: Original SLR search strategy for DARE and HTAD (via the CRD platform)

#	Search terms	Results (17 Oct 2018)
1	MeSH DESCRIPTOR Multiple Sclerosis, Chronic Progressive EXPLODE ALL TREES	20
2	((disseminated or insular or multiple) near4 sclerosis) AND (secondary progressive OR progressive OR secondary)	131
3	((secondary progressive OR secondary-progressive OR progressive OR secondary OR deteriorat* OR non relapsing OR non-relapsing) NEAR3 (ms OR multiple sclerosis OR disseminated sclerosis OR encephalomyelitis disseminate OR chariot disease OR insular sclerosis))	64
4	spms OR cpms	12
5	progressive secondary multiple sclerosis OR secondary progressive multiple sclerosis	47
6	#1 OR #2 OR #3 OR #4 OR #5 (NHS EED/DARE/HTA)	132
7	(#6) IN DARE	63*
8	(#6) IN HTA	33

*One empty record was retrieved so 62 hits

Table 72. Congress searches for the clinical SLR update

Congress	Site	Search Strategy	Results
Americas Committee for Treatment and Research in Multiple Sclerosis (ACTRIMS)	https://actrims.confex.com/actrims/2019/meetingapp.cgi/Home/0	Using the search function: “SPMS or secondary or relapsing”	164 results identified, 0 included

Table 73. Search terms used for other grey literature searches in the clinical SLR update

Source	Site	Search Strategy	Results
All Wales Medicines Strategy Group (AWMSG)	http://www.awmsg.org/awmsgonline/app/browsebnf?execution=e13s1	Using the 'Browse by BNF category' function in combination with searching for "multiple sclerosis" using browser Find function; results published since the original search were reviewed	2 results identified, 0 included
Canadian Agency for Drugs and	https://www.cadth.ca/	Searches conducted for “secondary progressive multiple sclerosis” and	10 records identified, 0 included

Source	Site	Search Strategy	Results
Technologies in Health (CADTH)		terms for each intervention	
Centre for Reviews and Dissemination (CRD)	https://www.york.ac.uk/crd/)	Searches conducted for “secondary progressive multiple sclerosis” and terms for each intervention	15 records identified, 0 included
ClinicalTrials.gov	https://www.clinicaltrials.gov/	Disease area: secondary progressive multiple sclerosis Last updated from: 17.10.18	20 records identified; 0 included
EU Clinical Trials Register (EU CTR)	https://www.clinicaltrialsregister.eu/ctr-search/search	Search Terms: Multiple Sclerosis Date limit: Posted since 17.10.18	6 records identified; 0 included
European Medicines Agency (EMA)	https://www.ema.europa.eu	Searches conducted for medicines listed in the ‘Multiple Sclerosis’ section of the database and revisions since the 17th October 2019	25 records identified; 0 included
Haute Autorite de Sante (HAS)	https://www.has-sante.fr/	Searches conducted for “multiple sclerosis” and terms for each intervention	1 record identified, 0 included
Institute for Quality and Efficiency in Health Care (IQWiG)	https://www.iqwig.de/	Searches conducted for “multiple sclerosis” and terms for each intervention	2 records identified, 0 included
National Institute for Health and Care Excellence (NICE)	https://www.nice.org.uk/	Searches conducted for "secondary progressive multiple sclerosis", results published since the original search were reviewed	5 results identified; 0 included
NIHR HTA Programme	https://www.nihr.ac.uk/	Searches for “multiple sclerosis”, after September 2018	15 results identified, 0 included
Scottish Medicines Consortium (SMC)	https://www.scottishmedicines.org.uk/	Searches conducted for "secondary progressive multiple sclerosis" and each eligible intervention	60 results identified; 0 included
Utility-weight collection collated by Tufts New England Medical Center's Catalogue of Preference Scores	http://healtheconomics.tuftsmedicalcenter.org/cear4/aboutus/whatisthecearegistry.aspx	Searches for each relevant intervention	0 results identified, 0 included
WHO ICTRP	http://apps.who.int/trialsearch/	Searches conducted for “multiple sclerosis” in title	0 records identified, 0 included

Source	Site	Search Strategy	Results
		or condition, 17/10/18 to 02/04/19	

6.1.1 Studies included following full-text review

Table 74: Publications included in the original SLR

#	Author, Year	Reference
EXPAND trial (NCT01665144)		
1	Kappos 2018	Kappos L, Bar-Or A, Cree BAC, et al. Siponimod versus placebo in secondary progressive multiple sclerosis (EXPAND): a double-blind, randomised, phase 3 study. The Lancet 2018;391:1263-1273.
2	Cree 2018	Cree B, Fox R, Giovannoni G, et al. Siponimod affects disability progression in SPMS patients independent of relapse activity: Results from the phase III EXPAND study. European Journal of Neurology 2018;25:70.
3	Benedict 2018a	Benedict RH, Cree B, Tomic D, et al. Siponimod improves cognitive processing speed in patients with SPMS: Results from Phase 3 EXPAND Study. European Journal of Neurology 2018;25:432.
4	Benedict 2018b	Benedict RHB, Cree B, Tomic D, et al. Impact of siponimod on cognition in patients with secondary progressive multiple sclerosis: Results from phase 3 expand study. Neurology 2018;90.
5	Kuhle 2018	Kuhle J, Kropshofer H, Barro C, et al. Siponimod reduces neurofilament light chain blood levels in secondary progressive multiple sclerosis patients. Neurology 2018;90.
6	Cree 2018	Cree B, Fox R, Giovannoni G, et al. Uncoupling the impact on relapses and disability progression: Siponimod in relapsing and non-relapsing patients with secondary progressive multiple sclerosis in the phase III expand study. Neurology 2018;90.
7	Bar 2017	Bar-Or A, Derfuss T, Vermersch P, et al. Longitudinal changes in lymphocyte subsets of siponimodtreated patients with SPMS. Multiple Sclerosis Journal 2017;23:660.
8	Mao 2017	Mao-Draayer Y, Wu Q, Wang Q, et al. Basic immunological profile changes of secondary progressive multiple sclerosis patients treated with BAF312 (SIPONIMOD). Journal of the Neurological Sciences 2017;381:783.
9	Gold 2017	Gold R, Giovannoni G, Cree B, et al. Impact of primary endpoint definitions and patient baseline characteristics on study outcomes in progressive multiple sclerosis. Multiple Sclerosis Journal 2017;23:660-661.
10	Vermersch 2017	Vermersch P, Bar-Or A, Cree B, et al. The EXPAND study results: Efficacy of siponimod in secondary progressive multiple sclerosis. European Journal of Neurology 2017;24:44.
11	Giovannoni 2017	Giovannoni G, Baror A, Cree B, et al. The EXPAND study results: Safety and tolerability of siponimod in patients with secondary progressive multiple sclerosis. European Journal of Neurology 2017;24:495.
12	Fox 2017a	Fox R, Kappos L, Bar-Or A, et al. Safety and tolerability of siponimod in patients with secondary progressive multiple sclerosis. Neurology 2017;88.
13	Kappos 2016a	Kappos L, Bar-Or A, Cree B, et al. Baseline subgroup characteristics of expand: A phase 3 study of siponimod (BAF312) for the treatment of secondary progressive multiple sclerosis. Neurology 2016;86.

#	Author, Year	Reference
14	Kappos 2014	Kappos L, Bar-Or A, Cree B, et al. Siponimod (BAF312) for the treatment of secondary progressive multiple sclerosis: Design of the phase 3 expand trial. Multiple Sclerosis 2014;20:927-928.
15	Kappos 2013a	Kappos L, Bar-Or A, Cree B, et al. Siponimod (BAF312) for the treatment of secondary progressive multiple sclerosis: Design of the phase 3 expand trial. Neurology 2013;80.
16	Kappos 2015	Kappos L, Bar-Or A, Cree B, et al. Siponimod (BAF312) for the treatment of secondary progressive multiple sclerosis (SPMS): baseline characteristics of the EXPAND study population. Multiple sclerosis. Volume 23, 2015:317-318.
17	Kappos 2017a	Kappos L, Bar-Or A, Cree B, et al. Efficacy of Siponimod in Secondary Progressive Multiple Sclerosis: Results of the Phase 3 Study. Neurology 2017;88.
18	Kappos 2013b	Kappos L, Bar-Or A, Cree B, et al. Siponimod (BAF312) for the treatment of secondary progressive multiple sclerosis: design of the phase 3 expand trial. Volume 80, 2013.
19	Fox 2017b	Fox R, Arnold D, Bar-Or A, et al. Effects of siponimod on MRI outcomes in patients with secondary progressive multiple sclerosis: results of the phase 3 EXPAND study. Multiple sclerosis journal. Conference: 7th joint ECTRIMS-ACTRIMS, MSPARIS2017. France. Volume 23, 2017:34-35.
20	CSR	CSR EXPAND
21	Kappos 2017b	Kappos L, Vermersch P, Bar-Or A, et al. Efficacy of siponimod on disability progression in SPMS patients with and without on-study relapses. Multiple sclerosis journal. Conference: 7th joint ECTRIMS-ACTRIMS, MSPARIS2017. France. Volume 23, 2017:397-398.
22	Kappos 2016b	Kappos L, Bar-Or A, Cree B, et al. Efficacy and safety of siponimod in secondary progressive multiple sclerosis-Results of the placebo controlled, double-blind, Phase III EXPAND study. Multiple Sclerosis 2016;22:828-829.
ASCEND trial (NCT01416181)		
23	Kapoor 2018a	Kapoor R, Ho PR, Campbell N, et al. Effect of natalizumab on disease progression in secondary progressive multiple sclerosis (ASCEND): a phase 3, randomised, double-blind, placebo-controlled trial with an open-label extension. The Lancet Neurology 2018;17:405-415.
24	Giovannoni 2017a	Giovannoni G, Freedman MS, Hartung HP, et al. Natalizumab improves walking and upper-limb disability compared with placebo in patients with secondary progressive multiple sclerosis: An integrated, post hoc area under the outcome-time curve analysis from the ASCEND trial. Multiple Sclerosis Journal 2017;23:36-37.
25	Giovannoni 2016	Giovannoni G, Steiner D, Sellebjerg F, et al. Sustained disability improvement in patients with secondary progressive multiple sclerosis (SPMS) assessed by a multicomponent endpoint: A post hoc analysis from the ASCEND study. Multiple Sclerosis 2016;22:671-672.
26	Kapoor 2016	Kapoor R, Steiner D, Miller A, et al. Subgroup analyses of natalizumab treatment response in ASCEND, a multicenter, double-blind, placebo-controlled, randomized phase 3 clinical trial in patients with secondary progressive multiple sclerosis (SPMS). Multiple Sclerosis 2016;22:874-875.
27	Steiner 2016	Steiner D, Arnold D, Freedman M, 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;87:e22.

#	Author, Year	Reference
28	Cano 2015	Cano S, Cleanthous S, Marquis P, et al. Measuring the impact of secondary progressive multiple sclerosis (SPMS) in the ASCEND trial: Equating the MSIS-29, MSWS-12, ABILHAND-56 and SF-36. Value in Health 2015;18:A713.
29	Steiner 2015	Steiner D, Hartung HP, Kapoor R, et al. Increasing levels of disability on objective measures of ambulation and upper extremity function are associated with increasing levels of patient-reported impairment in secondary progressive multiple sclerosis patients: Baseline data from ASCEND. Multiple Sclerosis 2015;23:310-311.
30	Kapoor 2015	Kapoor R, Arnold D, Miller A, et al. Gray matter volume correlates with information processing as measured by the symbol digit modalities test (SDMT) but not with physical disability as measured by the expanded disability status scale (EDSS) in patients with secondary progressive multiple sclerosis (SPMS): Analysis of baseline correlations from the ascend natalizumab study. Neurology 2015;84.
31	Giovannoni 2017b	Giovannoni G, Steiner D, Sellebjerg F, et al. Sustained disability improvement as assessed by a multicomponent endpoint in secondary progressive multiple sclerosis (SPMS) Patients: A post hoc analysis from ASCEND. Neurology 2017;88.
32	Cadavid 2013	Cadavid D, Brochet B, Mancardi G, et al. The MS-COG, a novel endpoint for measurement of cognitive function in multiple sclerosis clinical trials: baseline characteristics of the cognitive substudy of the ASCEND natalizumab secondary progressive multiple sclerosis study. Multiple sclerosis. Volume 19, 2013:508.
33	Mikol 2013	Mikol D, Freedman M, Goldman M, et al. ASCEND study of natalizumab efficacy on reducing disability in patients with secondary progressive multiple sclerosis: baseline demographics and disease characteristics. Multiple sclerosis. Volume 19, 2013:507-508.
34	Kapoor 2018b	Kapoor R, Sellebjerg F, Hartung HP, et al. Natalizumab Reduced Serum Levels of Neurofilament Light Chain in Secondary Progressive Multiple Sclerosis Patients From the Phase 3 ASCEND Study. Multiple sclerosis. Volume 24, 2018:988.
MS-SPI trial (NCT02220933)		
35	Morteau 2018	Morteau O, Lasser R, Sedel F, et al. Annual relapse rates (ARR) in patients with spinal progressive multiple sclerosis treated with MD1003 (high-dose pharmaceutical biotin). Multiple Sclerosis Journal 2018;24:31.
36	Laplaud 2018	Laplaud DA, Gout O, Clavelou P, et al. Effect of MD1003 (High-Dose Pharmaceutical Biotin) in Spinal Progressive Multiple Sclerosis (MS-SPI): Subgroup Analyses. Multiple sclerosis. Volume 24, 2018:33.
37	Laplaud 2017	Laplaud DA, Gout O, Clavelou P, et al. Effect of MD1003 (High-Dose Biotin) in spinal progressive multiple sclerosis (MS-SPI): subgroup analyses. Multiple sclerosis. Volume 23, 2017:402-403.
38	Tourbah 2015	Tourbah A, Lebrun-Frenay C, Edan G, et al. MD1003 (high doses of biotin) in progressive multiple sclerosis: Subgroup analyses of the MS-SPI trial. Multiple Sclerosis 2015;23:785.
39	Tourbah 2016	Tourbah A, Lebrun-Frenay C, Edan G, et al. MD1003 (high-dose biotin) for the treatment of progressive multiple sclerosis: A randomised, double-blind, placebo-controlled study. Multiple Sclerosis 2016;22:1719-1731.
MS-STAT trial (NCT00647348)		
40	MS-STAT trial	Chataway J, Schuerer N, Alsanousi A, et al. Effect of high-dose simvastatin on brain atrophy and disability in secondary progressive

#	Author, Year	Reference
		multiple sclerosis (MS-STAT): a randomised, placebo-controlled, phase 2 trial. Lancet (London, England). Volume 383, 2014:2213-2221.
41	Chan 2017	Chan D, Binks S, Nicholas JM, et al. Effect of high-dose simvastatin on cognitive, neuropsychiatric, and health-related quality-of-life measures in secondary progressive multiple sclerosis: secondary analyses from the MS-STAT randomised, placebo-controlled trial. The Lancet Neurology 2017;16:591-600.
42	Chan 2016	Chan D, Binks S, Nicholas J, et al. Effect of high-dose simvastatin on cognition in secondary progressive multiple sclerosis (MS-STAT cognitive): A randomised, placebo-controlled, Phase 2 trial. Multiple Sclerosis 2016;22:82-83.
43	Chataway 2015	Chataway J, Nicholas J, Wych J, et al. Smaller baseline brain volume and higher atrophy rate over two years is associated with poorer clinical outcomes: Post hoc analysis of the MS-STAT trial in secondary progressive MS. Neurology 2015;84.
44	Chataway 2012a	Chataway JS, Alsanousi A, Chan D, et al. The ms-stat trial: A phase II trial of high dose simvastatin for secondary progressive multiple sclerosis (SPMS): Initial results. Annals of Neurology 2012;72:S111.
45	Chataway 2011	Chataway J, Awad M, Meadmore K, et al. Cognitive and neuropsychiatric status in a large cohort of patients with secondary progressive multiple sclerosis. Journal of Neurology, Neurosurgery and Psychiatry 2011;82:e4.
46	Chataway 2010	Chataway J, Anderson V, Chan D, et al. The MS-Stat Trial: A phase II trial of high-dose simvastatin for secondary progressive multiple sclerosis: Baseline trial profile. Journal of Neurology, Neurosurgery and Psychiatry 2010;81:e55.
47	Chataway 2013	Chataway J, Schuerer N, Alsanousi A, et al. The ms-stat trial: High dose simvastatin slows brain atrophy and delays disability in secondary progressive multiple sclerosis: A phase II placebo-controlled trial. Neurology 2013;80.
48	Chataway 2012b	Chataway J, Alsanousi A, Chan D, et al. The MS-STAT trial: A randomised placebocontrolled phase II trial of high dose simvastatin in secondary progressive multiple sclerosis (SPMS). European Journal of Neurology 2012;19:87.
49	Chataway 2012	Chataway J, Alsanousi A, Chan D, et al. The MS-STAT trial: high dose simvastatin demonstrates neuroprotection without immune-modulation in secondary progressive multiple sclerosis (SPMS)-a phase II trial. Multiple sclerosis. Volume 18, 2012:509.
Morales 2017		
50	Morales 2017	Morales IB, Eleftheriou E, Maranda L, et al. The safety and efficacy of rituximab use in secondary-progressive multiple sclerosis (SPMS) at UMMHC: Five years follow up data. Neurology 2017;88.
51	Morales 2016	Morales IB, Eleftheriou E, Maranda L, et al. The safety and efficacy of rituximab use in secondary progressive multiple sclerosis (SPMS) at UMMHC: five years follow up data. Five years follow up data. Multiple Sclerosis 2016;22:805.
EUSPMS		
52	Kappos 1998	Kappos L, Polman C, Pozzilli C, et al. Placebo-controlled multicentre randomised trial of interferon β-1b in treatment of secondary progressive multiple sclerosis. Lancet 1998;352:1491-1497.
53	Kuhle 2016	Kuhle J, Hardmeier M, Disanto G, et al. A 10-year follow-up of the European multicenter trial of interferon β-1b in secondary-progressive

#	Author, Year	Reference
		multiple sclerosis. Multiple sclerosis (houndmills, basingstoke, england). Volume 22, 2016:533-543.
54	Sormani 2005	Sormani MP, Bruzzi P, Beckmann K, et al. The distribution of magnetic resonance imaging response to interferonβ-1b in multiple sclerosis. Journal of Neurology 2005;252:1455-1458.
55	Polman 2005	Polman CH, Kappos L, Dahlke F, et al. Interferon beta-1b treatment does not induce autoantibodies. Neurology 2005;64:996-1000.
56	Polman 2003	Polman C, Kappos L, White R, et al. Neutralizing antibodies during treatment of secondary progressive MS with interferon β-1b. Neurology 2003;60:37-43.
57	Molyneux 2001	Molyneux PD, Barker GJ, Barkhof F, et al. Clinical-MRI correlations in a European trial of interferon beta-1b in secondary progressive MS. Neurology 2001;57:2191-2197.
58	Kappos 2001	Kappos L, Polman C, Pozzilli C, et al. Final analysis of the European multicenter trial on IFNβ-1b in secondary-progressive MS. Neurology 2001;57:1969-1975.
59	Barkhof 2001	Barkhof F, Van Waesberghe JHTM, Filippi M, et al. T1 hypointense lesions in secondary progressive multiple sclerosis: Effect of interferon beta-1b treatment. Brain 2001;124:1396-1402.
60	Molyneux 2000	Molyneux PD, Kappos L, Polman C, et al. The effect of interferon beta-1b treatment on MRI measures of cerebral atrophy in secondary progressive multiple sclerosis. Brain 2000;123:2256-2263.
61	Sormani 2003	Sormani M, Bruzzi P, Beckmann K, et al. MRI metrics as surrogate endpoints for EDSS progression in SPMS patients treated with IFN beta-1b. Neurology. Volume 60, 2003:1462-1466.
62	Freeman 2001	Freeman J, Thompson A, Fitzpatrick R, et al. Interferon-beta1b in the treatment of secondary progressive MS: impact on quality of life. Neurology. Volume 57, 2001:1870-1875.
63	Miller 1999	Miller D, Molyneux P, Barker G, et al. Effect of interferon-beta1b on magnetic resonance imaging outcomes in secondary progressive multiple sclerosis: results of a European multicenter, randomized, double-blind, placebo-controlled trial. European Study Group on Interferon-beta1b in secondary progressive multiple sclerosis. Annals of neurology. Volume 46, 1999:850-859.
64	Polman 1995	Polman C, Dahlke F, Thompson A, et al. Interferon beta-1b in secondary progressive multiple sclerosis--outline of the clinical trial. Multiple sclerosis (houndmills, basingstoke, england). Volume 1 Suppl 1, 1995:S51-4.
65	Miller 1997	Miller D, Polman C, Pozzilli C, et al. MRI protocol for the European trial of Beta interferon-1b in secondary progressive multiple sclerosis. Journal of the neurological sciences. Volume 150, 1997:S251.
66	Thompson 1998	Thompson A, Kappos L, Polman C, et al. Interferon beta-1b delays progression of disability in secondary progressive multiple sclerosis: final results of the european multicentre study. Multiple sclerosis (houndmills, basingstoke, england). Volume 4, 1998:392.
67	Brex 2001	Brex P, Molyneux P, Smiddy P, et al. The effect of IFNbeta-1b on the evolution of enhancing lesions in secondary progressive MS. Neurology. Volume 57, 2001:2185-2190.
68	Kuhle 2004	Kuhle J, Hardmeier M, Rio J, et al. Long-term follow-up of the European Study of Interferon beta-1b (EUSPMS) in secondary progressive MS: predictors of treatment response. Multiple sclerosis (houndmills, basingstoke, england). Volume 10, 2004:S247.

#	Author, Year	Reference
NA SPMS		
69	Panitch 2004	Panitch H. Interferon beta-1b in secondary progressive MS: Results from a 3-year controlled study. Neurology 2004;63:1788-1795.
70	Goodkin 2000	Goodkin D. Interferon Beta-1b in secondary progressive MS: clinical and MRI results of a 3-Year randomized controlled trial. Neurology. Volume 54, 2000:2352.
NORDIC SPMS Study		
71	Andersen 2004	Andersen O, Elovaara I, Färkkilä M, et al. Multicentre, randomised, double blind, placebo controlled, phase III study of weekly, low dose, subcutaneous interferon beta-1a in secondary progressive multiple sclerosis. Journal of Neurology, Neurosurgery and Psychiatry 2004;75:706-710.
72	Beiske 2007	Beiske AG, Naess H, Aarseth JH, et al. Health-related quality of life in secondary progressive multiple sclerosis. Multiple Sclerosis 2007;13:386-392.
SPECTRIMS		
73	Francis 2001	Francis G. Randomized controlled trial of interferon-beta-1a in secondary progressive MS: Clinical results. Neurology 2001;56:1496-1504.
74	Li 2001	Li D, Zhao G, Paty D. Randomized controlled trial of interferon-beta-1a in secondary progressive MS: MRI results. Neurology. Volume 56, 2001:1505-1513.
75	Patten 2002	Patten S, Metz L. Interferon beta1a and depression in secondary progressive MS: data from the SPECTRIMS Trial. Neurology. Volume 59, 2002:744-746.
76	Sormani 2010	Sormani M, Stubinski B, Cornelisse P, et al. Magnetic resonance active lesions as individual-level surrogate for relapses in multiple sclerosis. Multiple sclerosis (houndmills, basingstoke, england), 2010:[Epub ahead of print].
Beutler 1996		
77	Beutler 1996	Beutler E, Sipe JC, Romine JS, et al. The treatment of chronic progressive multiple sclerosis with cladribine. Proceedings of the National Academy of Sciences of the United States of America 1996;93:1716-1720.
78	Sipe 1994a	Sipe JC, Romine JS, Koziol JA, et al. Cladribine in treatment of chronic progressive multiple sclerosis. Lancet 1994;344:9-13.
79	Sipe 1995	Sipe J, Romine J, Koziol J, et al. Cladribine treatment of chronic progressive (C/P) MS: a double-blind, crossover study with 2+ years' observation. Neurology. Volume 45 Suppl 4, 1995:A418.
80	Sipe 1994b	Sipe J, Romine J, Zyroff J, et al. Cladribine favorably alters the clinical course of progressive multiple sclerosis (MS). Neurology. Volume 44 Suppl 2, 1994:A357.
81	Wajgt 1997	Wajgt A, Strzyzewska S, Ochudlo S. The treatment of chronic progressive multiple sclerosis with cladribine. Journal of the neurological sciences. Volume Suppl, 1997:S116.
82	Rice 2000	Rice GPA, Filippi M, Comi G. Cladribine and progressive MS: Clinical and MRI outcomes of a multicenter controlled trial. Neurology 2000;54:1145-1155.
83	Bornstein 1991	Bornstein M, Miller A, Slagle S, et al. A placebo-controlled, double-blind, randomized, two-center, pilot trial of Cop 1 in chronic progressive multiple sclerosis. Neurology. Volume 41, 1991:533-539.

#	Author, Year	Reference
84	Fernandez 2018	Fernandez O, Izquierdo G, Fernandez V, et al. Adipose-derived mesenchymal stem cells (AdMSC) for the treatment of secondary-progressive multiple sclerosis: a triple blinded, placebo controlled, randomized phase I/II safety and feasibility study. Plos one. Volume 13, 2018.
IMPACT		
85	Cohen 2002	Cohen J, Cutter G, Fischer J, et al. Benefit of interferon beta-1a on MSFC progression in secondary progressive MS. Neurology. Volume 59, 2002:679-687.
86	Miller 2006	Miller D, Cohen J, Kooijmans M, et al. Change in clinician-assessed measures of multiple sclerosis and subject-reported quality of life: results from the IMPACT study. Multiple sclerosis (houndmills, basingstoke, england). Volume 12, 2006:180-186.
87	Krishnan 2012	Krishnan A, Goodman A, Potts J, et al. Slower walking speed is associated with reduced health-related quality of life in patients with SPMS. Neurorehabilitation and neural repair. Volume 26, 2012:661.
88	Cadavid 2010	Cadavid D, Lee S, Lucas N, et al. Effect of natalizumab on ambulatory improvement in relapsing-remitting and secondary progressive multiple sclerosis. Multiple Sclerosis 2010;16:S142.
Individual studies		
89	Patti 1999	Patti F, L'Episcopo MR, Cataldi ML, et al. Natural interferon-β treatment of relapsing-remitting and secondary- progressive multiple sclerosis patients. A two-year study. Acta Neurologica Scandinavica 1999;100:283-289.
90	Perrone 2014	Perrone C, Berriosmorales I, Beretich B, et al. Rituximab in the treatment of secondary-progressive multiple sclerosis. Multiple Sclerosis 2014;20:194.
91	Gunduz 2016	Gunduz T, Ozcan G, Çakar A, et al. Comparison of Mitoxantrone versus cyclophosphamide in patients with secondary progressive multiple sclerosis. European Journal of Neurology 2016;23:812.
92	Perini 2006	Perini P, Calabrese M, Tiberio M, et al. Mitoxantrone versus cyclophosphamide in secondary-progressive multiple sclerosis: A comparative study. Journal of Neurology 2006;253:1034-1040.
93	MS231 trial (International Natalizumab Multiple Sclerosis Trial)	Miller DH, Khan OA, Sheremata WA, et al. A controlled trial of natalizumab for relapsing multiple sclerosis. New England Journal of Medicine 2003;348:15-23.
94	Mostert 2013	Mostert J, Heersema T, Mahajan M, et al. The effect of fluoxetine on progression in progressive multiple sclerosis: A double-blind, randomized, placebo-controlled trial. ISRN Neurology 2013;1.
95	Vermersch 2012	Vermersch P, Benrabah R, Schmidt N, et al. Masitinib treatment in patients with progressive multiple sclerosis: a randomized pilot study. BMC Neurology 2012;12.
96	Bosco 1997	Bosco A, Cazzato G, Monti F, et al. Double-blind, placebo-controlled, randomized study of idebenone in patients with chronic progressive MS. Multiple sclerosis (houndmills, basingstoke, england). Volume 3 Suppl, 1997:349.
97	Wang 2018	Wang L, Qi CH, Zhong R, et al. Efficacy of alemtuzumab and natalizumab in the treatment of different stages of multiple sclerosis patients. Medicine (United States) 2018;97:e9908.

Table 75: SLR Update – Publications included in the SLR update

#	Author, Year	Reference
EXPAND trial (NCT01665144)		
1	Adlard, 2018	Adlard NE, Rendas-Baum R, Bjorner JB, et al. Responder Definition of the Multiple Sclerosis Impact Scale (Msis)-29 V2 among Patients with Secondary Progressive Multiple Sclerosis. Value in Health 2018;21 (Supplement 3):S390.
2	Department of Error, 2018	Erratum: Siponimod versus placebo in secondary progressive multiple sclerosis (EXPAND): a double-blind, randomised, phase 3 study (The Lancet (2018) 391(10127) (1263-1273), (S0140673618304756) (10.1016/S0140-6736(18)30475-6)). The Lancet 2018;392:2170.
3	Kappos, 2018	Kappos L, Vermersch P, Fox R, et al. Longer-term Safety with Siponimod Treatment in Multiple Sclerosis: Pooled Analysis of Data from the Bold and Expand Trials and their Extensions. Multiple Sclerosis and Related Disorders 2018;26:255-256.
SPECTRIMS		
4	Freedman, 2016	Freedman MS, Hayward B, Warth JD, et al. Clinical and MRI efficacy of IFN beta-1a SC tiw in MS patients with more advanced disease (EDSS 4.0-6.0). Multiple Sclerosis 2016;1):18.
5	Traboulsee, 2017	Traboulsee A, Li D, Tam R, et al. Subcutaneous interferon beta-1a three times weekly and the natural evolution of gadolinium-enhancing lesions into chronic black holes in relapsing and progressive multiple sclerosis: Analysis of PRISMS and SPECTRIMS trials. Multiple Sclerosis Journal Experimental Translational & Clinical 2017;3:2055217317745340.

6.1.2 Rationale for exclusion of trials used for indirect treatment comparisons from the SLR results

Table 76: Rationale for exclusion of trials used for indirect or treatment comparisons from the SLR results

Trial Reference	Inclusion status and reason
EXPAND trial	Included – Siponimod
ASCEND trial	Included – Natalizumab
MS-SPI trial	Excluded – Biotin
Wang 2018	Excluded – Alemtuzumab vs. Natalizumab
MS-STAT trial	Excluded – Simvastatin
Morales 2017	Excluded – Lack of comparable outcomes
Perrone 2014	Excluded – Lack of comparable outcomes
Gunduz 2016	Excluded – Mitoxantrone vs. cyclophosphamide
Perini 2006	Excluded – Mitoxantrone vs. cyclophosphamide
MS231 trial (International Natalizumab Multiple Sclerosis Trial)	Excluded – did not report ARR or CDP
Mostert 2013	Excluded – Fluoxetine
Vermersch 2012	Excluded – Masitinib
EUSPMS	Included – Interferon β
NA SPMS	Included – Interferon β
Nordic SPMS Study	Excluded – Unlicensed regimen of Interferon β-1a

SPECTRIMS trial	Included – Interferon β
Patti 1999	Excluded – did not report ARR or CDP
Beutler 1996	Excluded – Lack of comparable outcomes
Rice 2000	Excluded – Lack of comparable outcomes
Bornstein 1991	Excluded – Non-comparable outcome definitions
Fernandez 2018	Excluded – Stem cell therapy
IMPACT study	Included – Interferon β
Bosco 1997	Excluded – Idebenone

6.2 Appendix B: EXPAND

6.2.1 Relevant outcomes reported in EXPAND

Efficacy outcomes were assessed in the full analysis set, which comprised all study participants who were randomly assigned and received treatment. Following the intention-to-treat principle, all available data were used, irrespective of premature discontinuation of blinded study medication.

The statistical analysis for outcomes is summarised in Table 77.

Table 77. Description of statistical analysis carried out for each relevant outcome

Outcome	Method of analysis
Time to 3-month/ 6-month CDP	Differences were assessed using a Cox proportional hazards model and log-rank test. Kaplan–Meier estimates presented event rates by treatment group over time. Covariates in the Cox model were treatment, country, baseline EDSS score and SPMS group (with or without superimposed relapses, baseline definition). For the Cox proportional hazard model, participants with missing covariates were excluded from the analyses. Risk reduction was derived as (1 − hazard ratio) × 100. Observation of ≥ 374 events for 3-month CDP 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%.
Time to 3-month worsening of ≥ 20% in the T25FW	Differences were assessed using a Cox proportional hazards model and log-rank test. Kaplan–Meier estimates presented event rates by treatment group over time. Covariates in the Cox model were treatment, country, baseline EDSS score, baseline T25FW, and SPMS group (with or without superimposed relapses, baseline definition). For the Cox proportional hazard model, participants with missing covariates were excluded from the analyses. Risk reduction was derived as (1 − hazard ratio) × 100.
T2 lesion volume	Differences were assessed using a mixed model for repeated measures (assuming normally distributed change from baseline), with time of visit as the categorical factor. The model was adjusted for treatment, country, age, baseline T2 lesion volume, number of T1 Gd+ lesions at baseline, and SPMS group (with or without superimposed relapses, baseline definition). Adjusted mean was defined as the change from baseline in T2 lesion volume.
Percentage change in brain volume	Differences were assessed using a mixed model for repeated measures (assuming normally distributed data), with time of visit as the categorical factor.

Outcome	Method of analysis
	The model was adjusted for treatment, country, age, normalised brain volume at baseline, number of T1 Gd+ lesions at baseline, T2 lesion volume at baseline, and SPMS group (with or without superimposed relapses, baseline definition). Adjusted mean was defined as the change from baseline in brain volume.
MRI lesion number	Estimated by negative binomial regression.
Time to 6-month confirmed deterioration of SDMT oral score (*post hoc* analysis)	Differences were assessed using a Cox proportional hazards model. The model was adjusted for treatment, country, baseline EDSS, baseline SDMT-Oral score and SPMS group (with-/without superimposed relapses, baseline definition). Risk reduction was derived as (1 − hazard ratio) × 100.

ARR, annualised relapse rate; CDP, confirmed disability progression; EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; MRI, magnetic resonance imaging; SDMT, Symbol Digit Modalities Test; SPMS, secondary progressive multiple sclerosis; T25FW, timed 25-foot walk.
Source: Kappos et al., 2018[24]

6.2.2 Clinical effectiveness results EXPAND

Time to 3-month CDP

The primary efficacy objective was to compare siponimod versus placebo in delaying the time to 3-month CDP in patients with SPMS as measured by the EDSS. A 3-month CDP required that the EDSS score at progression, the 3-month confirmatory EDSS score and any EDSS scores obtained in between met the disability progression criteria. The confirmatory EDSS score could not have been recorded during an MS relapse.

Siponimod showed a 21.2% risk reduction compared with placebo for time to 3-month CDP based on EDSS that was statistically significant (Table 78, hazard ratio 0.79, p=0.0134).

Kaplan–Meier estimates for the percentage of patients free of 3-month CDP events were provided at Months 12, 24, and 36. Kaplan–Meier curves showed difference between siponimod and placebo, in favour of siponimod. Separation started early and was sustained over time (Figure 34). The log rank test was statistically significant, indicating a delay in time to 3-month CDP in the siponimod group (p=0.0129). Kaplan–Meier estimates indicated that the time to first quartile (25%) of patients experiencing 3-month CDP events was observed approximately 6 months later in patients randomised to siponimod relative to patients randomised to placebo.

Table 78: Time to 3-month CDP based on EDSS – Cox proportional hazards model

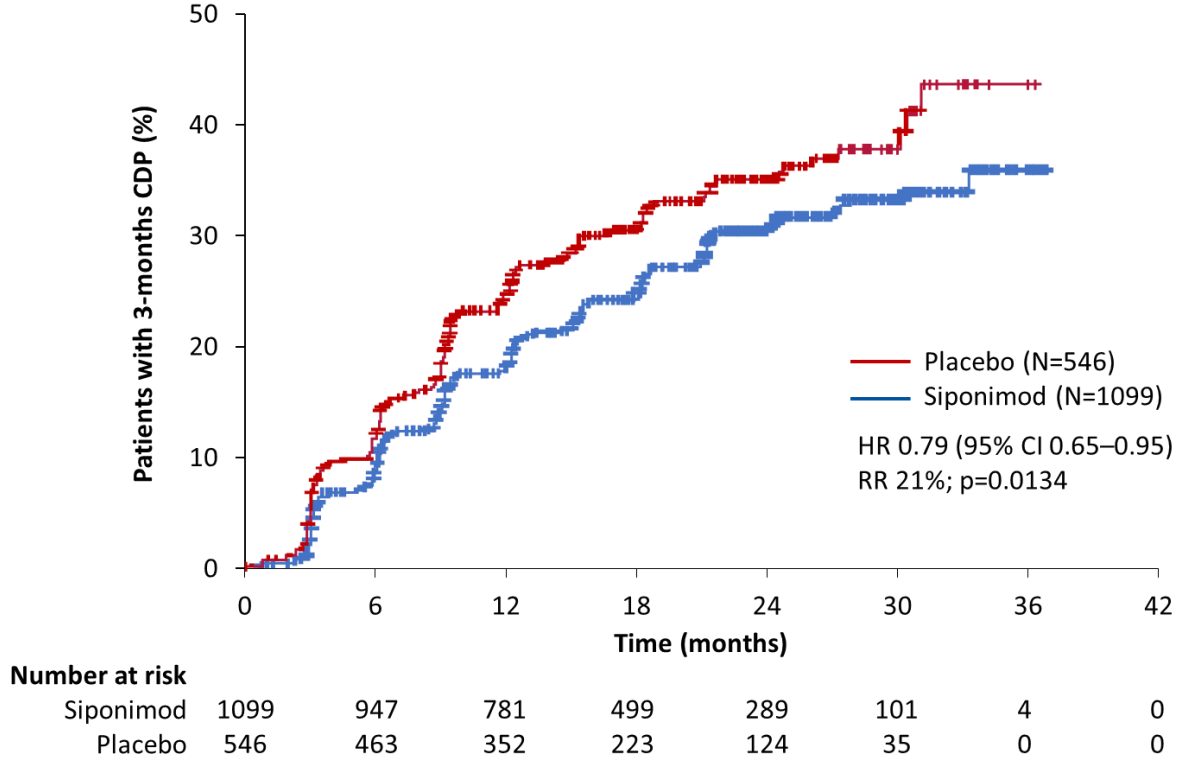
Treatment	n/N’	%	Comparison: Siponimod vs Placebo*		
			Risk reduction	Hazard ratio (95% CI)	p-value
Siponimod (N=1099)	288/1096	26.3	21.2%	0.79 (0.65; 0.95)	0.0134
Placebo (N=546)	173/545	31.7			

n/N’: n= number of subjects with events/N’=number of subjects included in the analysis (i.e. with non-missing covariates). *Using a Cox proportional hazards model with treatment, country/region, baseline EDSS, and SPMS group (with/without superimposed relapses, baseline definition) as covariates. Risk reduction is derived as (1-hazard ratio) * 100. For 3 siponimod patients and 1 placebo patient, information on the number of relapses in the last 2 years could not be derived (missing)

CDP: confirmed disability progression; CI: confidence interval; EDSS: expanded disability status scale; SPMS: secondary progressive multiple sclerosis.

Source: Kappos et al. 2018[24]

Figure 34: Time to 3-month CDP based on EDSS – Kaplan–Meier curves

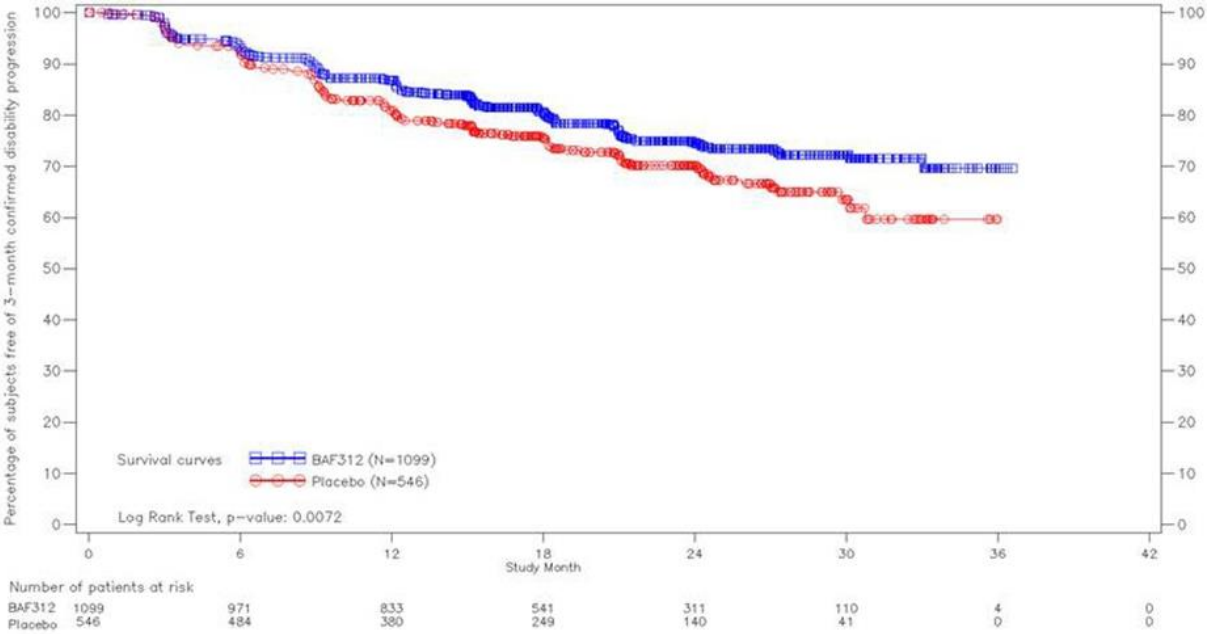


CDP: confirmed disability progression; CI: confidence interval; EDSS: expanded disability status scale; HR: hazard ratio; RR: risk ratio.

Source: Kappos et al. 2018.[24]

The time to 3-month CDP being sustained until last observation was analysed using the Cox proportional hazards model. This showed a risk reduction of 25.1% for siponimod relative to placebo, which was statistically significant (p=0.0060). This is graphically depicted using Kaplan–Meier curves (Figure 35).

Figure 35: Patients free of 3-month CDP based on EDSS and sustained until the end of the Core Part – Kaplan–Meier curves



CDP, confirmed disability progression; EDSS, expanded disability status scale.

Source: Novartis Data on File (Clinical Study Report for Siponimod)

Time to 6-month CDP

Siponimod treatment significantly delayed the time to 6-month CDP compared with placebo (Table 79). Risk reduction of 25.9% in 6-month CDP was observed for siponimod compared with placebo (hazard rate 0.74, p=0.0058). Kaplan–Meier curves (Figure 36) represent the same results.

Table 79: Time to 6-month CDP based on EDSS – Cox proportional hazards model

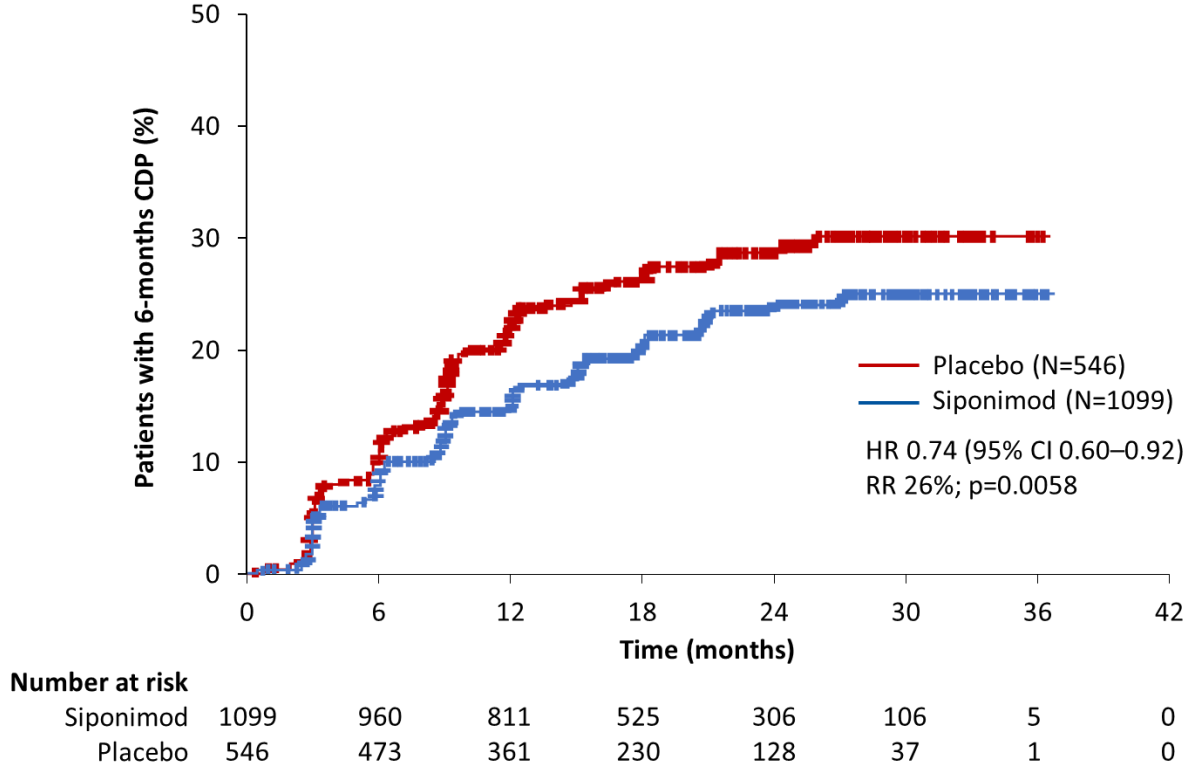
Treatment	n/N'	%	Comparison: Siponimod vs Placebo*		
			Risk reduction	Hazard ratio (95% CI)	p-value
Siponimod (N=1099)	218/1096	19.9	25.9%	0.74 (0.60; 0.92)	0.0058
Placebo (N=546)	139/545	25.5			

n/N': n= number of subjects with events/N'=number of subjects included in the analysis (i.e. with non-missing covariates). *Using a Cox proportional hazards model with treatment, country/region, baseline EDSS, and SPMS group (with/without superimposed relapses, baseline definition) as covariates. Risk reduction is derived as (1-hazard ratio) * 100

CDP, confirmed disability progression; CI, confidence interval; EDSS, enhanced disability status score; SPMS, secondary progressive multiple sclerosis.

Source: Kappos et al. 2018[24]

Figure 36: Time to 6-month CDP based on EDSS – Kaplan–Meier curves



CDP, confirmed disability progression; CI, confidence interval; EDSS, expanded disability status scale; HR, hazard ratio; RR, risk ratio.

Source: Kappos et al. 2018.[24]

Time to 6-month CDP sustained until last observation in the core part was analysed using the Cox proportional hazards mode. The results were supportive of the results obtained for the main analysis, showing a risk reduction of 22.0% for siponimod relative to placebo which was also statistically significant (p=0.0349).

6.2.2.1 Functional measures

Time to 3-month confirmed worsening in T25FW

The results for time to 3-month confirmed worsening in T25FW of at least 20% from baseline are summarised in Table 80. There was an observed risk reduction of 6.2% in favour of the siponimod group (p=0.4398).

Table 80: Time to 3-month confirmed worsening in T25FW of at least 20% from baseline – Cox proportional hazards model

Treatment	n/N'	%	Comparison: Siponimod vs Placebo*		
			Risk reduction	Hazard ratio (95% CI)	p-value
Siponimod (N=1099)	432/1087	39.7	6.2%	0.94 (0.80; 1.10)	0.4398
Placebo (N=546)	225/543	41.4			

n/N': n= number of subjects with events/N'=number of subjects included in the analysis (i.e. with non-missing covariates). *Using a Cox proportional hazards model with treatment, country/region, baseline EDSS, baseline T25FW, and SPMS group (with/without superimposed relapses, baseline definition) as covariates. Risk reduction is derived as (1-hazard ratio) * 100.

CI, confidence interval; EDSS, expanded disability status scale; SPMS, secondary progressive multiple sclerosis; T25FW, timed 25-foot walk test.

Source: Kappos et al. 2018;[24] Novartis Data on File (Clinical Study Report for Siponimod)

This secondary endpoint did not reach statistical significance. However, it is thought that T25FW may have suboptimal sensitivity for change in patients with more advanced MS (such as those in the EXPAND trial, with mean EDSS 5.4 at baseline),[24] as small increases in the EDSS can substantially affect their mobility. Nurses at a clinical advisory board organised by Novartis commented that the test may not be representative as it judges patients on just a single day, and it is not known how far the patient has already had to walk to the assessment centre. Additionally, patients often experience a high level of stress surrounding the test, which can lead to poor results. The reliability of this test is also affected by differences in test administration instructions (e.g. "static" vs "dynamic" start, "comfortable" vs. "maximum, but safe" pace),[128] meaning it may not be the most appropriate measure for ambulatory performance.

Multiple Sclerosis Walking Scale (MSWS-12)

In this study, patient walking ability was self-assessed by the patients using the MSWS-12. Change from baseline in MSWS-12 converted score is provided in Table 81. Total transformed scores on the MSWS-12 can range from 0-100 with higher scores reflecting greater impairment. The difference in adjusted means in the siponimod group showed smaller increases from baseline compared with placebo; however, the differences between groups were not statistically significant (the difference at Month 12 was nominally significant). The apparently smaller between-group differences at Month 24 compared with Month 12 should be interpreted in light of the smaller sample size and higher variability at Month 24.

Table 81: Change from baseline in MSWS-12 converted score, by time point – repeated measures model

Time-point	Adjusted means (SE)		Comparison of adjusted means Siponimod vs Placebo			
	Siponimod (N'=1022)	Placebo (N'=516)	Difference	SE	95% CI	p-value
Month 12	1.53 (0.678)	3.36 (0.908)	−1.83	1.030	(−3.85; 0.19)	0.0764
Month 24	4.16 (0.848)	5.38 (1.167)	−1.23	1.359	(−3.89; 1.44)	0.3671

N'=number of subjects included in the analysis (i.e. with a baseline and at least one post-baseline MSWS-12 converted score). Obtained from fitting a repeated measures model (assumes normally distributed data) with visit as categorical factor. Model was adjusted for treatment, region/country, baseline MSWS-12 converted score. Adjusted means refers to the change from baseline in MSWS-12.

CI, confidence interval; MSWS-12, multiple sclerosis walking scale; SE, standard error

Source: Kappos et al. 2018;[24] Novartis Data on File (Clinical Study Report for Siponimod)

6.2.2.2 MRI activity

T2 lesion volume

The results for change from baseline in T2 lesion volume at Month 12 and 24 are summarised in Table 82. The adjusted mean refers to the change from baseline in T2 lesion volume at each time point. The change from baseline in T2 lesion volume at both Month 12 and Month 24 was statistically significant, nominal p-values of <0.0001 were observed for between-treatment comparisons at both time points as well as for the average over Month 12 and Month 24.

Table 82: Change from baseline in T2 lesion volume (mm^3) by time point – repeated measures model

Time-point	Adjusted means (SE)		Comparison of adjusted means Siponimod vs Placebo			
	Siponimod (N'=995)	Placebo (N'=495)	Difference	SE	95% CI	p-value
Month 12	204.9 (67.47)	818.0 (87.29)	−613.1	95.39	(−800.2; −426.0)	<0.0001
Month 24	162.9 (73.90)	940.4 (97.20)	−777.5	108.62	(−990.6; −564.4)	<0.0001
Average over Months 12 and 24	183.9 (66.33)	879.2 (85.43)	−695.3	92.79	(−877.3; −513.3)	<0.0001

N'=number of subjects included in the analysis (i.e. with at least MRI scan post-baseline and non-missing covariates). Obtained from fitting a repeated measures model (model assumes normally distributed data) with visit as a categorical factor. Model was adjusted for treatment, country/region, baseline T2 lesion volume, number of T1 Gd-enhancing lesions at baseline, SPMS group (with/without superimposed relapses, baseline definition). Adjusted mean refers to the change from baseline in T2 lesion volume.

CI, confidence interval; MRI, magnetic resonance imaging; SE, standard error; SPMS, secondary progressive multiple sclerosis.

Source: Kappos et al. 2018;[24] Novartis Data on File (Clinical Study Report for Siponimod).

The yearly change in T2 lesion volume was analysed using a random coefficients model. The yearly change estimate was 96.61 mm^3 in the siponimod group compared with 460.51 mm^3 in the placebo group, showing a statistically significant difference between groups (−363.90 mm^3,

p<0.0001). These results show a clinically relevant reduction in T2 lesion volume in siponimod treated patients compared with those receiving placebo. The limitation of this analysis was it assumes that change in T2 lesion from baseline is linear over time.

T1 Gd-enhancing lesions

The proportion of patients free of T1 Gd-enhancing lesions is summarised in Table 83. At baseline, approximately 75% of patients in each group did not have T1 Gd-enhancing lesions. Over all post-baseline scans, 89.4% of siponimod patients and 66.9% of placebo patients were free of T1 Gd-enhancing lesions.

The results for number of T1 Gd-enhancing lesions by time point are summarised in Table 84. The mean number of lesions per scan was low in each treatment group. Statistically significant differences, favouring siponimod, were seen for number of T1 Gd-enhancing lesions at Month 12 and Month 24 (p<0.0001).

Table 83: Proportion of patients free of T1 Gd-enhancing lesions, by time point – summary statistics

	Siponimod, N=1099 n/m	Placebo, N=546 n/m
Proportion of patients free of T1 Gd-enhancing lesions (in this scan)		
Month 12	954/1019 (93.6)	391/507 (77.1)
Month 24	593/622 (95.3)	250/304 (82.2)
Proportion of patients free of T1 Gd-enhancing lesions (all post-baseline scans)		
All post-baseline scans	917/1026 (89.4)	341/510 (66.9)

n=number of subjects who are free of lesions. For all post-baseline scans, m=number of subjects with at least one post-baseline result. At time-points evaluated on a single MRI scan, m=number of subjects with result in this scan.

Source: Kappos et al. 2018,[24] Novartis Data on File (Clinical Study Report for Siponimod)

Table 84: T1 Gd-enhancing lesions per patient per scan, by time point – repeated measures negative binomial regression

Time-point	Adjusted mean (95% CI)*		Between-treatment comparison* Siponimod vs Placebo			
	Siponimod (N'=996)	Placebo (N'=496)	Rate reduction	Rate ratio	95% CI	p-value
Number of T1 Gd-enhancing lesions (in this scan)**						
Month 12	0.080 (0.058; 0.111)	0.640 (0.488; 0.839)	87.4%	0.126	0.083; 0.191	<0.0001
Month 24	0.074 (0.040; 0.138)	0.418 (0.288; 0.607)	82.2%	0.178	0.087; 0.362	<0.0001
Cumulative number of T1 Gd-enhancing lesions (all post-baseline scans)						
All post-baseline scans	0.08 (0.07; 0.10)	0.60 (0.47; 0.76)	86.7%	0.14	0.10; 0.19	<0.0001

N'=number of patients included in the analysis (i.e. with at least one MRI scan post baseline and non-missing values for the covariates included in the model). Adjusted mean (or rate) refers to the adjusted number of lesions per subject per scan. Rate reduction is derived as (1- rate ratio) * 100. *Obtained from fitting negative binomial regression model adjusted for treatment, age, baseline number of T1 Gd-enhancing lesions (offset=number of scheduled MRI scans). **A repeated measures regression model was implemented with visit as a categorical factor.

CI, confidence interval; MRI, magnetic resonance imaging.

Source: Kappos et al. 2018;[24] Novartis Data on File (Clinical Study Report for Siponimod).

The number of Gd lesions at each time point and cumulative number of T1 Gd-enhancing lesions/per scan (i.e. total number of lesions observed over all time-points divided by the total number of scans) were lower at each post-baseline time point in the siponimod group compared with the placebo group.

New or newly enlarging T2 lesions

A larger proportion of patients randomised to siponimod remained free of new or enlarging T2 lesions compared with placebo (Table 85). The proportions of patients free of new or enlarging T2 lesions compared with the previous scan were 62.2% and 78.8% for siponimod and 46.2% and 50.7% for placebo patients at Months 12 and 24, respectively. For all post-baseline scans (performed annually), 56.9% of siponimod patients and 37.3% of placebo patients were free of new or enlarging T2 lesions.

The results for number of new or enlarging T2 lesions by time point are summarised in Table 86. The rate ratio was the ratio of adjusted mean number of new/enlarging T2 lesions for siponimod versus placebo and rate reduction was derived from rate ratio. The mean number of new/enlarging T2 lesions compared with the previous scan favoured siponimod over placebo at Month 12 (73.4% rate reduction) and Month 24 (85.8%), and was statistically significant (p<0.0001), showing fewer patients with new/enlarging T2 lesions relative to placebo.

Table 85: Proportion of patients free of new or enlarging T2 lesions, by time point – summary statistics

	Siponimod, N=1099 n/m	Placebo, N=546 n/m
Proportion of patients free of new or enlarging T2 lesions (in this scan relative to previous scan)		
Month 12	636/1023 (62.2)	235/509 (46.2)
Month 24	493/626 (78.8)	154/304 (50.7)
Proportion of patients free of new or enlarging T2 lesions (overall)		
All post-baseline scans	584/1026 (56.9)	190/510 (37.3)

n=number of subjects who are free of lesions. At last assessment time-points, m=number of subjects at least one post-baseline result. At time-points evaluated on a single MRI scan, m=number of subjects with result in this scan.

Source: Kappos et al. 2018;[24] Novartis Data on File (Clinical Study Report for Siponimod).

Table 86: New or enlarging T2 lesions, by time point – repeated measures negative binomial regression

Time-point	Adjusted mean (95% CI)*		Between-treatment comparison* Siponimod vs Placebo			
	Siponimod (N'=997)	Placebo (N'=496)	Rate reduction	Rate ratio	95% CI	p-value
Number of new or enlarging T2 lesions (in this scan)**						
Month 12 (relative to baseline)	1.003 (0.858; 1.172)	3.776 (3.148; 4.528)	73.4%	0.266	0.215; 0.328	<0.0001
Month 24	0.489	3.437	85.8%	0.142	0.103; 0.196	<0.0001

(relative to Month 12)	(0.371; 0.644)	(2.800; 4.220)				
Number of new or enlarging T2 lesions (all post-baseline scans)						
All post-baseline scans	0.70 (0.58; 0.84)	3.60 (3.03; 4.29)	80.6%	0.19	0.16; 0.24	<0.0001

N'=number of patients included in the analysis (i.e. with at least one MRI scan post first dose and non-missing values for the covariates included in the model). Adjusted mean (rate) refers to the adjusted number of lesions per patient per year. The rate ratio is the ratio of adjusted means (or rate) of siponimod versus Placebo. Rate reduction is derived as (1 - rate ratio) *100. *Obtained from fitting a repeated measures negative binomial regression model with visit as a categorical factor. Model was adjusted for treatment, region/country, age, baseline number of Gd-enhancing T1 weighted lesions (offset=time between visits). All post-baseline visits up to and including Month 24 have been included.

CI, confidence interval; MRI, magnetic resonance imaging.

Source: Kappos et al. 2018,[24] Novartis Data on File (Clinical Study Report for Siponimod)

Percentage brain volume change (PBVC)

The analysis of PBVC relative to baseline is provided by time-point in Table 87. The PBVC relative to baseline was −0.283% for siponimod and −0.458% for placebo at Month 12 (p<0.0001). The decrease in PBVC was also significantly lower in patients treated with siponimod at Month 24 (p=0.0196).

Table 87: PBVC relative to baseline, by time point – repeated measures model

Time-point	Adjusted mean (SE)		Comparison of adjusted means Siponimod vs Placebo			
	Siponimod (N'=894)	Placebo (N'=436)	Rate reduction	Rate ratio	95% CI	p-value
Month 12	−0.283 (0.0264)	−0.458 (0.0341)	0.175	0.0367	0.103; 0.247	<0.0001
Month 24	−0.711 (0.0356)	−0.839 (0.0476)	0.128	0.0549	0.021; 0.236	0.0196
Average over Months 12 and 24	−0.50 (95% CI: −0.55; −0.44)	−0.65 (95% CI: −0.72; −0.58)	0.15	-	0.07; 0.23	0.0002

N'=number of subjects included in the analysis (i.e. with at least MRI scan post-baseline and non-missing covariates)

Obtained from fitting a repeated measures model (for normally distributed data) with visit as a categorical factor. Model was adjusted for treatment, country/region, age, normalised brain volume at baseline, number of T1 Gd-enhancing lesions at baseline, T2 volume at baseline, and SPMS group (with/without superimposed relapses, baseline definition). Adjusted mean refers to PBVC relative to baseline. All post-baseline visits up to and including Month 36 have been included.

CI, confidence interval; PBVC, percentage brain volume change; SE, standard error; SPMS, secondary progressive multiple sclerosis.

Source: Kappos et al. 2018;[24] Novartis Data on File (Clinical Study Report for Siponimod).

6.2.2.3 Relapse-related measures

Annual Relapse Rate (ARR)

The adjusted group-based (aggregate) ARRs showed low incidence of relapses in the study population (Table 88). Analysis of adjusted ARR using negative binomial model for confirmed

relapses showed a 55.5% rate reduction for confirmed relapses for siponimod compared with placebo (ARR ratio 0.445, p<0.0001).

Table 88: ARR for confirmed relapses – negative binomial regression

Treatment	Adjusted ARR (95% CI)*	Comparison: Siponimod vs Placebo*		
		Rate reduction	ARR ratio (95% CI)	p-value
Siponimod (N=1099)	0.071 (0.055; 0.092)	55.5%	0.445 (0.337; 0.587)	<0.0001
Placebo (N=546)	0.160 (0.123; 0.207)			

Analysis period: from first day of study drug up to end of core part. *Obtained from fitting a negative binomial regression model adjusted for treatment, country/region, baseline EDSS, baseline number of T1 Gd-enhancing lesions, and SPMS group (with/without superimposed relapses, baseline definition) (offset: time in analysis period in years).

ARR, annual relapse rate; CI, confidence interval; EDSS, expanded disability status scale.

Source: Kappos et al. 2018[24]

Time to first relapse

The analysis of time to first confirmed relapse showed a risk reduction of 46.4% that favoured siponimod (hazard ratio 0.54, p<0.0001) (Table 89). Time to first confirmed relapse was significantly delayed by siponimod (log-rank test, p<0.0001).

Kaplan–Meier curves depicting the percentage of patients who were free of confirmed relapse are provided in Figure 37. The Kaplan–Meier curves show a difference between siponimod and placebo in the percentage of patients free of confirmed relapse and the log rank test indicated a significant difference between groups (p<0.0001).

Table 89: Time to first confirmed relapse – Cox proportional hazards model

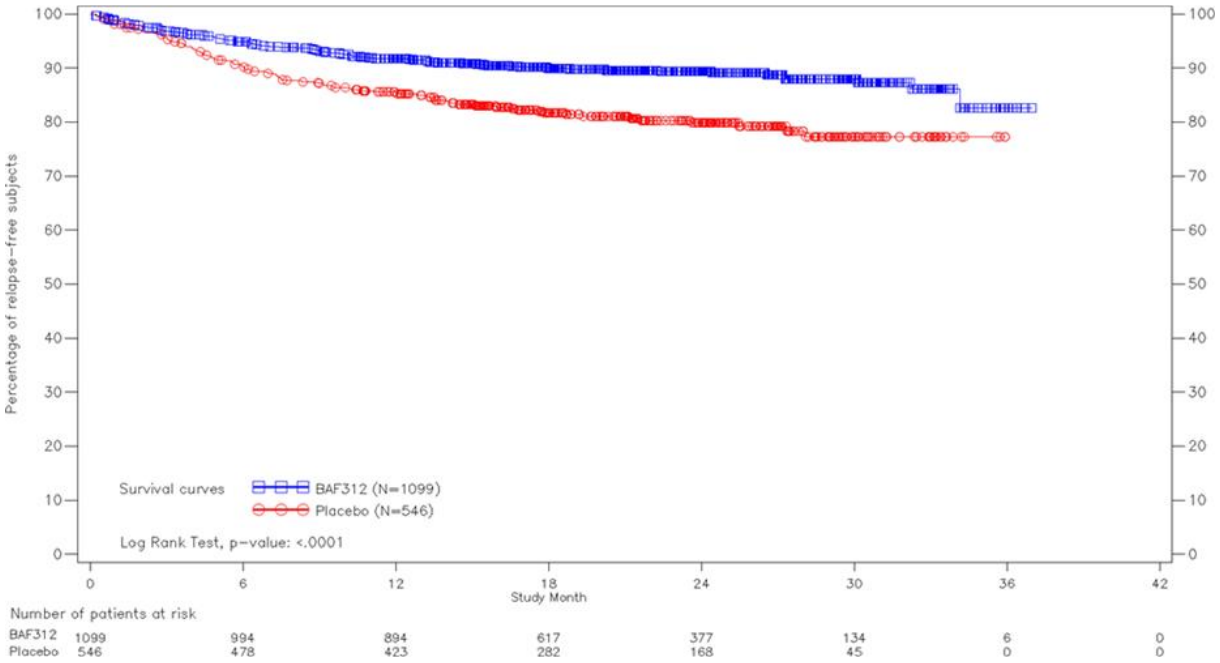
Treatment	n/N’	%	Comparison: Siponimod vs Placebo*		
			Risk reduction	Hazard ratio (95% CI)	p-value
Siponimod (N=1099)	113/1061	(10.7)	46.4%	0.54 (0.41; 0.70)	<0.0001
Placebo (N=546)	100/528	(18.9)			

n/N’: n= number of patients with events/N’=number of patients included in the analysis (i.e. with non-missing covariates). *Using a Cox proportional hazards model with treatment, country/region, baseline EDSS, baseline number of T1 Gd-enhancing lesions, and SPMS group (with/without superimposed relapses, baseline definition) as covariates. Risk reduction is derived as (1- hazard ratio) * 100.

CI, confidence interval; EDSS, expanded disability status scale; SPMS, secondary progressive multiple sclerosis.

Source: Kappos et al. 2018,[24] Novartis Data on File (Clinical Study Report for Siponimod)

Figure 37: Percentage of relapse-free (confirmed relapse) subjects – Kaplan–Meier curves



Source: Novartis Data on File (Clinical Study Report for Siponimod)

Proportion of patients with relapse

The proportion of patients with relapse (confirmed relapse and any relapse) is summarised by treatment group in Table 90. Relapses were observed in a lower percentage of patients treated with siponimod (16.7%) compared with placebo (26.0%).

Table 90: Proportion of patients with relapse

	Siponimod (N=1099) n (%)	Placebo (N=546) n (%)
Patients with any relapse (confirmed or unconfirmed)	184 (16.7)	142 (26.0)
Patient with confirmed relapse	113 (10.3)	102 (18.7)

Source: Novartis Data on File (Clinical Study Report for Siponimod).

6.2.2.4 Health-related quality of life

Multiple Sclerosis Impact Scale (MSIS-29)

A higher score on the MSIS-29 was indicative of greater impact of MS on day-to-day life from a patient's perspective.

For physical impact scores, the adjusted mean differences of −2.89 at Month 12 (p=0.0034, unadjusted for multiplicity) favoured siponimod, but this was not maintained at Month 24 (p=0.3000, unadjusted for multiplicity) (Appendix L). The apparently smaller between-group differences at Month 24 compared with Month 12 should be interpreted in light of the small sample size and higher variability at Month 24. The average over all visits for adjusted mean difference was −2.09, which showed a difference (p=0.0231) favouring siponimod.

For psychological impact scores, statistical significance was not achieved at Month 12 or Month 24 (p=0.0604 and 0.6703, respectively). The average over all visits for adjusted mean difference was −1.97, which showed a difference (p=0.0441) favouring siponimod.

EQ-5D-3L

The EQ-5D included a health state classification and a visual analogue scale (VAS) score. The health state classification was converted to a utility index score based on the value set for the UK.

For the EQ-5D utility index scores,[129] the small adjusted mean difference between treatment groups of 0.025 at Month 12 showed a difference (p=0.0392, unadjusted for multiplicity) favouring siponimod, but this was not maintained at Month 24 (p=0.0913, unadjusted for multiplicity) (Appendix L). The changes from baseline in the siponimod group were −0.023 at Month 12 and −0.039 at Month 24 and −0.048 and −0.069 at the respective timepoints in the placebo group. The average over all visits for adjusted mean difference was 0.029, which showed a difference (p=0.0085) favouring siponimod.

For the VAS score statistical significance for the adjusted mean differences was not achieved at Month 12 or Month 24 (p=0.0722, p=0.4712, respectively).

6.2.2.5 Time to wheelchair analysis

As EXPAND demonstrated the ability of siponimod to slow disability progression and cognitive decline in an SPMS population, an analysis was undertaken to evaluate the effect of siponimod compared to placebo in delaying disability progression to EDSS ≥7 (i.e. needing a wheelchair), sustained until the end of the EXPAND study, in patients with SPMS.

Methods

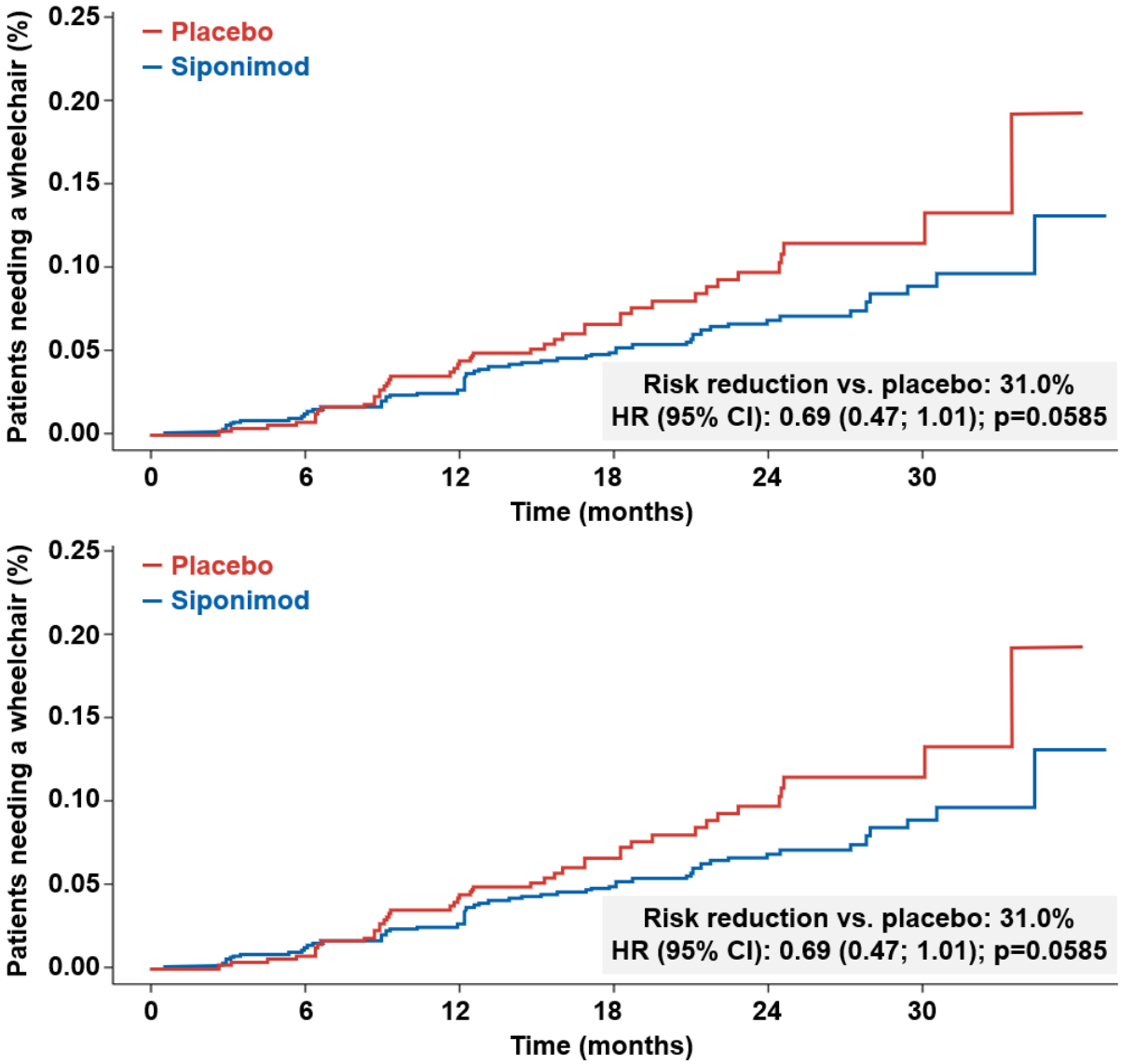
A *post hoc* analysis of the EXPAND study population evaluating the time to reach EDSS ≥7, based on sustained progression until the last assessment in the core part of the EXPAND study (up to three years), using two models:[29]

- **Survival analysis** – performed on the overall study population and a subset of patients from the EXPAND study with a baseline EDSS of 6.5 at a high risk of needing a wheelchair (siponimod, n=293; placebo, n=119). Time to sustained progression was assessed by a Cox proportional hazards model, with treatment as the covariate. Analyses excluded all EDSS assessments performed during relapse. An adjusted/weighted survival analysis was performed in the overall population to match the distribution of baseline EDSS between the groups
- **Multi-state model** – performed on the overall EXPAND study population (siponimod, n=1,099; placebo, n=546). Three disease states were defined (EDSS ≤5, 5.5-6, and 6.5) and the transitions from one state to the next and sojourn times in each state were calculated. Time to EDSS ≥7 from any disease state using all transitions through all intermediate states, was predicted. Results were extrapolated from estimated parameters to calculate median time to progression to EDSS ≥7 for the overall population (assuming that treatment effect is preserved).

Results: survival analysis

In the overall study population, after adjustment for baseline EDSS, a lower proportion of patients progressed to EDSS ≥7.[29] A 31.0% risk reduction versus placebo was observed for siponimod (HR, 0.69; 95% CI, 0.47–1.01; p=0.0585).

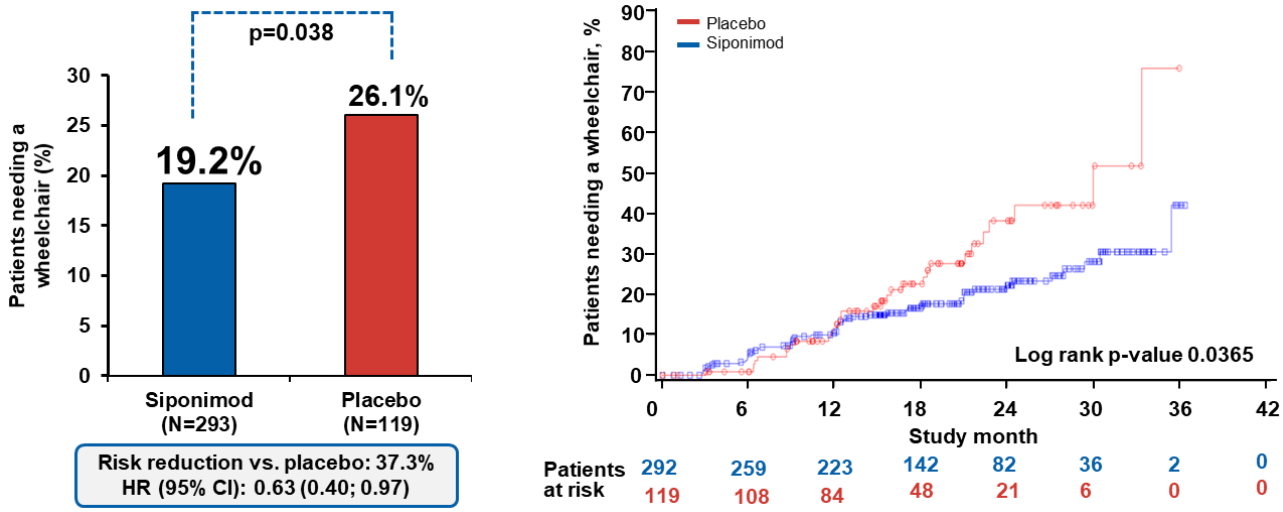
Figure 38: Proportion of patients needing a wheelchair after adjusting for baseline EDSS – overall study population



Adjusted/weighted: Survival estimates were calculated assuming EDSS distribution was balanced between the treatment groups
CI, confidence interval; EDSS, Expanded Disability Status Scale; HR, hazard ratio
Source: Vermersch et al., 2019.[29]

In patients with EDSS 6.5 at baseline, a lower proportion of siponimod-treated patients progressed to EDSS ≥7, compared to placebo (19.2% vs 26.1%; Figure 39).[29] This represents a 37.3% reduction in the risk of progressing to EDSS ≥7 compared with placebo (HR [95% CI]: 0.63 [0.40-0.97]; P=0.038).

Figure 39: Proportion of patients with sustained progression to EDSS ≥7[a] – subgroup analysis



[a]After onset of progression, all assessments had EDSS ≥7 until the end of the core part
CI, confidence interval; EDSS, Expanded Disability Status Scale; HR, hazard ratio
Source: Vermersch et al., 2019.[29]

Results: multi-state model

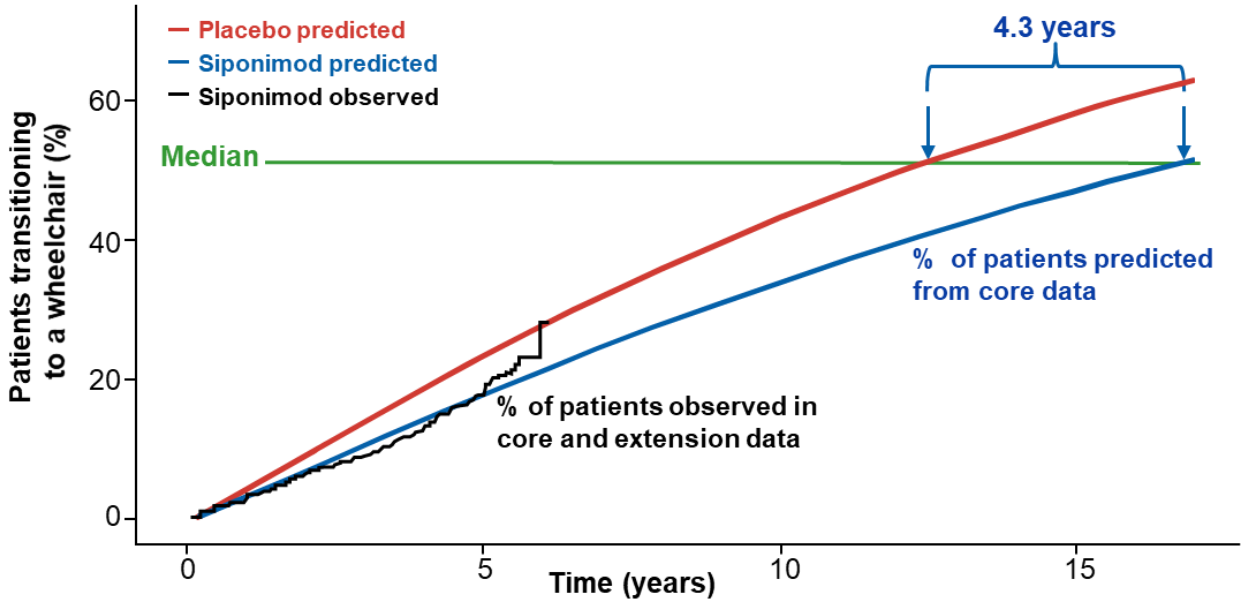
Siponimod reduced the risk of progression to EDSS ≥7 in individuals with EDSS ≥6.5, compared to placebo (HR = 0.72 [0.48–1.06]; Table 91). Under the assumption of the model (consistent effect over time), compared to placebo, siponimod extended the median time to EDSS ≥7 by 4.3 years in the overall population (12.0 years vs. 16.3 years; Figure 40).

Table 91: Transition to wheelchair –multi-state model

	Hazard ratio	Lower CI	Upper CI
EDSS ≤5 - 5.5-6	0.79	0.63	1.00
EDSS 5.5-6 - ≤5	0.96	0.73	1.27
EDSS 5.5-6 - ≥6.5	1.14	0.93	1.39
EDSS ≥6.5 - 5.5-6	1.15	0.87	1.50
EDSS ≥6.5 - Wheelchair	0.72	0.48	1.06

CI, confidence interval; EDSS, expanded disability status scale.
Source: Vermersch et al., 2019.[29]

Figure 40: Proportion of patients transitioning to a wheelchair (EDSS ≥7) – extrapolation to median time to progression



Source: Vermersch et al., 2019.[29]

Conclusion

The post hoc analyses suggest that siponimod delayed time to wheelchair dependence, further supporting the clinical relevance of the effect of siponimod on delaying physical disability progression in patients with SPMS beyond the core part of the EXPAND trial.[29] The models extrapolate far beyond the duration of observation in EXPAND, therefore the results should be considered with caution.

6.2.2.6 Sensitivity analysis of CDP independent of relapse: Estimands analysis

In addition to its efficacy on CDP based on EDSS, siponimod demonstrated a strong effect on inflammatory outcomes such as MRI activity and relapse rate. Incomplete relapse recovery results in measurable disability progression, potentially skewing the results of CDP, whereas subclinical MRI measures do not directly affect the measurement of CDP. As such, on-study relapses were considered as “intercurrent events” with respect to determining CDP, as discussed in the draft ICH E9(R1) addendum on estimands and sensitivity analysis in clinical trials.[130] Therefore sensitivity analyses were undertaken on the estimate of effect on CDP unrelated to effect on relapses.

A principal stratum analysis was undertaken to estimate the treatment effect of siponimod on disability progression in non-relapsing patients. This analysis is required as it is not possible to determine the true “non-relapser” subgroup: pre-study non-relapsers may go on to relapse during the study and the on-study non-relapsers group is affected by the treatment effects of siponimod.

Additionally, hypothetical strategies analyses were undertaken to test the separation of the treatment effect on disability progression from that on relapses by assuming either that no relapses happened or that relapses happened equally between arms.

Results of the sensitivity analyses are presented below.

Evaluation of efficacy on CDP in non-relapsing patients

The estimand to address the treatment effect of siponimod on disability progression in non-relapsing patients was defined as follows:

- *Population*: non-relapsers i.e. patients who would not relapse over the specific period of time regardless of treatment assignment (siponimod or placebo), within the targeted SPMS population defined by inclusion/exclusion criteria of EXPAND
- *Variable*: occurrence of 3-month CDP over the specified period of time
- *Intercurrent event*: the intercurrent event of on-study relapse is captured through the population definition
- *Population-level summary*: risk ratio

The non-relapser population of interest is one of four mutually exclusive subgroups, principal strata which are defined according to the potential occurrence of an MS relapse in a given time window:

- *Non-relapsers*: the principal stratum (PS) of patients that would not relapse regardless of treatment
- *Definite relapsers*: the PS of patients that would relapse regardless of treatment
- *Benefiters*: the PS of patients that would relapse if assigned to placebo, and would not relapse if assigned to siponimod
- *Harmed*: the PS of patients that would not relapse if assigned to placebo, and would relapse if assigned to siponimod

It was assumed that no patients fall into the “harmed” principal stratum. This assumption is plausible as given the anti-inflammatory mechanism of siponimod, it is highly unlikely that a patient who would not have relapsed if untreated would experience a relapse if assigned to the active treatment arm. Deviation from this monotonicity assumption could happen in the presence of rebound effect: this was explored in sensitivity analysis which showed both partial and full relaxation of the monotonicity assumption have negligible impact on the conclusions of the primary principal stratum analysis (data not presented).

The estimation of the proportion of patients in each of the remaining strata and the treatment effect in the “non-relapsing” stratum was carried out with Bayesian logistic regression for the disability progression rate at 12, 18 and 24 months. The regression model was adjusted for baseline EDSS and indicator of relapses in the 2 years prior to study, and the non-relapsing population risk ratios were subsequently obtained by standardisation (Table 92).

Table 92: Effect of siponimod in subgroup of “non-relapsing patients” – principal stratum analysis

Endpoint	Principal stratum – non-relapsers* Estimates of relative risk (posterior median and 95% CI)		
	12 months	18 months	24 months
3-month CDP	0.80 (0.56; 1.08)	0.86 (0.57; 1.24)	0.82 (0.48; 1.32)
6-month CDP	0.67 (0.44; 0.93)	0.71 (0.42; 1.09)	0.71 (0.37; 1.21)

*Patients who would not relapse over the specified period of time on study regardless of treatment assignment
CDP, confirmed disability progression; CI, confidence interval.

The estimated percentages of non-relapsers range from 80–87% for the time intervals considered, indicating that a substantial majority of patients included in this study belong to the non-relapser principal stratum.

Numerically the relative risk for 3-month CDP is between 0.80 and 0.86, indicating a possible 14–20% risk reduction by siponimod treatment not driven by an effect on relapses. This result is consistent with the effect on the overall population for time to 3-months CDP (HR=0.79).

The relative risk for 6-month CDP is between 0.67 and 0.71 indicating a larger risk reduction not driven by an effect on relapses. Six-month CDP is less likely to be driven by relapses. This may explain a RR close but numerically stronger to the HR reported on the overall population (0.74) for time to 6-month CDP.

Treatment effect on disability progression independent of a treatment effect on relapses in the overall population

The question of treatment effect on disability progression independent of an effect on relapses in the overall population is a hypothetical question in the sense of ICH guideline E9 (R1).[130]

Two versions of a hypothetical estimand were defined, denoted as “hypothetical prescriptive” and “hypothetical natural” estimand, respectively. The two versions have the same attributes for population, variable and population-level summary, but differ in the handling of the intercurrent event (relapse). The versions of the main estimand to address the second scientific question of interest were defined as follows:

- *Population* – SPMS population defined by inclusion/exclusion criteria
- *Variable* – Occurrence of 3 month confirmed disability progression over the specified period of time
- *Intercurrent event* – The intercurrent event of on-study relapse will be handled using two hypothetical strategies: assuming no patients would experience intercurrent relapses (hypothetical prescriptive), or assuming patients in both treatment arms would have the same risk of experiencing intercurrent relapses (hypothetical natural)
- *Population-level summary* – Hazard ratio

An analysis targeting the “hypothetical prescriptive” estimand was provided by a Cox model with censoring at the time of first relapse. The validity of this estimate relied on 2 assumptions:

- The reasonable assumption that the effect of siponimod on CDP before the first relapse reflects the general effect of siponimod on the course of the disease excluding periods affected by relapsing events (i.e. independent of effect on relapses).
- The assumption that the rate of progressive disability accumulation between relapses is independent from relapse rate. Should this assumption not be valid, the censoring at time of relapse which is strongly related to treatment received would be informative, leading to biased estimates for the standard Cox model. To correct and assess the extent of such potential bias a Cox model with Inverse Probability Censoring Weight (IPCW) was used.

An analysis targeting the “hypothetical natural” estimand was based on a simulation approach where studies are simulated from empirical distributions but with the constraint of having similar relapse rate in both arms.

Of note, the hypothetical prescriptive scenario is meaningful from a clinical perspective as it studies treatment effect on the progressive accumulation of disability between relapsing episodes. On the contrary, the hypothetical natural scenario is difficult to interpret as it focuses on pre- and post-relapse CDP in a situation that ignores one major effect of treatment effect and

that will therefore never be observed. For this reason and considering also the strength of the assumptions required for the estimate to be valid, this second analysis should be considered with more caution.

Table 93: Estimation of effect of siponimod on CDP in all SPMS patients independent of treatment effect on relapses

Endpoint	Cox model with censoring at time of first relapse	Cox model with IPCW*	Simulations based on empirical distribution**
3-month CDP	0.872 (0.705; 1.079)	0.856 (0.703; 1.043)	0.821 (0.678; 0.990)
6-month CDP	0.776 (0.613; 0.982)	0.771 (0.619; 0.961)	0.774 (0.626; 0.963)

*Inverse Probability Censoring Weight; HR estimation and confidence interval. **HR estimation and confidence interval. Simulation by relapse prognostic levels. Cox models included baseline EDSS score and presence relapse in the 2 years prior to inclusion as covariates
CDP, confirmed disability progression; EDSS, expanded disability status scale; HR, hazard ratio; IPCW, inverse probability censoring weight.

Table 93 shows that the estimated effect for 3-month CDP is maintained and becomes even stronger when correcting bias due to treatment effect on relapses with IPCW. Nominal statistical significance is observed on 6-month CDP while for 3-month CDP upper limit of 95% CI is around 1.

Simulation results for the hypothetical natural situation show similar or stronger trends in the same direction.

The stability of the HR for 6-month CDP after bias correction confirms the expected lower sensitivity of this endpoint to occurrence of relapses.

6.2.2.7 Sensitivity analysis: Impact of primary endpoint definitions from EXPAND and other clinical trials

In addition to EXPAND, results from three other studies in progressive MS have become available in the past two years:

- INFORMS on fingolimod in PPMS[106]
- ASCEND on natalizumab in SPMS[42]
- ORATORIO on ocrelizumab in PPMS[101]

In all four trials, EDSS based CDP was used either as the only primary endpoint or as a component of composite PEPs. However in the ORATORIO study, the primary endpoint definition was different with subjects discontinuing treatment prematurely with a tentative progression being considered to have confirmed progression. Sensitivity analyses for EXPAND were conducted by investigating the impact of primary endpoint definitions from EXPAND and ORATORIO, and by modelling the hazard ratio of 3-month CDP for siponimod in study populations comparable to INFORMS, ASCEND or ORATORIO.[131]

Methods

EDSS-based CDP was re-analysed using the primary endpoint definitions from ORATORIO.[131] Subsequently, a Cox regression model on EXPAND IPD was used to predict the hazard ratio for siponimod, based on average patient baseline characteristics from ORATORIO, ASCEND and INFORMS. Variable selection methods were used to identify covariates most predictive of the outcome, and the following candidate covariates based on baseline characteristics were utilised:

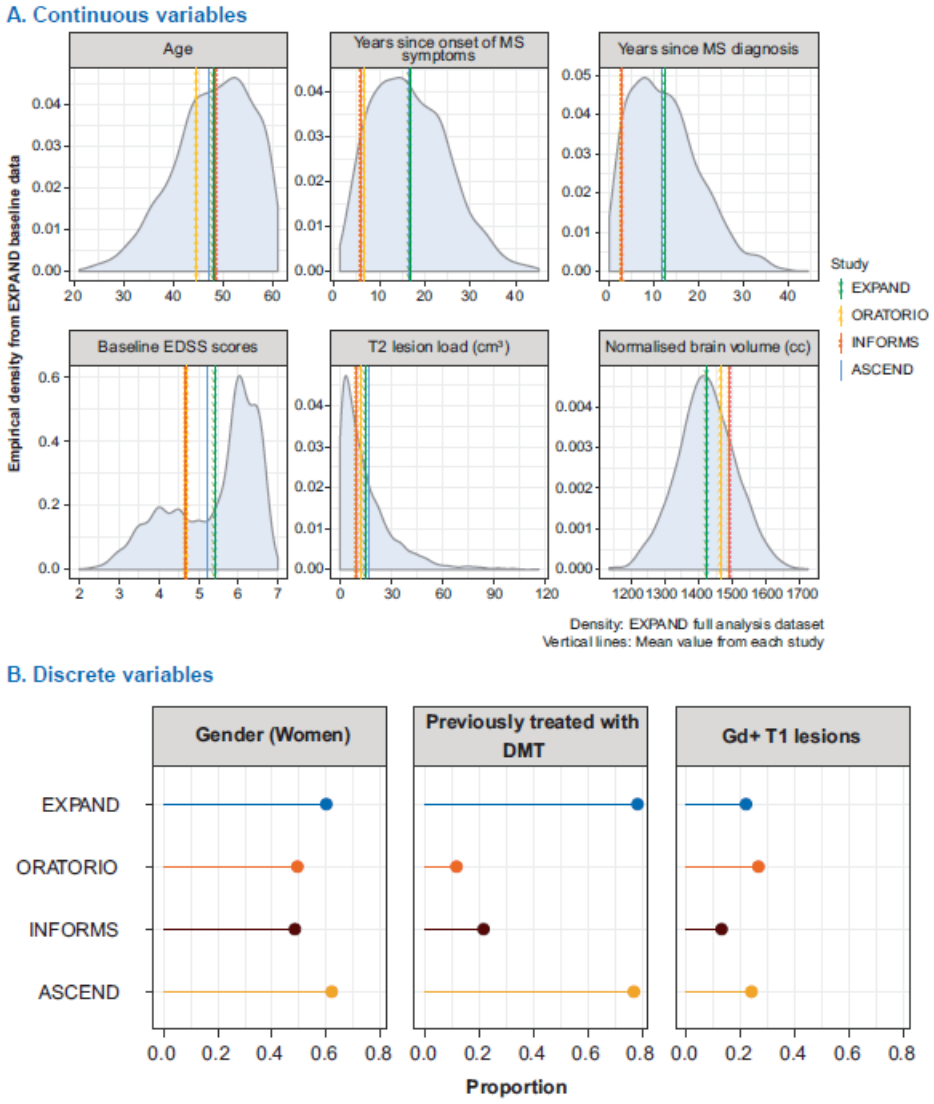
- Continuous: Age, EDSS, brain volume, T2 lesion volume, and disease duration since diagnosis/symptoms
- Discrete: Presence of gadolinium-enhancing (Gd+) lesions, previous disease-modifying therapies (DMT) and gender

Results

Baseline characteristics

The baseline characteristics of the various study populations are presented in Figure 41.[131] Overall the study populations were comparable, however the EXPAND and ASCEND study populations had higher baseline EDSS, and longer disease duration since diagnosis or first symptoms. The proportions of women and patients previously treated with DMTs were also higher in these studies. In addition, the number of Gd+ T1 lesions and the number of treatment naïve patients were higher in ORATORIO trial.

Figure 41: Comparison of Baseline Characteristics



DMT, disease modifying therapies; EDSS, expanded disability status scale; Gd+, gadolinium-enhancing; MS, multiple sclerosis.

Impact of different primary endpoint definitions

In the EXPAND trial predefined primary outcome, the observed HR for reduction in the risk of 3-month CDP was in favour of siponimod versus placebo (HR=0.79; 95% confidence interval [CI]: 0.65; 0.95).[24]

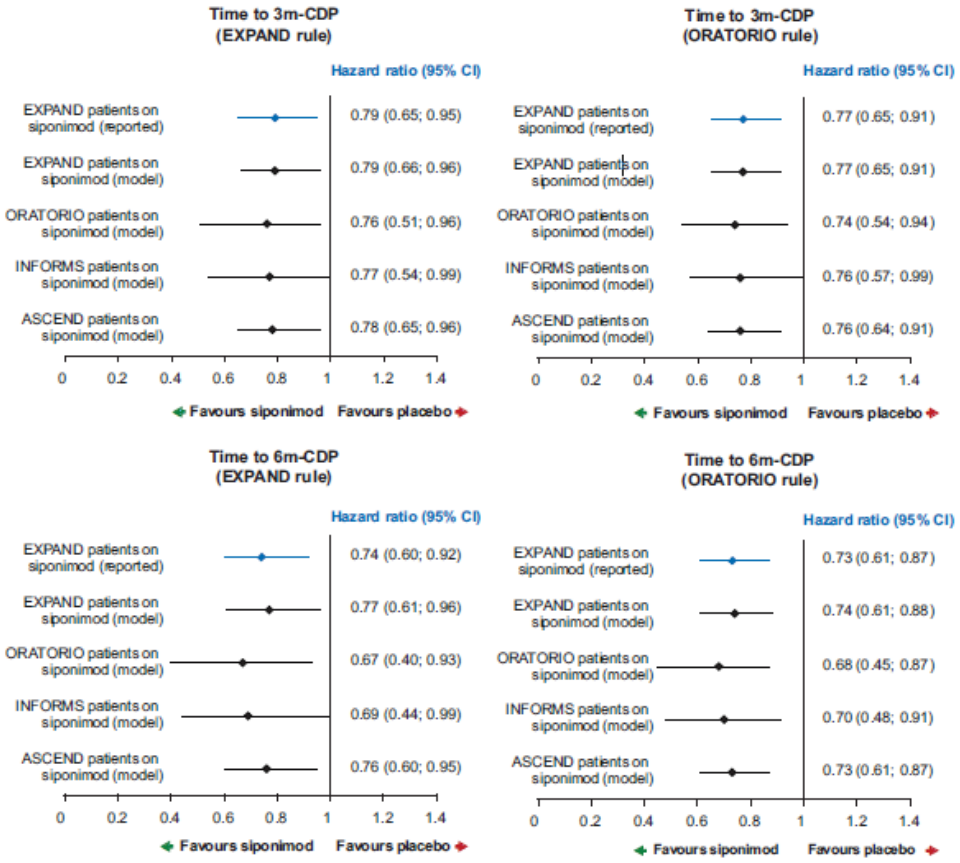
When using the PEP definition of the ORATORIO trial for EXPAND population, the calculated HRs and 95% CIs were similar to the observed ones in EXPAND; for example, by the ORATORIO definition ORATORIO, the HR of siponimod was 0.76 (95% CI: 0.63; 0.91).[131]

Model-based prediction of 3-month CDP

Model-based HR predictions of 3m-CDP for siponimod in other study populations indicate similar results to that seen in EXPAND, with largely overlapping 95% CIs (Figure 42).[131] However, slightly lower HRs were observed in the simulation of the ORATORIO/INFORMS populations.

The model was developed solely based on the EXPAND population (SPMS). This approach has a caveat as the model does not include a factor or covariate for the diagnosis of PPMS versus SPMS. This was partially addressed by the inclusion of covariates such as time since onset of symptoms/MS diagnosis and proportion of patients with previous DMT use, which are considered as surrogates for diagnosis of PPMS versus SPMS.

Figure 42: Reported and predicted hazard ratios for time to 3-month CDP



Conclusions

The exploratory analyses on primary endpoint definitions from EXPAND and ORATORIO and the model predictions for different baseline characteristics further support the effects of siponimod on

disability progression.[131] The model enabled the prediction of outcomes for placebo-controlled siponimod trials with hypothetical patient populations matching (on average) those of other placebo controlled studies in progressive MS populations ORATORIO, ASCEND and INFORMS.

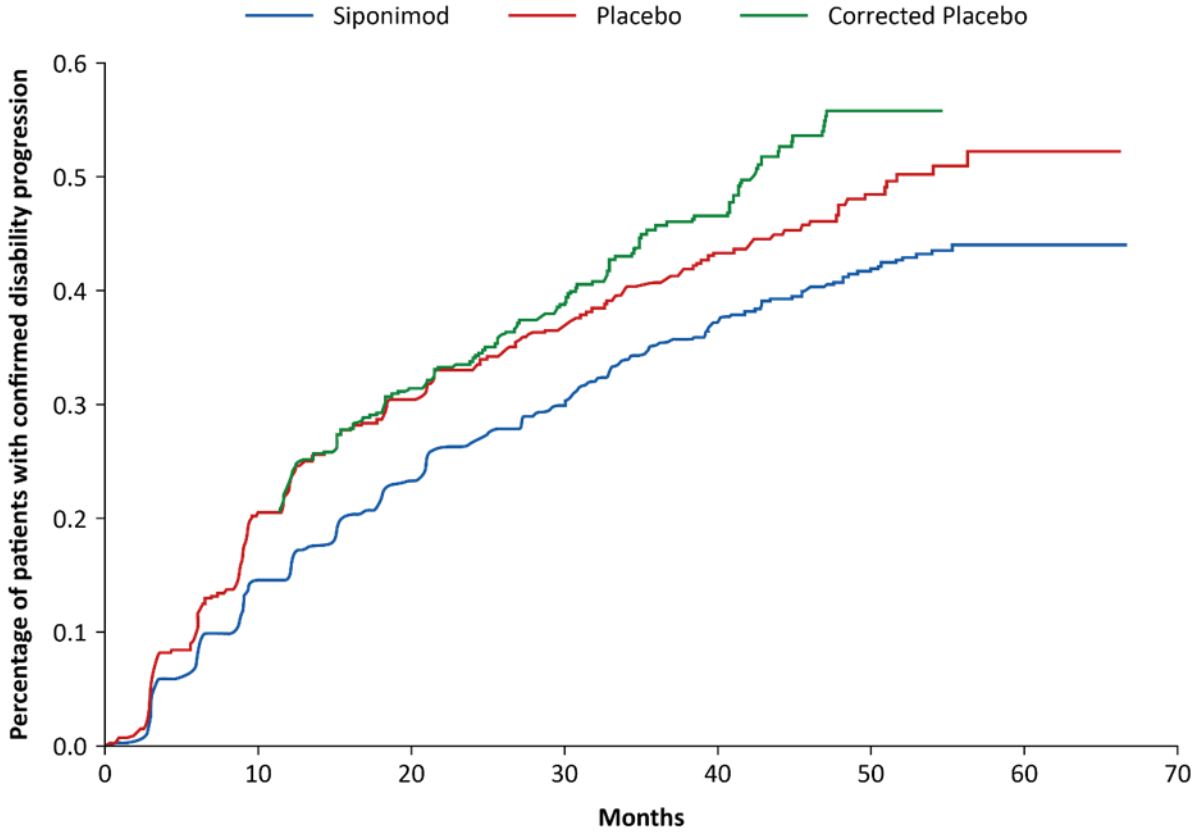
6.2.2.8 Open-label extension phase data

Following the core part of the EXPAND trial, all patients were switched on to open-label siponimod, and information on long-term efficacy and safety are being recorded for up to 10 years (the extension part of the trial is still ongoing at the time of this submission).

A RPSFT model was used on the time to CDP Kaplan-Meier curves to correct the placebo arm for crossing over to siponimod treatment, by modelling how the placebo arm would have looked if the placebo patients had not crossed over to open-label siponimod.

Figure 43 presents the Kaplan-Meier curves for time to 6-month CDP for siponimod, the combined core and extension results for the placebo arm, and the RPSFT-corrected placebo arm data. The hazard ratio for 6-month CDP for siponimod compared with RPSFT-corrected placebo after 5.5 years is measured as 0.69 (95% CI: 0.54–0.88). This is compared with a hazard ratio of 0.74 (95% CI: 0.60–0.92) at the end of the core part of the EXPAND trial, showing evidence that treatment effect has been observed to be maintained for siponimod over the duration of the extension phase of the trial.

Figure 43: Time to 6-month CDP data from the extension phase of the EXPAND trial



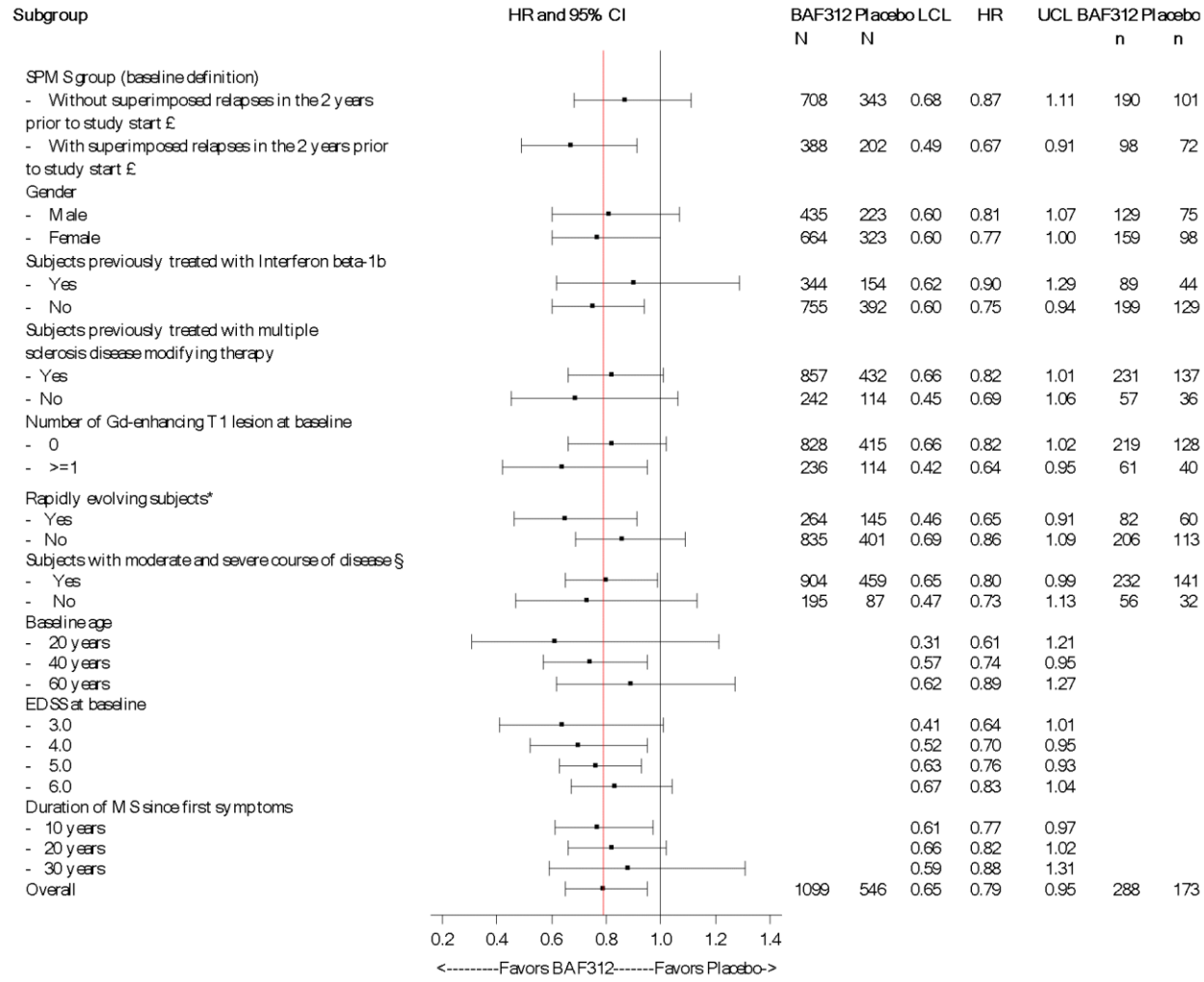
6.2.2.9 Subgroup analysis

Pre-defined subgroup analysis

Subgroup analyses were performed for time to 3-month CDP and time to 6-month CDP according to the following predefined criteria: presence or absence of a relapse in the 2 years before randomisation; rapid progression prior to randomisation (an increase in EDSS score of ≥ 1.5 points in the 2 years before randomisation); MS Severity Score of ≥ 4 at baseline; sex; participants previously treated with IFNβ1b; participants previously treated with DMTs; number of Gd+ lesions at baseline; rapidly evolving disease; baseline age; EDSS at baseline; and disease duration since onset.

HRs were consistent with the primary analysis for all subgroups across both outcomes. However, HRs for siponimod versus placebo in each of the subgroups were not always significant, owing to the fact that the study was not powered for the subgroup analyses (Figure 44 and Figure 45).

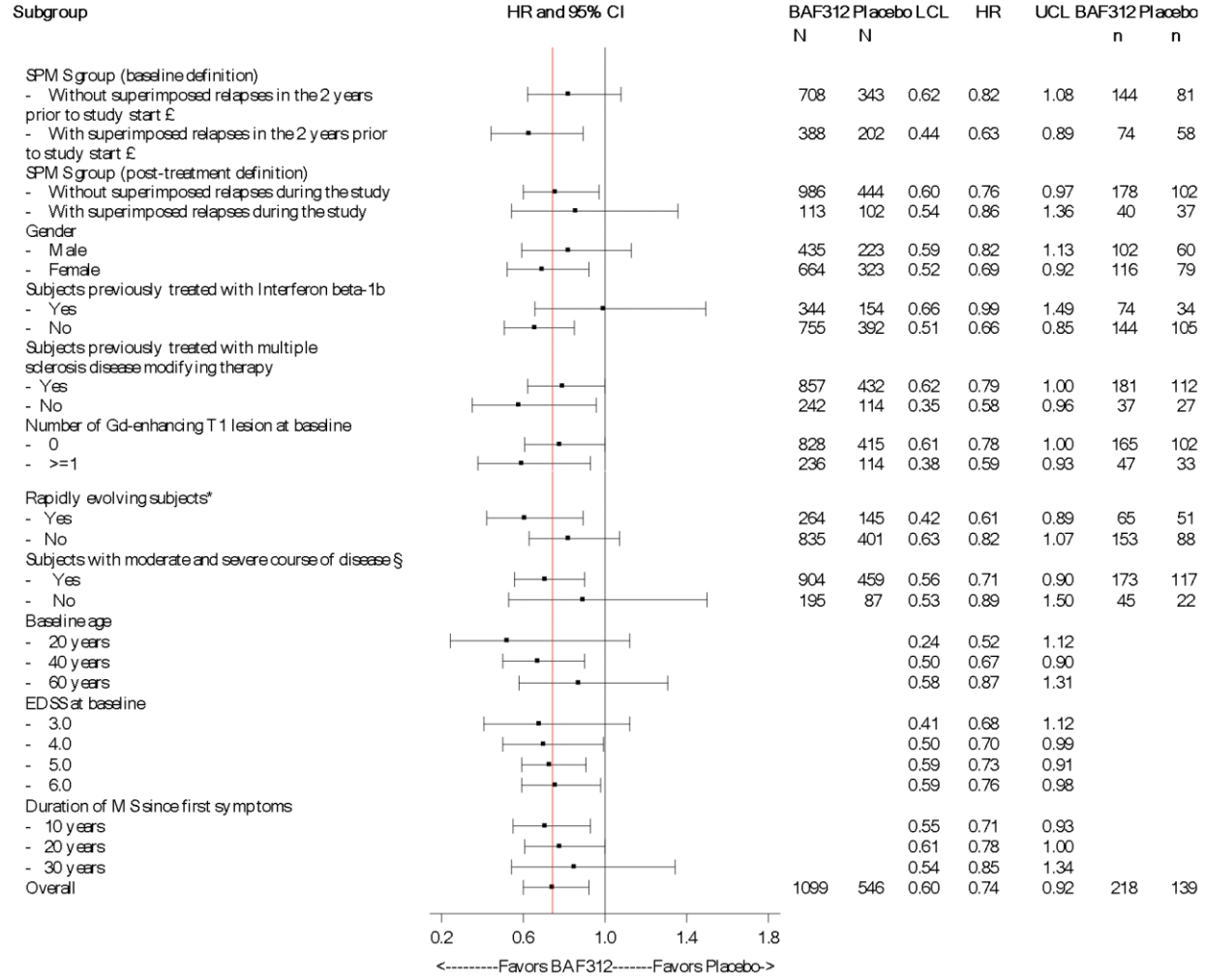
Figure 44: Forest plot showing time to 3-month CDP in predefined patient subgroups, full analysis set



Results using a Cox proportional hazard model with treatment, country/region, baseline EDSS, SPMS group (with-/without superimposed relapses, baseline definition) and the subgroup (if other than SPMS group) as covariates. £ Date of study start corresponds to the date of screening visit. § Moderate or severe course of disease is defined as Global MSSS of 4 or more at baseline. * Rapidly evolving subjects are defined as subjects with 1.5 or greater EDSS change in the 2 years prior to or at study start and disability progression in the 2 years prior to study start was not adjudicated. Subjects previously treated with Interferon beta-1b (IFNB)/disease

modifying therapy (MS-DMT) are defined as subjects who received and stopped IFNB/MS-DMT prior to first dose of study treatment.
BAF12, siponimod; CDP, confirmed disability progression; CI, confidence interval; EDSS, Expanded Disability Status Scale; Gd, gadolinium; HR, hazard ratio; LCL, lower limit of the HR 95% confidence interval; MS, multiple sclerosis; N, number of participants included in the analysis; n, number of participants with events; SPMS, secondary progressive multiple sclerosis; UCL, upper limit of the HR 95% confidence interval.
Source: Novartis Data on File.[132]

Figure 45. Forest plot showing time to 6-month CDP in predefined patient subgroups, full analysis set



Results using a Cox proportional hazard model with treatment, country/region, baseline EDSS, SPMS group (with-/without superimposed relapses, baseline definition) and the subgroup (if other than SPMS group) as covariates. £ Date of study start corresponds to the date of screening visit. § Moderate or severe course of disease is defined as Global MSSS of 4 or more at baseline. * Rapidly evolving subjects are defined as subjects with 1.5 or greater EDSS change in the 2 years prior to or at study start and disability progression in the 2 years prior to study start was not adjudicated. Subjects previously treated with Interferon beta-1b (IFNB)/disease modifying therapy (MS-DMT) are defined as subjects who received and stopped IFNB/MS-DMT prior to first dose of study treatment.
BAF12, siponimod; CDP, confirmed disability progression; CI, confidence interval; EDSS, Expanded Disability Status Scale; Gd, gadolinium; HR, hazard ratio; LCL, lower limit of the HR 95% confidence interval; MS, multiple sclerosis; N, number of participants included in the analysis; n, number of participants with events; SPMS, secondary progressive multiple sclerosis; UCL, upper limit of the HR 95% confidence interval.
Source: Novartis Data on File.[133]

Post hoc subgroup analysis: Relapsing SPMS Subgroup

Baseline characteristics

The baseline characteristics of the relapsing SPMS population, defined as subjects with relapses in the 2 years prior to the study, as outlined in Table 94. Compared with the ITT population, the relapsing subgroup included a higher number of patients experiencing relapses in the previous 2 years prior to screening (expected), a higher percentage of patients with gadolinium-enhancing T1 lesions and had a lower mean age (46.2 years vs. 48.0 in the ITT population).

Table 94: Relapsing SPMS subgroup: baseline characteristics

Demographic Variable	Siponimod N=516	Placebo N=263
Age (years), mean (SD)	45.9 (8.43)	46.9 (8.46)
Female, n (%)	254 (65.5)	129 (63.9)
Duration of MS since diagnosis (years), mean (SD)	11.18 (7.57)	10.84 (6.67)
Duration of MS since first symptom (years), mean (SD)	15.07 (7.97)	15.44 (8.28)
Time since conversion to SPMS (years), mean (SD)	2.86 (3.07)	2.82 (3.23)
Number of relapses in the last 2 years prior to screening, mean (SD)	1.9 (1.35)	1.9 (1.22)
Number of relapses in the last year prior to screening, mean (SD)	0.7 (0.72)	0.8 (0.71)
Time since the onset of the most recent relapse (months), mean (SD)	16.17 (21.22)	14.11 (16.48)
EDSS, mean (SD)	5.41 (1.04)	5.40 (1.03)
⩾1 Gd-enhancing T1 lesions, n (%)	108 (28.6)	53 (26.9)

EDSS, Expanded Disability Status Scale; Gd, gadolinium; MS, multiple sclerosis; SD, standard deviation; SPMS, secondary progressive multiple sclerosis.

Time to 3-month and 6-month CDP

Siponimod treatment significantly delayed the time to 6-month (HR 0.63, p=0.0087) and 3-month CDP (HR 0.67, p=0.0108) in the active SPMS subgroup compared with placebo (Table 95).

Table 95: Relapsing SPMS subgroup: Time to 3-month and 6-month CDP based on EDSS – Cox proportional hazards model

Treatment	n/N'	(%)	Comparison: Siponimod vs Placebo		
			Hazard Ratio (95% CI)	% Difference	p-value
3 month CDP					
Siponimod	98/388	25.3	0.67 (0.50, 0.91)	-32.7	0.0108
Placebo	72/202	35.6			
6 month CDP					
Siponimod	74/388	19.1	0.63 (0.45, 0.89)	−36.9	0.0087
Placebo	58/202	28.7			

N=number of subjects in treatment arm and subgroup, n=number of patients with event, N'=number of patients included in the analysis, (i.e. with non-missing covariates).
The Cox regression model includes the predictors treatment and baseline EDSS.
CDP, confirmed disability progression; CI, confidence interval; EDSS, expanded disability status scale; SPMS, secondary progressive multiple sclerosis.

ARR

Negative binomial regression analysis of ARR for patients in the relapsing subgroup demonstrated an ARR ratio of 0.579 (p=0.0041) for siponimod compared with placebo ().

Table 96: Relapsing SPMS subgroup: Negative binomial regression of ARR for confirmed relapses

Treatment	Adjusted ARR (95% CI)	Comparison: Siponimod vs Placebo		
		ARR Ratio (95% CI)	% Difference	p-value
Siponimod	0.124 (0.097, 0.159)	0.579 (0.399, 0.841)	−42.1	0.0041
Placebo	0.214 (0.162, 0.284)			

N=number of subjects in treatment arm and subgroup, n=overall number of relapses in the analysis period for all subjects, N'=number of patients included in the analysis, time = total number of days in the analysis period for all subjects.
The negative binomial includes the predictors treatment and baseline EDSS.
ARR, annualised relapse rate; CI, confidence interval; EDSS, expanded disability status scale; SPMS, secondary progressive multiple sclerosis.

6.2.2.10 Exploratory efficacy results

Symbol Digit Modalities Test

The symbol digit modalities test (SDMT) has been suggested as the preferred test for assessing cognitive processing speed by the Multiple Sclerosis Outcome Assessments Consortium (MSOAC) which developed its recommendations in collaboration with the FDA and EMA.[134] Additionally, among the tests of processing speed, SDMT has the strongest relationship with brain MRI metric that is associated with cognitive performance.[135] As such, SDMT is presented here.

The score was based on number of correct answers in 90 seconds. At Month 12, the comparison of adjusted mean change in correct responses between siponimod and placebo showed a small but significant difference of 1.085 (p=0.0132), which increased to 2.303 at Month 24 (p=0.0002) showing that patients on siponimod had more correct answers in 90 seconds thus showing less deterioration in processing speed compared with placebo. The difference in adjusted means over all time-points was 1.384 (p=0.007). There was an improvement in the siponimod group at Month 12 and Month 24, whereas, in the placebo group a worsening of mean scores was observed at each time point.

Table 97: Change from baseline in SDMT oral score, by visit – Repeated measures model

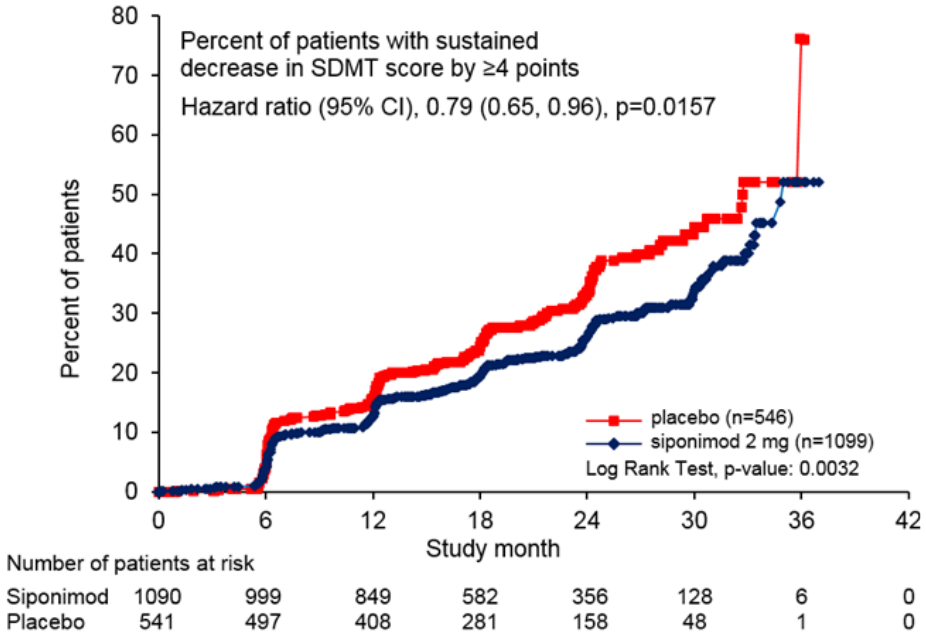
	Adjusted means (SE)			Comparison of adjusted means		
Time Point	Siponimod N'=1019	Placebo N'=516	Difference	SE	95% CI	p-value
Month 6	0.02 (0.273)	−0.76 (0.356)	0.79	0.402	0.00; 1.57	0.0510
Month 12	0.14 (0.288)	−0.94 (0.384)	1.08	0.437	0.23; 1.94	0.0132*
Month 18	0.94 (0.319)	−0.29 (0.431)	1.23	0.497	0.25; 2.21	0.0135*
Month 24	1.12 (0.377)	−1.18 (0.521)	2.30	0.610	1.11; 3.50	0.0002*

N' = number of subjects included in the analysis (i.e. with at least one SDMT score at baseline and post-baseline).
Obtained from fitting a repeated measures model for normally distributed data, with visit as categorical factor. Model was adjusted for treatment, country, and baseline SDMT score. Adjusted mean refers to the change from baseline in SDMT score.

All post-baseline visits up to and including Month 30 have been included.
* Indicates statistical significance (2-sided) at the 0.05 level.
CI, confidence interval; SDMT, symbol digit modalities test; SE, standard error

Treatment with siponimod additionally results in an overall risk reduction for decrease in SDMT score versus placebo (≥4 points) by 21.3% (p=0.0157). A 4-point change is considered to be the minimum clinically important difference.[26, 27]

Figure 46: Sustained decrease in SDMT score by ≥4 points



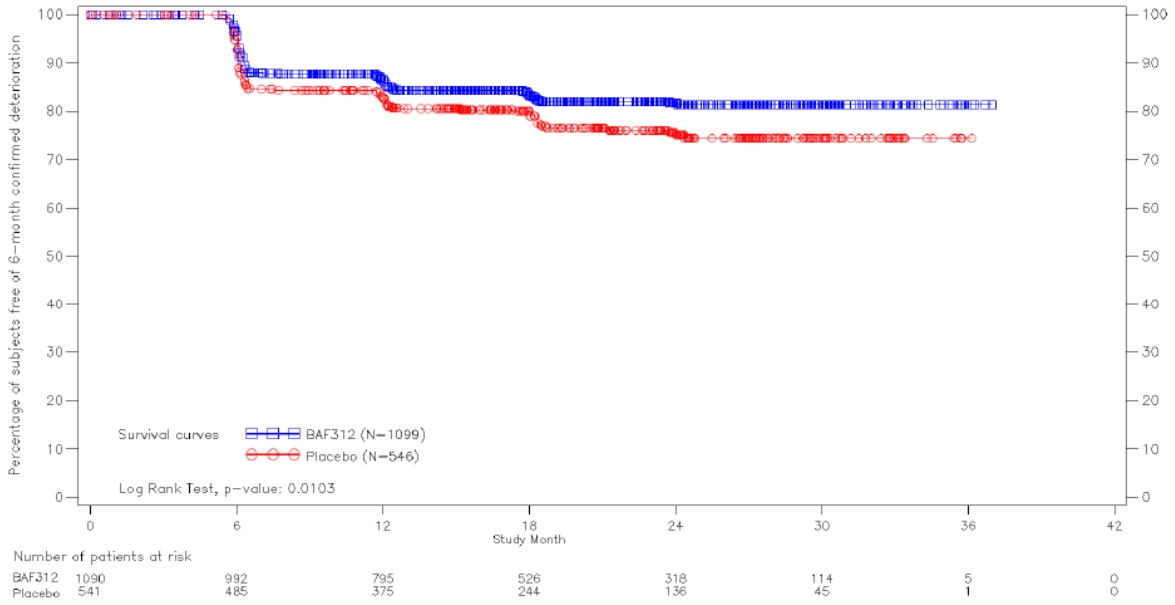
A responder analysis, defined as the proportion of patients with an increase in the SDMT greater than 4 points (considered to be the minimum clinically important difference), was conducted (Table 98, Figure 47). This analysis demonstrates a statistically significant 25.3% risk reduction in time to 6-month confirmed deterioration with siponimod treatment compared with placebo (p=0.0163).

Table 98: Time to 6-month confirmed deterioration based on SDMT-Oral score – Cox proportional hazards model

Treatment	n/N'	%	Comparison* Siponimod vs placebo			
			Risk reduction	Hazard ratio	95% CI	p-value
Siponimod	174/1087	16.0	25.3%	0.75	0.59; 0.95	0.0163
Placebo	113/540	20.9%				

N' = number of subjects included in the analysis (i.e. with at least one SDMT score at baseline and post-baseline). *Using a Cox proportional hazards model with treatment, country, baseline EDSS, baseline SDMT-Oral score and SPMS group (with-/without superimposed relapses, baseline definition). Risk reduction is derived as (1- hazard ratio) * 100. 6-month confirmed deterioration is defined as a negative response (decrease from baseline by 4 or more points) which is confirmed, in the absence of relapse, after 6 months.
CI, confidence interval.

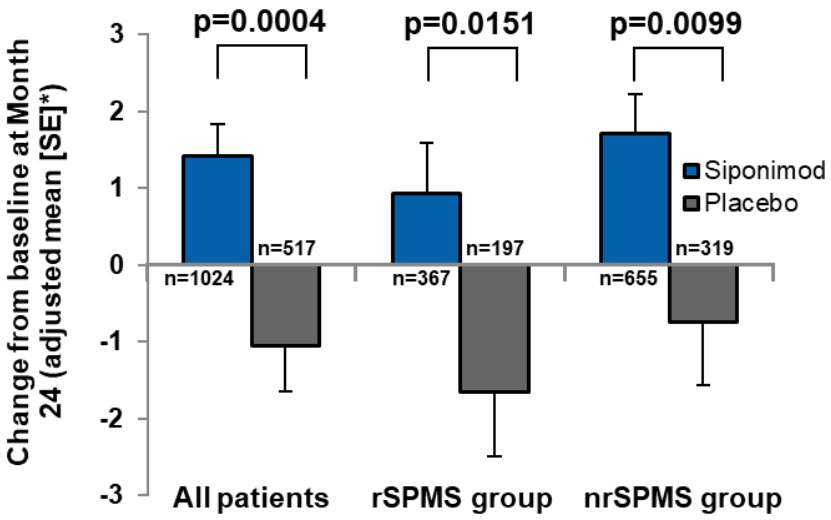
Figure 47: Percentage of subjects free of 6-month confirmed deterioration based on SDMT-Oral score – Kaplan-Meier curves



Last known date to be at risk is the last SDMT assessment date. 6-month confirmed deterioration is defined as a negative response (decrease from baseline by 4 or more points) which is confirmed, in the absence of relapse, after 6 months.
BAF12, siponimod.

Analysis of SDMT scores based on relapse history in the two years prior to randomisation demonstrates the beneficial effect of siponimod independent of relapses (Figure 48); significant differences in change from baseline were observed between placebo and siponimod in both groups, although was greater in relapsing SPMS patients (siponimod, +0.926; placebo, -1.647; difference = +2.57; p=0.0151) than the non-relapsing SPMS patients (siponimod, +1.703 points; placebo, -0.74 points; difference = +2.44, p=0.0099).[28]

Figure 48: Effect of siponimod on SDMT scores



n, number of patients with at least one SDMT score at baseline and post baseline.
nrSPMS, non relapsing secondary progressive MS; rSPMS, relapsing secondary progressive MS; SDMT, Symbol Digit Modalities Test (higher score indicates better performance); SE, standard error.
Source: Benedict et al., 2018.[28]

MSFC

The MSFC z-scores were calculated from the subscale results (T25FW, 9-HPT, and PASAT). The scores for these 3 components were combined to create a single score that was used to detect changes over time. This was done by creating z-scores for each component and averaging them to create the overall z-score.

Change from baseline in MSFC z-scores, and in the individual subscale scores (adjusted means) did not show significant differences between siponimod and placebo (Table 99).

Table 99: Change in baseline in MSFC z-score and subscale results, by visit

Time Point	Adjusted means (SE)			Comparison of adjusted means		
Z-Score	**Siponimod (N'=967)**	**Placebo (N'=494)**	**Difference**	**SE**	**95% CI**	**p-value**
Month 12	0.00 (0.014)	−0.02 (0.021)	0.03	0.025	−0.02; 0.07	0.3063
Month 24	−0.07 (0.021)	−0.06 (0.032)	−0.01	0.039	−0.08; 0.07	0.8199
Average over all visits	−0.03 (0.013)	−0.03 (0.019)	0.01	0.023	−0.04; 0.05	0.8032
9-HPT Score	**(N'=1054)**	**(N'=535)**				
Month 12	1.02 (0.452)	1.07 (0.643)	−0.05	0.787	−1.59; 1.49	0.9495
Month 24	2.27 (0.581)	2.81 (0.852)	−0.54	1.031	−2.57; 1.48	0.5991
Average over all visits	1.34 (0.374)	1.58 (0.533)	−0.24	0.651	−1.52; 1.04	0.7119
T25FW	**(N'=1043)**	**(N'=532)**				
Month 12	4.36 (0.678)	4.22 (0.965)	0.14	1.179	−2.18; 2.45	0.9073
Month 24	9.36 (1.052)	5.74 (1.569)	3.62	1.888	−0.09; 7.34	0.0556
Average over all visits	5.04 (0.577)	4.08 (0.822)	0.95	1.005	−1.02; 2.93	0.3423
PASAT Score	**(N'=1005)**	**(N'=508)**				
Month 12	2.24 (0.304)	1.76 (0.435)	0.48	0.531	−0.56; 1.52	0.3671
Month 24	3.11 (0.425)	2.30 (0.638)	0.81	0.767	−0.69; 2.32	0.2899
Average over all visits	2.36 (0.275)	1.76 (0.396)	0.59	0.482	−0.35; 1.54	0.2196

N' = number of subjects included in the analysis (i.e with at least one score result at baseline and post-baseline).

Obtained from fitting a repeated measures model for normally distributed data with visit as categorical factor. Model was adjusted for treatment and baseline score. Adjusted mean refers to the change from baseline in score.
All post-baseline visits up to Month 36 have been included.
* Indicates statistical significance (2-sided) at the 0.05 level.
Abbreviations: 9-HPT: nine-hole peg test; CI: confidence interval; MSFC: multiple sclerosis functional composite; PASAT: paced auditory serial addition test; SE: standard error; T25FW: timed 25-foot walk test.
Source: Novartis Data on File

Exploratory analyses requested during clarification

An exploratory analysis on whether siponimod delays progression both in patients with and without relapses or signs or MRI activity during the study period has not been conducted. In order to allow causal inference on treatment effect a subgroup analysis must be defined solely on baseline characteristics. It then preserves the similarity of the patients between the two treatment arms that came from original randomization. Analyses of subgroup based on post randomization criteria are inappropriate, most particularly when the criteria are strongly influenced by treatment. This is the case in the suggested exploratory analysis where both on-study relapses and signs of MRI activity (presence of T1 Gd lesions, new or enlarging T2 lesions, increase in T2 lesion volume) have been shown to be strongly positively impacted by treatment with siponimod. Due to the complete loss of comparability between the two treatment arms in such analysis, the results obtained would not be interpretable.

6.2.3 EXPAND safety data

In total, 1645 participants were included in the safety set: 1099 in the siponimod group and 546 participants in the placebo groups.

A numerically higher proportion of participants receiving siponimod than those receiving placebo reported at least one treatment-related AE (88.7% [n = 975] vs 81.5% [n = 445]; Table 100) or SAE (17.9% [n = 197] vs 15.2% [n = 83]). Furthermore, a numerically higher proportion of participants discontinued their study permanently because of a treatment-related AE in the siponimod group versus the placebo group (7.6% [n = 84] vs 5.1% [n = 28]) or interrupted their study drug temporarily because of a treatment-related AE (6.9% [n = 76] vs 2.9% [n = 16]).

Four deaths occurred in both the siponimod and placebo groups (0.4% [n= 4] vs 0.7% [n = 4], respectively). In the siponimod group, the reasons for death were metastatic gastrointestinal melanoma (within 4 months of commencing siponimod), septic shock in a patient with terminal colon cancer, urosepsis (following two doses of rituximab; siponimod was discontinued more than 10 weeks earlier) and suicide. Deaths in the placebo group were due to haemorrhagic stroke, lung cancer, gastric cancer and for an unknown reason. Two additional deaths were reported but not included in the safety analysis: one participant died suddenly (unspecified reason) during screening and one participant withdrew consent from the study with metastatic lung cancer after having received siponimod for 11 months and died (unspecified reason) 5 months after discontinuing study medication.

Table 100: Overview of AEs

	Siponimod (N = 1099)		**Placebo (N = 546)**	
Participants with ≥ 1 treatment-related AE, n (%)	975	(88.7)	445	(81.5)
Participants with ≥ 1 treatment-related SAE, n (%)	197	(17.9)	83	(15.2)

	Siponimod (N = 1099)		Placebo (N = 546)	
Participants discontinuing from study drug permanently owing to treatment-related AEs, n (%)	84	(7.6)	28	(5.1)
Discontinued owing to SAEs	36	(3.3)	13	(2.4)
Discontinued owing to non-serious AEs	48	(4.4)	15	(2.7)
Participants with treatment-related AEs leading to temporary interruption of study drug, n (%)	76	(6.9)	16	(2.9)
Participants who died, n (%)	4	(0.4)	4	(0.7)

AE, adverse event; N, number of participants in the population; n, number of participants with events; SAE, serious adverse event.
Source: Data on file.

The most frequently reported AEs (reported in > 10% of participants) occurred at similar frequencies in both the siponimod and placebo groups, and included headaches (15% [n = 159] vs 13% [n = 71]), nasopharyngitis (14% [n = 149] vs 15% [n = 79]), urinary tract infections (12% [n = 133] vs 15% [n = 80]) and falls (12% [n = 128] vs 11% [n = 59]).

A full summary of the most frequently reported AEs (reported in ≥ 5% in any group) is provided in Table 101.

Table 101: Most frequently reported AEs (≥ 5% in any group)

	Siponimod (N = 1099), n (%)	Placebo (N = 546), n (%)
Headache	159 (15)	71 (13)
Nasopharyngitis	149 (14)	79 (15)
Urinary tract infection	133 (12)	80 (15)
Fall	128 (12)	59 (11)
Hypertension	115 (11)	41 (8)
Fatigue	100 (9)	51 (9)
Upper respiratory tract infection	91 (8)	41 (8)
Dizziness	75 (7)	26 (5)
Nausea	74 (7)	19 (4)
Influenza	73 (7)	40 (7)
Diarrhoea	70 (6)	23 (4)
Back pain	67 (6)	43 (8)
Alanine aminotransferase level increased	65 (6)	8 (2)
Pain in extremity	60 (6)	21 (4)
Arthralgia	49 (5)	35 (6)
Depression	49 (5)	30 (6)

AE, adverse event; N, number of participants in the population; n, number of participants with events.
Source: Kappos et al., 2018.[24]

The most frequently reported SAEs (reported in ≥ 0.5% of participants) occurred at similar frequencies in both the siponimod and placebo groups, and included urinary tract infections (1% [n = 13] vs 1% [n = 6]), basal cell carcinoma (1% [n = 11] vs 1% [n = 6]) and increased alanine aminotransferase levels (1% [n = 10] vs < 1% [n = 2]).

A full summary of frequently reported SAEs (reported in ≥ 0.5% of participants) is provided in Table 102.

Table 102: Most frequently reported SAEs (≥ 0.5% in any group)

	Siponimod (N = 1099), n (%)	Placebo (N = 546), n (%)
Urinary tract infection	13 (1)	6 (1)
Basal cell carcinoma	11 (1)	6 (1)
Alanine aminotransferase level increased	10 (1)	2 (< 1)
Aspartate aminotransferase level increased	5 (< 1)	1 (< 1)
Concussion	5 (< 1)	0
Depression	5 (< 1)	2 (< 1)
Suicide attempt	4 (< 1)	3 (1)
MS relapse	2 (< 1)	7 (1)
Gait disturbance	1 (< 1)	3 (1)
Paraparesis	0	3 (1)

MS, multiple sclerosis; N, number of participants in the population; n, number of participants with events; SAE, serious adverse event.
Source: Kappos et al., 2018.[24]

A numerically higher proportion of participants in the siponimod group than in the placebo group reported AEs consistent with S1P receptor modulation (

Table 103). These included herpes zoster infections (2.3% [n = 25] vs 0.7% [n = 4]), macular oedema (1.8% [n = 20] vs 0.2% [n = 1]), hypertension (10.5% [n = 137] vs 7.5% [n = 50]), convulsions (1.7% [n = 19] vs 0.4% [n = 2]), grade 4 lymphopenia (2.7% [n = 27/1088] vs 0.2% [n = 1/546]) and liver function abnormality (10.1% [n = 110/1088] vs 3.7% [n = 20/546]). Furthermore, a higher proportion of participants in the siponimod group than in the placebo group experienced cardiac disorder AEs during treatment initiation (days 1–15; 11.8% vs 10.1%). Rates of infections (49.0% [n = 539] vs 49.1% [n = 268]) and malignancies (1.8% [n = 20] vs 2.6% n = 14]) were similar between the two groups.

Table 103: AEs of special interest

AEs of special interest, n (%)[a]	Siponimod (N = 1099)		Placebo (N = 546)	
Cardiac disorders during treatment initiation (days 1–15)[b]	130	(11.8)	55	(10.1)
Infections[b]	539	(49.0)	268	(49.1)
Herpes zoster	25	(2.3)	4	(0.7)
Hypertension[c]	137	(10.5)	50	(7.5)
Malignancy[a,d]	20	(1.8)	14	(2.6)
Macular oedema[e]	20	(1.8)	1	(0.2)
Convulsions	19	(1.7)	2	(0.4)
Grade 4 lymphopenia (< 0.15 × 10^9/L), n/m[f]	29/1088	(2.7)	1/546	(0.2)
Liver function tests elevations, n/q[f]	110/1088	(10.1)	20/546	(3.7)
ALAT or ASAT > 3 × ULN	61/1088	(5.6)	8/546	(1.5)

[a]Identified risks with clinical relevance; [b]System organ class; [c]Standard MedDRA query (MedDRA version 19.0); [d]Novartis MedDRA query; [e]Preferred term; [f]Based on laboratory evaluations.
AE, adverse event; ALAT, alanine aminotransferase; ASAT, aspartate aminotransferase; MedDRA, Medical Dictionary for Regulatory Activities; N, number of participants in the population; n, number of participants with events; ULN, upper limit of normal.
Source: Data on file.

In total, 82% of participants (n = 1346/1651) underwent continuous mobile cardiac telemetry for up to 6 days. During double-blinded treatment initiation the maximum reduction in mean heart rate on day 1 was 5.3 beats per minute (bpm) in the siponimod group (4 hours post-dose) and 1.2 bpm in the placebo group (1 hour post-dose). On day 7, mean reductions were 3.1 bpm and 2.0 bpm, respectively (3 hours post-dose for both). For 6% of participants (n = 68) receiving siponimod and 3% (n = 17) receiving placebo, bradycardia, decreased heart rate or sinus bradycardia were reported as AEs. No atrioventricular (AV) blocks type Mobitz II, advanced/high-grade AV blocks or third-degree AV blocks were reported in the study.[24]

6.3 Appendix C: Matching-adjusted indirect comparisons

6.3.1 Quantitative analysis of similarity

To validate the choice of the 10% threshold for similarity used in the feasibility assessment, a quantitative analysis using the standardised mean differences was used. Based on published thresholds, baseline characteristics were categorised into ‘minimal difference’, ‘moderate difference’ and ‘major difference’ when compared to EXPAND (Table 104). These results show that the quantitative analysis produces very similar results to when using the 10% threshold for similarity, supporting the use of the 10% threshold for the feasibility assessment.

Table 104: Summary of imbalances based on standardised mean differences

Baseline Patient Characteristics	EXPAND	ASCEND	North American Study	IMPACT	European Study	SPECTRIMS
Age (mean years)	48	47.2	46.8	47.6	41	42.8
Proportion female (%)	60	62	63	64	61	63
Mean EDSS score	5.4	5.6	5.1	5.2	5.1	5.4
Proportion of patients with EDSS score ≥6.0 (%)	56	63	NR	48	45	NR
Time since onset of MS symptoms (mean years)	16.8	16.5	NR	NR	NR	NR
Duration of MS (mean years)	12.6	12.1	14.7	16.5	13.1	13.3
Duration of SPMS (mean years)	3.8	4.8	4.0	NR	2.2	4.0
Normalised brain volume (mean cm^3)	1423	1423	NR	NR	NR	NR
Proportion of patients with Gd+ lesions of T1-weighted images (%)	21	24	NR	36	NR	NR
Total volume of T2 lesions on T2-weighted images (mean mm^3)	15,321	16,793	NR	NR	NR	NR
Proportion of patients without previous use of a DMT (%)	22	23**	100*	100*	100‡	100*
Mean Timed 25-Foot Walk Test (seconds)	16.7	NR	NR	14.5	NR	NR
Time since most recent relapse (months)	59	57	NR	44.4	NR	NR

Proportion of patients relapse-free in prior year (%)	78	84	NR	61	NR	NR
Proportion of patients relapse-free in prior 2 years (%)	64	71	55	NR	30	53
Number of relapses per patient in the prior year (mean)	0.2	NR	NR	0.6	NR	NR
Number of relapses per patient in the previous 2 years (mean)	0.7	NR	0.8	NR	NR	0.9

Green = 'minimal difference', standardized mean difference <0.1; Yellow = 'moderate difference', standardized mean difference = 0.1–<0.2; Red = 'major difference', standardized mean difference ≥0.2. * A value of 100% was assumed because IFN-experienced patients were excluded at screening, as described in the exclusion criteria of the trial, and other DMTs were not available at the time of enrolment.** Gold R et al. (2017) Impact of Primary Endpoint Definitions and Patient Baseline Characteristics on Study Outcomes in Progressive Multiple Sclerosis. *Poster presented at the 7th Joint Congress Sclerosis-Americas Committee for Treatment and Research in Multiple Sclerosis; 25-28 October 2017; Paris, France*. *P1239*. Value derived using DigitizeIt: Bormann I (Web Page) DigitizeIt V 2.3.3. Updated 2016. Available online at: http://www.digitizeit.de. Accessed: 2019 July 3. ‡ No prior IFN use in the European trial. F. Dahlke, personal correspondence, November 30th, 2018. ᵠ SMD thresholds: *Austin PC (2009) Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. Stat Med 28 (25): 3083-3107.*
EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; DMT, disease-modifying therapy; IFN, interferon; ITT, intention-to-treat; MS, multiple sclerosis; NR, not reported; n/a, not available; ,SPMS, secondary progressive multiple sclerosis.

6.3.2 Methods and outcomes of studies included in indirect or mixed treatment comparisons

A summary of the methods of the studies included in the MAIC are presented in the below sections.

6.3.2.1 Siponimod vs INFβ-1a (Rebif®): SPECTRIMS

Study Design

The Secondary Progressive Efficacy Clinical Trial of Recombinant Interferon-beta-1a in MS (SPECTRIMS)[103, 117] was an RCT evaluating the efficacy and safety of two doses (22 µg and 44 µg) of subcutaneous IFNβ-1a (Rebif®) administrated three times weekly for three years, vs. placebo, for the treatment of 618 patients with SPMS. Despite different routes of placebo administration, the study design of SPECTRIMS was similar to EXPAND (Table 105).

Table 105: Pairwise Comparison of Study Design – EXPAND vs. SPECTRIMS

Study ID	Author Year	Phase	Study Design	Sample Size[a]	MS Population	Study Duration	Comparator	Treatment
EXPAND	Kappos 2018	III	Randomised Double-blind Parallel group	1651	SPMS	3 years	Placebo PO QD	Siponimod 2 mg PO QD
SPECTRIMS	SPECTRIMS Study Group 2001	n/a	Randomised Double-blind	618	SPMS	3 years	Placebo SC TIW	IFNβ-1a 22 µg SC TIW 44 µg SC TIW

	Li 2001		Parallel group					
Comparability		n/a	✓	n/a	✓	✓	! [b]	n/a

✓ = Studies are similar; ! = Differences exist between the trials. [a]ITT population. [b]Common comparator despite difference in administration.
IFNβ-1a, interferon-beta-1a; ITT, intention-to-treat; MS, multiple sclerosis; PO, oral; QD, once daily; SC, subcutaneous; SPMS, secondary progressive multiple sclerosis; TIW, three times weekly;

Inclusion and Exclusion Criteria

The comparability of the inclusion/exclusion criteria is summarised in Table 106. The MS population, included range of baseline EDSS, and the required history of RRMS/relapsing disease were identical between the trials. However, unlike EXPAND, SPECTRIMS did not include patients with history of IFN treatment; this is a significant limitation of unadjusted comparisons because it could represent a strong source of bias. However, this could be potentially matched in MAICs because the population of EXPAND is broader. Additionally, the requirements for documented progression (i.e., within a number of months prior to the trial) differed between the studies, but EXPAND also included a broader population in this respect. The requirements for how recently patients were allowed to have relapsed prior to screening differed between the studies, but because EXPAND allowed a narrower set of patients in this regard, it prevented potential matching using EXPAND IPD on this criterion.

The SPECTRIMS study included a subgroup of patients with active SPMS, but with a narrower definition of active SPMS than that used in EXPAND.

Table 106: Pairwise Comparison of Inclusion/Exclusion Criteria – EXPAND vs. SPECTRIMS

Criteria	EXPAND	SPECTRIMS	Comparability
MS Population	SPMS	SPMS	✓
Baseline EDSS range	3.0-6.5	3.0-6.5	✓
Age range	18-60	18-55	!
Prior IFN therapy	Allowed	No prior IFN use	!
Number of relapses in X months prior	3 months	2 months	X
Documented progression within X months prior	24 months	6 months	!
History of RRMS	Required	Required	✓
Duration of MS	No restriction	NR	n/a
Duration of SPMS	No restriction	NR	n/a
MS severity score	No restriction	NR	n/a
T25FW test	No restriction	NR	n/a
Active SPMS definition	Presence of relapses in 2 years before study or Gd+ T1 lesions at baseline	Presence of relapses in the 2 years preceding the study	!

✓ = Criterion is identical; ! = Differences exist between trials and the EXPAND patient population is broader (i.e. matching may be possible); X = Differences exist between the trials and the EXPAND patient population is not broader (i.e. matching is not possible).
EDSS, expanded disability status scale; IFN, interferon; MS, multiple sclerosis; NR, not reported; RRMS, relapse-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis; T25FW, Timed 25-Foot Walk.

Outcome Definitions

The outcome definitions for ARR, time to 3-month CDP and discontinuation in SPECTRIMS were all identical to those in EXPAND (Table 107). Time to 6-month CDP was not reported in SPECTRIMS. ARR and 6-month CDP were reported for the active SPMS subgroup.

Table 107: Pairwise Comparison of Outcome Definitions – EXPAND vs. SPECTRIMS

	ARR	Time to 3-month CDP	Time to 6-month CDP	Discontinuation
EXPAND	Number of total relapses per patient-years	1.0-point inc. in EDSS score: 3.0-5.0 0.5-point inc. in EDSS score:5.5-6.5	1.0-point inc. in EDSS score: 3.0-5.0 0.5-point inc. in EDSS score: 5.5-6.5	The proportion of randomised patients who discontinued treatment for any reason
SPECTRIMS	Number of total relapses per patient-years	1.0-point inc. in EDSS score: 3.0-5.0 0.5-point inc. in EDSS score:5.5-6.5	NR	The proportion of randomised patients who discontinued treatment for any reason
Comparability	✓	✓	n/a	✓

✓ = Outcome is reported in the comparator trial with the same or very similar definition to EXPAND; ! = Outcome is reported in the comparator trial, but the definition differs from EXPAND.
ARR, annualised relapse rate; CDP, confirmed disability progression; EDSS, expanded disability status scale; inc, increase; NR, not reported.

Baseline Patient Characteristics

Seven key patient baseline characteristics that were reported by EXPAND were reported in the SPECTRIMS trial (Table 108). Of these characteristics, the following were similar (within 10%) to EXPAND: proportion of females, mean EDSS score, duration of MS, and duration of SPMS. The following baseline characteristics differed (by >10%) between the trials: mean age, proportion of patients relapse-free in the prior two years, and number of relapses per patient in the previous two years (Table 108). The SPECTRIMS study did not report baseline characteristics for the subgroup of patients with active SPMS, therefore characteristics for the overall SPECTRIMS study population were compared with those of the EXPAND active SPMS subgroup. Only two characteristics were similar (within 10%), with the other five reported characteristics, including proportion of patients relapse-free in the 2 years before study start, differing by >10% between the trials.

Table 108: Pairwise Comparison of Baseline Patient Characteristics – EXPAND vs. SPECTRIMS

Characteristic	Total Population			Active SPMS		
	EXPAND	SPECTRIMS	Comparability	EXPAND	SPECTRIMS	Comparability (total SPECTRIMS vs active EXPAND)

Age (mean years)	48.0	42.8	!	46.6	NR	✓
Proportion female (%)	60	63	✓	36.2	NR	!
Mean EDSS score	5.4	5.4	✓	5.44	NR	✓
Proportion of patients with EDSS score ≥6.0 (%)	56	NR	n/a	55.7	NR	n/a
Time since onset of MS symptoms (mean years)	16.8	NR	n/a	15.56	NR	n/a
Duration of MS (mean years)	12.6	13.3	✓	11.49	NR	!
Duration of SPMS (mean years)	3.8	4.0	✓	3.19	NR	!
Normalised brain volume (mean cm3) c	1423	NR	n/a	1421.1	NR	n/a
Proportion of patients with Gd+ lesions of T1-weighted images (%)	21	NR	n/a	45.9	NR	n/a
Total volume of T2 lesions on T2-weighted images (mean mm3)	15,321	NR	n/a	17,659	NR	n/a
Proportion of patients without previous use of a DMT (%)	22	NR	n/a	23.4	NR	n/a
Mean Timed 25-Foot Walk Test (seconds)	16.7	NR	n/a	16.92	NR	n/a
Time since most recent relapse (months)	59	NR	n/a	30.53	NR	n/a
Proportion of patients relapse-free in prior year (%)	78	NR	n/a	54.6	NR	n/a
Proportion of patients relapse-free in prior 2 years (%)	64	53	!	24.1	NR	!
Number of relapses per patient in the prior year (mean)	0.2	NR	n/a	0.5	NR	n/a
Number of relapses per patient in the previous 2 years (mean)	0.7	0.9	!	1.4	NR	!

✓ = Both studies report the characteristic and the values are similar (within 10%); ! = Both studies report the characteristic and the values are dissimilar (by >10%). A 10% threshold for similarity was subjectively selected to qualitatively assess heterogeneity; choice of the 10% threshold was supported by a quantitative analysis using estimated standardized mean differences.
DMT, disease-modifying treatment; EDSS, expanded disability status scale; Gd+, gadolinium-enhancing; MS, multiple sclerosis; NR, not reported; SPMS, secondary progressive multiple sclerosis.

Placebo-Arm Outcomes

The placebo-arm outcomes for ARR and discontinuation in SPECTRIMS were >10% different than values reported by EXPAND (Table 109). This was also the case for ARR in the active SPMS subgroups, while discontinuation rate was not reported for the active SPMS subgroup in SPECTRIMS.

Table 109: Pairwise Comparison of Placebo-Arm Outcomes – EXPAND vs. SPECTRIMS

Study ID	Placebo Administration	ARR	Annualised Rate of Discontinuation
Total Population			
EXPAND	PO QD	0.16	0.084
SPECTRIMS	SC TIW	0.71	0.057

Comparability		!	!
Active SPMS Population			
EXPAND	PO QD	0.202	n/a – not reported in SPECTRIMS study
SPECTRIMS	SC TIQ	1.08	
Comparability		!	

✓ = Outcome value is similar (within 10%) compared to EXPAND; ! = Outcome value is dissimilar (>10% different) compared to EXPAND. A 10% threshold for similarity was subjectively selected to qualitatively assess heterogeneity; choice of the 10% threshold was supported by a quantitative analysis using estimated standardized mean differences.
ARR, annualised relapse rate; PO, oral; QD, once daily; SC, subcutaneous; TIW, three times weekly.

Conclusion

The presence of significant clinical heterogeneity between SPECTRIMS and EXPAND undermines the validity of ITCs based on summary-level data. Failure to account for these differences can lead to misleading comparisons of treatment effect. The requirements for conducting MAICs between SPECTRIMS and EXPAND (i.e., similar study design, similar or broader inclusion criteria in EXPAND, and similar outcome definitions) were all considered to be met, with the caveat that not all differences in study populations could be accounted for during the matching and adjusting process. Despite this, MAICs would still have the advantage over Bucher ITCs because they consider a combination of IPD and aggregate data to adjust for observed differences in characteristics among trials, thereby providing a more robust and valid indirect comparison than Bucher ITC.

Baseline characteristics were not reported for the active SPMS subgroup in SPECTRIMS, therefore it would have to be assumed that the characteristics for the overall population could be applied to the active subgroup when conducting a MAIC. This assumption was not considered to be robust.

6.3.2.2 Siponimod vs. IFNβ-1b (Betaferon®): North American Study

Study Design

The North American Study[118] was a three-year RCT evaluating the efficacy and safety of two doses (250 µg and 160 µg/m^2) of subcutaneous IFNβ-1b (Betaferon®) administrated every other day, vs. placebo, for the treatment of 939 patients with SPMS. Despite differences in study duration and route of placebo administration, the study design of the North American Study was overall similar to EXPAND (Table 110).

Table 110: Pairwise Comparison of Study Design – EXPAND vs. North American Study

Study ID	Author Year	Phase	Study Design	Sample Size[a]	MS Population	Study Duration	Comparator	Treatment
EXPAND	Kappos 2018	III	Randomised Double-blind Parallel group	1651	SPMS	3 years	Placebo **PO** QD	Siponimod 2 mg PO QD
North American Study	Panitch 2004	NR	Randomised Double-blind	939	SPMS	3 years[b]	Placebo **SC** Q2D	IFNβ-1b 160 µg/m^2 SC Q2D

			Parallel group					(unlicensed dose) 250 µg SC Q2D
Comparability		n/a	✓	n/a	✓	!	! [c]	n/a

✓ = Studies are similar; ! = Differences exist between the trials.
[a] ITT population. [b] Early termination. Mean duration of follow-up was 998 days for the 250-µg group, 1013 days for the 160-µg/m2 group, and 1003 days for the placebo group. [c] Common comparator despite difference in administration.
IFNβ-1b, Interferon-beta-1b; ITT, intention-to-treat; MS, multiple sclerosis; PO, oral; Q2D, once every two days; SC, subcutaneous; SPMS, secondary progressive multiple sclerosis.

Inclusion and Exclusion Criteria

The comparability of the inclusion/exclusion criteria is summarised in Table 111. The disease population, included EDSS range, and the requirement of a history of RRMS/relapsing disease course were identical for these studies. However, unlike EXPAND, the North American Study did not include patients with history of IFN treatment; this is a significant limitation of unadjusted comparisons because it could represent a strong source of bias. However, this could be potentially matched in MAICs because the population of EXPAND is broader. Additionally, the requirements for documented progression (i.e., within a number of months prior to the trial) differed between the studies, but EXPAND also included a broader population in this respect. However, the North American Study also required patients to have documentation of at least one relapse with progressive deterioration for at least six months, which EXPAND did not report, preventing potential matching using EXPAND IPD for this criterion. The included ranges of age and relapse history differed from EXPAND, but the included population was broader in the North American Study, preventing potential matching using EXPAND IPD on this criterion.

The North American Study did not include an active SPMS subgroup.

Table 111: Pairwise Comparison of Inclusion/Exclusion Criteria – EXPAND vs. North American Study

Criteria	EXPAND	North American Study	Comparability
MS Population	SPMS	SPMS	✓
Baseline EDSS range	3.0-6.5	3.0-6.5	✓
Age range	18-60	18-65	X
Prior IFN therapy	Allowed	No prior IFN use	!
Number of relapses in X months prior	3 months	2 months	X
Documented progression within X months prior	24 months	24 months and at least one relapse with progressive deterioration for ≥6 months	X
History of RRMS	Required	Required	✓
Duration of MS	No restriction	≥ 2 years	!
Duration of SPMS	No restriction	NR	n/a
MS severity score	No restriction	NR	n/a
T25FW test	No restriction	NR	n/a
Active SPMS definition	Presence of relapses in 2 years before study or	None	n/a

	Gd+ T1 lesions at baseline		

✓ = Criterion is identical; ! = Differences exist between trials and the EXPAND patient population is broader (i.e. matching may be possible); X = Differences exist between the trials and the EXPAND patient population is not broader (i.e. matching is not possible).
EDSS, expanded disability status scale; IFN, interferon; IFNβ, interferon-beta; MS, multiple sclerosis; NR, not reported; RRMS, relapse-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis; T25FW, Timed 25-Foot Walk.

Outcome Definitions

Outcome definitions for ARR and discontinuation in the North American Study were identical to those in EXPAND (Table 112). The definition of "disability progression" used in the 6-month CDP outcome differed between the studies, in that patients with a baseline EDSS of 5.5 required an increase of 0.5 to qualify as experiencing "progression" in EXPAND, but required an increase of 1.0 in the North American Study. The definitions were otherwise identical and were considered to be reasonably equivalent based on clinical opinion. Time to 3-month CDP was not reported in the North American Study.

Table 112: Pairwise Comparison of Outcome Definitions – EXPAND vs. North American Study

	ARR	Time to 3-month CDP	Time to 6-month CDP	Discontinuation
EXPAND	Number of total relapses per patient-years	1.0-point inc. in EDSS score: 3.0-5.0 0.5-point inc. in EDSS score:5.5-6.5	1.0-point inc. in EDSS score: 3.0-5.0 0.5-point inc. in EDSS score:5.5-6.5	The proportion of randomised patients who discontinued treatment for any reason
North American Study	Number of total relapses per patient-years	NR	1.0-point inc. in EDSS score: 3.0-5.5 0.5-point inc. in EDSS score:6.0-6.5	The proportion of randomised patients who discontinued treatment for any reason
Comparability	✓	n/a	!	✓

✓ = Outcome is reported in the comparator trial with the same or very similar definition to EXPAND; ! = Outcome is reported in the comparator trial, but the definition differs from EXPAND.
ARR, annualised relapse rate; CDP, confirmed disability progression; EDSS, expanded disability status scale; NR, not reported.

Baseline Patient Characteristics

Only seven key patient baseline characteristics that were reported by EXPAND were reported in the North American Study. Of these characteristics, the following were similar (within 10%) to EXPAND: mean age, the proportion of females, mean EDSS score, and duration of SPMS. The following characteristics differed (by >10%): duration of MS, the proportion of patients relapse-free in prior two years, and number of relapses per patient in the previous two years (Table 113). As the North American Study did not include an active SPMS subgroup, the overall study population characteristics were compared with the active SPMS sub-population in EXPAND to see if they could be matched. Only two characteristics were similar (within 10%), with the other five reported characteristics differing by >10% between the trials. The proportion of patients relapse-free and the mean number of relapses per patient in the first 2 years before the study were among the characteristics that differed by >10%.

Table 113: Pairwise Comparison of Baseline Patient Characteristics – EXPAND vs. North American Study

Characteristic	Total Population			Active SPMS		
	EXPAND	North American	Comparability	EXPAND	North American	Comparability (total North American vs active EXPAND)
Age (mean years)	48.0	46.8	✓	46.6	—	✓
Proportion female (%)	60	63	✓	36.2	—	!
Mean EDSS score	5.4	5.1	✓	5.44	—	✓
Proportion of patients with EDSS score ≥6.0 (%)	56	NR	n/a	55.7	—	n/a
Time since onset of MS symptoms (mean years)	16.8	NR	n/a	15.56	—	n/a
Duration of MS (mean years)	12.6	14.7	!	11.49	—	!
Duration of SPMS (mean years)	3.8	4.0	✓	3.19	—	!
Normalised brain volume (mean cm3) c	1423	NR	n/a	1421.1	—	n/a
Proportion of patients with Gd+ lesions of T1-weighted images (%)	21	NR	n/a	45.9	—	n/a
Total volume of T2 lesions on T2-weighted images (mean mm3)	15,321	NR	n/a	17,659	—	n/a
Proportion of patients without previous use of a DMT (%)	22	NR	n/a	23.4	—	n/a
Mean Timed 25-Foot Walk Test (seconds)	16.7	NR	n/a	16.92	—	n/a
Time since most recent relapse (months)	59	NR	n/a	30.53	—	n/a
Proportion of patients relapse-free in prior year (%)	78	NR	n/a	54.6	—	n/a
Proportion of patients relapse-free in prior 2 years (%)	64	55	!	24.1	—	!
Number of relapses per patient in the prior year (mean)	0.2	NR	n/a	0.5	—	n/a
Number of relapses per patient in the previous 2 years (mean)	0.7	0.8	!	1.4	—	!

✓ = Both studies report the characteristic and the values are similar (within 10%); ! = Both studies report the characteristic and the values are dissimilar (by >10%). A 10% threshold for similarity was subjectively selected to qualitatively assess heterogeneity; choice of the 10% threshold was supported by a quantitative analysis using estimated standardized mean differences.
DMT, disease-modifying treatment; EDSS, expanded disability status scale; Gd+, gadolinium-enhancing; MS, multiple sclerosis; NR, not reported; SPMS, secondary progressive multiple sclerosis.

Placebo-arm Outcomes

The placebo-arm outcomes for ARR and discontinuation in the North American Study were >10% different compared to the values reported by EXPAND (Table 114).

Table 114: Pairwise Comparison of Placebo-Arm Outcomes – EXPAND vs. North American Study

Study ID	Placebo Administration	ARR	Annualised Rate of Discontinuation
EXPAND	PO QD	0.16	0.084
North American Study	SC Q2D	0.28	0.093
Comparability		!	!

✓ = Outcome value is similar (within 10%) compared to EXPAND; ! = Outcome value is dissimilar (>10% different) compared to EXPAND.
ARR, annualised relapse rate; PO, oral; QD, once daily; Q2D, once every 2 days (every other day); SC, subcutaneous.

Conclusion

Similar to the previously described comparisons, the presence of significant clinical heterogeneity between the North American Study and EXPAND undermines the validity of ITCs based on summary-level data. Again, failure to account for these differences can lead to misleading comparisons of treatment effect. The requirements for conducting MAICs between the North American Study and EXPAND (i.e., similar study design, similar or broader inclusion criteria in EXPAND, and similar outcome definitions) were all considered to be met, with the caveat that not all differences in study populations could be accounted for during the matching and adjusting process. Despite this, MAICs would still have the advantage over Bucher ITCs because they consider a combination of IPD and aggregate data to adjust for observed differences in characteristics among trials, thereby providing a more robust and valid indirect comparison than Bucher ITC.

The North American Study did not include an active SPMS subgroup and the overall population was not considered to represent an active SPMS population closely enough for a MAIC or ITC in this population to be robust.

6.3.2.3 Siponimod vs. IFNβ-1b (Betaferon®): European Study

Study Design

The European Study[113, 114] was a three-year Phase III RCT evaluating the efficacy and safety of 250 µg subcutaneous IFNβ-1b (Betaferon®) administrated every other day, vs. placebo, for the treatment of 718 patients with SPMS. Despite differences in study duration and the route of placebo administration, the study design of the European Study trial was overall similar to EXPAND (Table 115).

Table 115: Pairwise Comparison of Study Design – EXPAND vs. European Study

Study ID	Author Year	Phase	Study Design	Sample Size[a]	MS Population	Study Duration	Comparator	Treatment
EXPAND	Kappos 2018	III	Randomised Double-blind Parallel group	1651	SPMS	3 years	Placebo PO QD	Siponimod 2 mg PO QD

European Study	European Study Group 1998 Kappos 2001	III	Randomised Double-blind Parallel group	718	SPMS	3 years[b]	Placebo SC Q2D	IFNβ-1b 250 µg SC Q2D
Comparability		n/a	✓	n/a	✓	!	! [c]	n/a

✓ = Studies are similar; ! = Differences exist between the trials. [a] ITT population. [b] Early termination at month 33. Mean duration of follow-up was 1054 and 1068 days in the placebo and IFNβ-1b group, respectively. [c] Common comparator despite difference in administration.
IFNβ-1b, interferon-beta-1b; ITT, intention-to-treat; MS, multiple sclerosis; PO, oral; QD, once daily; Q2D, once every two days; SC, subcutaneous; SPMS, secondary progressive multiple sclerosis.

Inclusion and Exclusion Criteria

The comparability of the inclusion/exclusion criteria is summarised in Table 116. The disease population, EDSS range, documented progression, and the requirement of a history of RRMS/relapsing disease course were identical for these studies. However, unlike EXPAND, the European Study did not include patients with history of IFN treatment; this is a significant limitation of unadjusted comparisons because it could represent a strong source of bias. However, this could be potentially matched in MAICs because the population of EXPAND is broader. Additionally, the age range differed between the studies, but EXPAND also included a broader population in this respect. The European Study required that patients have had no relapses in one month before the study, while EXPAND required three months; the included population was broader in the European Study, preventing potential matching using EXPAND IPD on this criterion.

The European Study included a subgroup of patients with active SPMS, but with a narrower definition of active SPMS than that used in EXPAND.

Table 116: Pairwise Comparison of Inclusion/Exclusion Criteria – EXPAND vs. European Study

Criteria	EXPAND	European Study	Comparability
MS Population	SPMS	SPMS	✓
Baseline EDSS range	3.0-6.5	3.0-6.5	✓
Age range	18-60	18-55	!
Prior IFN therapy	Allowed	No prior IFN use	!
No relapses in X months prior	3 months	1 month	X
Documented progression within X months prior	24 months	24 months	✓
History of RRMS	Required	Required	✓
Duration of MS	No restriction	≥ 2 years	n/a
Duration of SPMS	No restriction	NR	n/a
MS severity score	No restriction	NR	n/a
T25FW test	No restriction	NR	n/a
Active SPMS definition	Presence of relapses in 2 years before	Relapse within 2 years	!

	study or Gd+ T1 lesions at baseline	before the study	

✓ = Criterion is identical; ! = Differences exist between trials and the EXPAND patient population is broader (i.e. matching may be possible); X = Differences exist between the trials and the EXPAND patient population is not broader (i.e. matching is not possible).
EDSS, expanded disability status scale; IFN, interferon; MS, multiple sclerosis; NR, not reported; RRMS, relapse-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis; T25FW, Timed 25-Foot Walk.

Outcome Definitions

Outcome definitions for ARR and discontinuation in the European Study were identical to those in EXPAND (Table 117). The definition of "disability progression" used in the 3-month CDP outcome differed between the studies, in that patients with a baseline EDSS of 5.5 required an increase of 0.5 to qualify as experiencing "progression" in EXPAND, but required an increase of 1.0 in the European Study. The definitions were otherwise identical and were considered to be reasonably equivalent based on medical experts in the field. Time to 6-month CDP was not reported in the European Study. Relevant outcomes were not reported for the active SPMS subgroup.

Table 117: Pairwise Comparison of Outcome Definitions – EXPAND vs. European Study

	ARR	Time to 3-month CDP	Time to 6-month CDP	Discontinuation
EXPAND	Number of total relapses per patient-years	1.0-point inc. in EDSS score: 3.0-5.0 0.5-point inc. in EDSS score: 5.5-6.5	1.0-point inc. in EDSS score: 3.0-5.0 0.5-point inc. in EDSS score: 5.5-6.5	The proportion of randomised patients who discontinued treatment for any reason
European Study	Number of total relapses per patient-years	1.0-point inc. in EDSS score: 3.0-5.5 0.5-point inc. in EDSS score: 6.0-6.5	NR	The proportion of randomised patients who discontinued treatment for any reason
Comparability	✓	!	n/a	✓

✓ = Outcome is reported in the comparator trial with the same or very similar definition to EXPAND; ! = Outcome is reported in the comparator trial, but the definition differs from EXPAND.
ARR, annualised relapse rate; CDP, confirmed disability progression; EDSS, expanded disability status scale; NR, not reported.

Baseline Patient Characteristics

Only six key patient baseline characteristics that were reported by EXPAND were reported in the European Study. Of these characteristics, the following were similar to EXPAND (within 10%): the proportion of females, mean EDSS score, and duration of MS. The following baseline characteristics differed (by >10%): mean age, duration of SPMS, and the proportion of patients relapse-free in the prior two years (Table 118). The European Study did not report baseline characteristics for the subgroup of patients with active SPMS, therefore characteristics for the overall study population were compared with those of the EXPAND active SPMS subgroup. Only two characteristics were similar (within 10%), with the other five reported characteristics, including proportion of patients relapse-free in the two years before study start, differing by >10% between the trials.

Table 118: Pairwise Comparison of Baseline Patient Characteristics – EXPAND vs. European Study

Characteristic	Total Population			Active SPMS		
	EXPAND	European Study	Comparability	EXPAND	European Study	Comparability (total EUSPMS vs active EXPAND)
Age (mean years)	48.0	41.0	!	46.6	NR	!
Proportion female (%)	60	61	✓	36.2	NR	!
Mean EDSS score	5.4	5.1	✓	5.44	NR	✓
Proportion of patients with EDSS score ≥6.0 (%)	56	45	!	55.7	NR	!
Time since onset of MS symptoms (mean years)	16.8	NR	n/a	15.56	NR	n/a
Duration of MS (mean years)	12.6	13.1	✓	11.49	NR	!
Duration of SPMS (mean years)	3.8	2.2	!	3.19	NR	✓
Normalised brain volume (mean cm^3)	1423	NR	n/a	1421.1	NR	n/a
Proportion of patients with Gd+ lesions of T1-weighted images (%)	21	NR	n/a	45.9	NR	n/a
Total volume of T2 lesions on T2-weighted images (mean mm3)	15,321	NR	n/a	17,659	NR	n/a
Proportion of patients without previous use of a DMT (%)	22	NR	n/a	23.4	NR	n/a
Mean Timed 25-Foot Walk Test (seconds)	16.7	NR	n/a	16.92	NR	n/a
Time since most recent relapse (months)	59	NR	n/a	30.53	NR	n/a
Proportion of patients relapse-free in prior year (%)	78	NR	n/a	54.6	NR	n/a
Proportion of patients relapse-free in prior 2 years (%)	64	30	!	24.1	NR	!
Number of relapses per patient in the prior year (mean)	0.2	NR	n/a	0.5	NR	n/a
Number of relapses per patient in the previous 2 years (mean)	0.7	NR	n/a	1.4	NR	n/a

✓ = Both studies report this characteristic, and the value is within 10% compared to EXPAND; ! = Both studies report this characteristic, but the value differs by >10% compared to EXPAND. A 10% threshold for similarity was subjectively selected to qualitatively assess heterogeneity; choice of the 10% threshold was supported by a quantitative analysis using estimated standardized mean differences.
DMT, disease-modifying treatment; EDSS, expanded disability status scale; Gd+, gadolinium-enhancing; MS, multiple sclerosis; NR, not reported; SPMS, secondary progressive multiple sclerosis.

Placebo-arm Outcomes

The placebo-arm outcomes for ARR and discontinuation in the European Study were >10% different than values reported by EXPAND (Table 119). ARR and annualised discontinuation rate were not reported for the active SPMS subgroup in the European Study.

Table 119: Pairwise Comparison of Placebo-Arm Outcomes – EXPAND vs. European Study

Study ID	Placebo Administration	ARR	Annualised Rate of Discontinuation
Total Population			
EXPAND	PO QD	0.16	0.084
European Study	SC Q2D	0.57	0.132
Comparability		!	!
Active SPMS Population			
EXPAND	PO QD	n/a – not reported in European Study	n/a – not reported in European Study
European Study	SC Q2D		
Comparability			

✓ = Outcome value is similar (within 10%) compared to EXPAND; ! = Outcome value is dissimilar (>10% different) compared to EXPAND. A 10% threshold for similarity was subjectively selected to qualitatively assess heterogeneity; choice of the 10% threshold was supported by a quantitative analysis using estimated standardized mean differences.
ARR, annualised relapse rate; PO, oral; QD, once daily; Q2D, once every 2 days (every other day); SC, subcutaneous.

Conclusion

As in the previously described pairwise feasibility assessment, the presence of significant clinical heterogeneity between the European Study and EXPAND undermines the validity of ITCs based on summary-level data. Again, failure to account for these differences can lead to misleading comparisons of treatment effect. The requirements for conducting MAICs between EXPAND and the European Study (i.e., similar study design, similar or broader inclusion criteria in EXPAND, and similar outcome definitions) were all considered to be met, with the caveat that not all differences in study populations could be accounted for during the matching and adjusting process. Despite this, MAICs would still have the advantage over Bucher ITCs because they consider a combination of IPD and aggregate data to adjust for observed differences in characteristics among trials, thereby providing a more robust and valid indirect comparison than Bucher ITC.

As neither baseline characteristics nor relevant outcomes were reported for the active SPMS subgroup in the European Study, an MAIC for this subgroup was not deemed feasible.

6.3.2.4 Siponimod vs. Natalizumab (Tysabri®): ASCEND

Study Design

ASCEND was a Phase III 96-week RCT with an optional two year open-label extension evaluating the efficacy and safety of 300 mg intravenous natalizumab (Tysabri®) administered every four weeks, vs. placebo, for the treatment of 889 patients with SPMS. Although there are some differences in study duration and the route of placebo administration with EXPAND, the study design of the ASCEND trial was overall similar to EXPAND (Table 120).

Table 120: Pairwise Comparison of Study Design – EXPAND vs. ASCEND

Study ID	Author Year	Phase	Study Design	Sample Size[a]	MS Population	Study Duration	Comparator	Treatment
EXPAND	Kappos 2018	III	Randomised Double-blind Parallel group	1651	SPMS	3 years	Placebo **PO** QD	Siponimod 2 mg PO QD
ASCEND	Kapoor 2018	III	Randomised Double-blind Parallel group	889	SPMS	2 years[b]	Placebo **IV** Q4W	Natalizumab 300 mg IV Q4W
Comparability		n/a	✓	n/a	✓	!	! [c]	n/a

✓ = Studies are similar; ! = Differences exist between the trials. [a] ITT population. [b] Outcomes were assessed over a 96-week treatment period. [c] Common comparator despite difference in administration.
ITT, intention-to-treat; IV, intravenous; MS, multiple sclerosis; PO, oral; QD, once daily; Q4W, once every four weeks; SPMS, secondary progressive multiple sclerosis.

Inclusion and Exclusion Criteria

The comparability of the inclusion/exclusion criteria is summarised in Table 121. The disease population, range of included EDSS, and the requirement for no relapses 3 months preceding screening were identical between the trials. There were differences in the included age range and the requirements for documented progression (i.e., within a number of months prior to the trial); additionally, ASCEND excluded patients who had been treated with IFNs in the prior 4 weeks. However, EXPAND included broader populations with respect to these characteristics (Table 121). Therefore, matching the EXPAND IPD to this population was potentially possible through an MAIC analysis. Although a history of RRMS was not reported as a required inclusion criterion in ASCEND (unlike EXPAND), this was considered an unimportant discrepancy because a history of relapsing disease is implied in the diagnosis of SPMS.

The ASCEND study did not include an active SPMS subgroup.

Table 121: Pairwise Comparison of Inclusion/Exclusion Criteria – EXPAND vs. ASCEND

Criteria	EXPAND	ASCEND	Comparability
MS Population	SPMS	SPMS	✓
Baseline EDSS range	3.0-6.5	3.0-6.5	✓
Age range	18-60	18-58	!
Prior IFN therapy	Allowed	No prior IFN use 4 weeks prior to study	!
No relapses in X months prior	3 months	3 months	✓
Documented progression within X months prior	24 months	12 months	!
History of RRMS	Required	NR	n/a
Duration of MS	No restriction	NR	n/a

Duration of SPMS	No restriction	≥ 2 years	!
MS severity score	No restriction	Score of 4 or higher	!
T25FW test	No restriction	<30 seconds	!
Active SPMS definition	Presence of relapses in 2 years before study or Gd+ T1 lesions at baseline	None	n/a

✓ = Criterion is identical; ! = Differences exist between trials and the EXPAND patient population is broader (i.e. matching may be possible); X = Differences exist between the trials and the EXPAND patient population is not broader (i.e. matching is not possible).
EDSS, expanded disability status scale; IFN, interferon; IFNβ, interferon-beta; MS, multiple sclerosis; NR, not reported; RRMS, relapse-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis; T25FW, Timed 25-Foot Walk.

Outcome Definitions

The outcome definitions for ARR and discontinuation in ASCEND were identical to those in EXPAND (Table 122).

Importantly, the definition of time to 6-month CDP in ASCEND differed substantially from EXPAND in two ways. First, the increase in EDSS required to qualify as “disability progression” differed for patients with baseline EDSS of 5.5: in ASCEND, those specific patients required a 1.0-point increase in EDSS, while in EXPAND, they required a 0.5-point increase. In this regard, the definition of “disability progression” was considered to be reasonably equivalent as a conservative assumption, given that the EXPAND definition is more sensitive to changes in EDSS for those patients.

However, secondly and more importantly, the time to 6-month CDP reported by ASCEND was a composite outcome of multiple scales: CDP was achieved by a patient if there was sufficient change in any one or any combination of three different scales (including EDSS, the T25FW, and the 9-hole peg test [9-HPT]). It was not possible to account for this composite outcome using the EXPAND IPD, and based on currently available public data, there is no reported time to 6-month CDP based only on EDSS in ASCEND. The effect of including the T25FW and 9-HPT on the sensitivity of measuring 6-month CDP presents an unknown and potentially large source of heterogeneity and bias between the studies that could not be mitigated.

Therefore, in order to draw a comparison between EXPAND and ASCEND for 6-month CDP, the proportion of patients who experienced 6-month CDP by or at 96 weeks in each trial was compared instead, because this outcome is reported in ASCEND in a disaggregated manner that allows for the extraction of a EDSS-specific 6-month CDP outcome (Table 122).

The proportion of patients who experienced 6-month CDP at 96 weeks was extracted from the EXPAND IPD. EXPAND patients censored (i.e., missing or lost to follow-up) at or before 96 weeks were imputed using the conservative assumption that all censored patients had experienced 6-month CDP. Note that the method of imputation for censored data (if any) used in the ASCEND study to generate this outcome was not reported in currently available public data to our knowledge. Finally, time to 3-month CDP was not reported in ASCEND.

Table 122: Pairwise Comparison of Outcome Definitions – EXPAND vs. ASCEND

	ARR	Time to 3-month CDP	Time to 6-month CDP	Proportion of patients with 6-month CDP (96w)[a]	Discontinuation
EXPAND	Number of total relapses per patient-years	1.0-point inc. in EDSS score: 3.0-5.0 0.5-point inc. in EDSS score: 5.5-6.5	1.0-point inc. in EDSS score: 3.0-5.0 0.5-point inc. in EDSS score: 5.5-6.5	1.0-point inc. in EDSS score: 3.0-5.0 0.5-point inc. in EDSS score: 5.5-6.5	The proportion of randomised patients who discontinued treatment for any reason
ASCEND	Number of total relapses per patient-years	NR	1.0-point inc. in EDSS score: 3.0-5.5 0.5-point inc. in EDSS score: 6.0-6.5 Inc. of ≥20% in T25FW Inc. ≥20% in 9-HPT	1.0-point inc. in EDSS score: 3.0-5.5 0.5-point inc. in EDSS score: 6.0-6.5	The proportion of randomised patients who discontinued treatment for any reason
Comparability	✓	n/a	X	! [a]	✓

✓ = Outcome is reported in the comparator trial with the same or very similar definition to EXPAND; ! = Outcome is reported in the comparator trial, but the definition differs from EXPAND; X = Outcome is reported in the comparator trial, but the definition cannot be compared to that in EXPAND. [a] Because ASCEND reported time to 6-month CDP only as a composite of multiple scales, which is not comparable with the EDSS-specific outcome in other trials such as EXPAND, indirect comparisons for this outcome are instead based on the proportion of patients who experienced 6-month CDP (96 weeks) as measured by the EDSS scale alone (reported in the supplementary appendix of ASCEND).
ARR, annualised relapse rate; CDP, confirmed disability progression; EDSS, expanded disability status scale; inc., increase; MAIC, matching-adjusted indirect comparison; NR, not reported; T25FW, Timed 25-Foot Walk; 9-HPT, Nine Hole Peg Test; w, week(s).

Baseline Patient Characteristics

Most of the reported baseline characteristics were the similar (within 10%) between the trials: age, the proportion female, mean EDSS score, time since onset of MS symptoms and the duration of MS, normalised brain volume, and the volume of T2 lesions on T2-weighted images. The following baseline characteristics differed (by >10%) between the trials: the proportion of patients with an EDSS score greater than 6.0, the duration of SPMS, the proportion of patients with Gd+ lesions on T1-weighted images, and the T25FW test (Table 123). As the ASCEND study did not include an active SPMS subgroup, the overall study population characteristics were compared with the active SPMS sub-population in EXPAND to see if they could be matched. Six characteristics were similar (within 10%), with the remaining eight reported characteristics differing by >10% between the trials. The proportion of patients with T1-weighted Gd+ lesions, time since most recent relapse and proportions of patients relapse-free in the year and two years before study start were among the characteristics differing by >10%.

Table 123: Pairwise Comparison of Baseline Patient Characteristics – EXPAND vs. ASCEND

Characteristic	Total Population	Active SPMS

	EXPAND	ASCEND	Comparability	EXPAND	ASCEND	Comparability (total ASCEND vs active EXPAND)
Age (mean years)	48.0	47.2	✓	46.6	—	✓
Proportion female (%)	60	62	✓	36.2	—	!
Mean EDSS score	5.4	5.6	✓	5.44	—	✓
Proportion of patients with EDSS score ≥6.0 (%)	56	63	!	55.7	—	!
Time since onset of MS symptoms (mean years)	16.8	16.5	✓	15.56	—	✓
Duration of MS (mean years)	12.6	12.1	✓	11.49	—	✓
Duration of SPMS (mean years)	3.8	4.8	!	3.19	—	!
Normalised brain volume (mean cm3) c	1423	1423	✓	1421.1	—	✓
Proportion of patients with Gd+ lesions of T1-weighted images (%)	21	24	!	45.9	—	!
Total volume of T2 lesions on T2-weighted images (mean mm3)	15,321	16,793	✓	17,659	—	✓
Proportion of patients without previous use of a DMT (%)	22	NR	n/a	23.4	—	n/a
Mean Timed 25-Foot Walk Test (seconds)	16.7	11.2 [a]	!	16.92	—	!
Time since most recent relapse (months)	59	57	✓	30.53	—	!
Proportion of patients relapse-free in prior year (%)	78	84	✓	54.6	—	!
Proportion of patients relapse-free in prior 2 years (%)	64	71	✓	24.1	—	!
Number of relapses per patient in the prior year (mean)	0.2	NR	n/a	0.5	—	n/a
Number of relapses per patient in the previous 2 years (mean)	0.7	NR	n/a	1.4	—	n/a

✓ = Both studies report the characteristic and the values are similar (within 10%); ! = Both studies report the characteristic and the values are dissimilar (by >10%). A 10% threshold for similarity was subjectively selected to qualitatively assess heterogeneity; choice of the 10% threshold was supported by a quantitative analysis using estimated standardized mean differences. [a] Median value.
DMT, disease-modifying treatment; EDSS, expanded disability status scale; Gd+, gadolinium-enhancing; MS, multiple sclerosis; NR, not reported; SPMS, secondary progressive multiple sclerosis.

Placebo-arm Outcomes

The placebo-arm outcomes for ARR were similar between ASCEND and EXPAND, but the 1-year rate of discontinuation in the ASCEND trial was >10% different from the value from EXPAND (Table 124).

Table 124: Pairwise Comparison of Placebo-Arm Outcomes – EXPAND vs. ASCEND

Study ID	Placebo Administration	ARR	Annualised Rate of Discontinuation
EXPAND	PO QD	0.16	0.084
ASCEND	IV Q4W	0.17	0.186
Comparability		✓	!

✓ = Outcome value is similar (within 10%) compared to EXPAND; ! = Outcome value is dissimilar (>10% different) compared to EXPAND. A 10% threshold for similarity was subjectively selected to qualitatively assess heterogeneity; choice of the 10% threshold was supported by a quantitative analysis using estimated standardized mean differences.
ARR, annualised relapse rate; IV, intravenous; PO, oral; QD, once daily; Q4W, once every four weeks.

Conclusion

The comparison between EXPAND and ASCEND in this feasibility assessment did not share one of the key differences present in the other previously-described comparisons (i.e., whether IFN-experienced patients were allowed at screening), but there were some notable differences nonetheless. The requirements for conducting MAICs between ASCEND and EXPAND (i.e., similar study design, and similar or broader inclusion criteria in EXPAND) were all considered to be met, with the caveat that not all differences in study populations could be accounted for during the matching and adjusting process. Despite this, MAICs would still have the advantage over Bucher ITCs because they consider a combination of IPD and aggregate data to adjust for observed differences in characteristics among trials thereby providing a more robust and valid indirect comparison over traditional Bucher ITCs. Of note, a Bucher ITC or MAIC of time to 6-month CDP was not determined to be feasible given the different outcome definitions used in the two studies. In lieu of a more suitable time to CDP outcome, indirect comparisons could be conducted based on the proportion of patients who had experienced 6-month CDP at 96 weeks.

The ASCEND study did not include an active SPMS subgroup and the overall population was not considered to represent an active SPMS population closely enough for a MAIC or ITC in this population to be robust.

6.3.2.5 Siponimod vs. IFNβ-1a (Avonex®): IMPACT

Study Design

The International MS Secondary Progressive Avonex Controlled Trial (IMPACT)[104] was a two-year RCT evaluating 60 µg intramuscular IFNβ-1a (Avonex®) administrated once weekly vs. placebo for the treatment of 436 SPMS patients. Despite differences in study duration and the route of placebo administration, the study design of the IMPACT trial was overall similar to EXPAND (Table 125).

Table 125: Pairwise Comparison of Study Design – EXPAND vs. IMPACT

Study ID	Author Year	Phase	Study Design	Sample Size[a]	MS Population	Study Duration	Comparator	Treatment
EXPAND	Kappos 2018	III	Randomised Double-blind	1651	SPMS	3 years	Placebo PO QD	Siponimod 2 mg PO QD

			Parallel group					
IMPACT	Cohen 2002	NA	Randomised Double-blind Parallel group	436	SPMS	2 years	Placebo IM QW	IFNβ-1a 60 µg IM QW
Comparability		n/a	✓	n/a	✓	!	! [c]	n/a

✓ = Studies are similar; ! = Differences exist between the trials. [a] ITT population. [b] Outcomes were assessed over a 96-week treatment period. [c] Common comparator despite difference in administration.
IFNβ-1a, interferon-beta-1a; IM, intramuscular; ITT, intention-to-treat; MS, multiple sclerosis; PO, oral; QD, once daily; QW, once weekly; SPMS, secondary progressive multiple sclerosis.

Inclusion and Exclusion Criteria

The comparability of the inclusion/exclusion criteria is summarised in Table 126. The MS population and age range were identical for these studies. However, unlike EXPAND, IMPACT did not include patients with history of IFN treatment; this is a significant limitation of unadjusted comparisons because it could represent a strong source of bias. However, this could be potentially matched in MAICs because the population of EXPAND is broader. Additionally, the EDSS range and the requirements for documented progression (i.e., within a number of months prior to the trial) differed between the studies but EXPAND also included a broader population in this respect. A requirement of a history of RRMS/relapsing disease course, as well as no relapses in the months prior to the study were not specified as inclusion/exclusion criteria in IMPACT.

The IMPACT study included a subgroup of patients with active SPMS, but with a narrower definition of active SPMS than that used in EXPAND.

Table 126: Pairwise Comparison of Inclusion/Exclusion Criteria – EXPAND vs. IMPACT

Criteria	EXPAND	IMPACT	Comparability
MS Population	SPMS	SPMS	✓
Baseline EDSS range	3.0-6.5	3.5-6.5	!
Age range	18-60	18-60	✓
Prior IFN therapy	Allowed	No prior IFNβ use	!
No relapses in X months prior	3 months	NR	n/a
Documented progression within X months prior	24 months	12 months	!
History of RRMS	Required	NR	n/a
Duration of MS	No restriction	NR	n/a
Duration of SPMS	No restriction	NR	n/a
MS severity score	No restriction	NR	n/a
T25FW test	No restriction	NR	n/a
Active SPMS definition	Presence of relapses in 2 years before study or Gd+ T1 lesions at baseline	Presence of relapses in year before enrolment	!

✓ = Criterion is identical; ! = Differences exist between trials and the EXPAND patient population is broader (i.e. matching may be possible); X = Differences exist between the trials and the EXPAND patient population is not broader (i.e. matching is not possible).
EDSS, expanded disability status scale; IFN, interferon; IFNβ, interferon-beta; MS, multiple sclerosis; NR, not reported; RRMS, relapse-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis; T25FW, Timed 25-Foot Walk.

Outcome Definitions

Outcome definitions for ARR and discontinuation in IMPACT were identical to those in EXPAND (Table 127). The definition of "disability progression" used in the 3-month CDP outcome differed between the studies, in that patients with a baseline EDSS of 5.5 required an increase of 0.5 to qualify as experiencing "progression" in EXPAND, but required an increase of 1.0 in IMPACT. The definitions were otherwise identical and were considered to be reasonably equivalent based on clinical opinion. Time to 6-month CDP was not reported in IMPACT. Relevant outcomes were not reported for the active SPMS subgroup.

Table 127: Pairwise Comparison of Outcome Definitions – EXPAND vs. IMPACT

	ARR	Time to 3-month CDP	Time to 6-month CDP	Discontinuation
EXPAND	Number of total relapses per patient-years	1.0-point inc. in EDSS score: 3.0-5.0 0.5-point inc. in EDSS score: 5.5-6.5	1.0-point inc. in EDSS score: 3.0-5.0 0.5-point inc. in EDSS score: 5.5-6.5	The proportion of randomised patients who discontinued treatment for any reason
IMPACT	Number of total relapses per patient-years	1.0-point inc. in EDSS score: 3.0-5.5 0.5-point inc. in EDSS score: 6.0-6.5	NR	The proportion of randomised patients who discontinued treatment for any reason
Comparability	✓	!	n/a	✓

✓ = Outcome is reported in the comparator trial with the same or very similar definition to EXPAND; ! = Outcome is reported in the comparator trial, but the definition differs from EXPAND.
ARR, annualised relapse rate; CDP, confirmed disability progression; EDSS, expanded disability status scale; inc, increase; NR, not reported.

Baseline Patient Characteristics

Ten key patient baseline characteristics that were reported by EXPAND were reported in the IMPACT. Of these characteristics, most differed from EXPAND (by >10%): the proportion of patients with EDSS ≥6.0, duration of MS, proportion of patients with Gd+ lesions, mean T25FW test, time since most recent relapse, proportion of patients relapse-free in prior year, and number of relapses per patient in the prior year. Only two characteristics were similar to EXPAND (within 10%): the proportion of females and the mean EDSS score (Table 128). The IMPACT study did not report baseline characteristics for the subgroup of patients with active SPMS, therefore characteristics for the overall IMPACT study population were compared with those of the EXPAND active SPMS subgroup. Only two characteristics were similar (within 10%), with the remaining eight reported characteristics differing by >10% between the trials. The proportion of patients with T1-weighted Gd+ lesions, time since most recent relapse, and proportion of patients relapse-free and mean number of relapses per patient in the year before study start were among the characteristics differing by >10%.

Table 128: Pairwise Comparison of Baseline Patient Characteristics – EXPAND vs. IMPACT

Characteristic	Total Population			Active SPMS		
	EXPAND	IMPACT	Comparability	EXPAND	IMPACT	Comparability (total IMPACT vs active EXPAND)
Age (mean years)	48.0	47.6	✓	46.6	NR	✓
Proportion female (%)	60	64	✓	36.2	NR	!
Mean EDSS score	5.4	5.2	✓	5.44	NR	✓
Proportion of patients with EDSS score ≥6.0 (%)	56	48	!	55.7	NR	!
Time since onset of MS symptoms (mean years)	16.8	NR	n/a	15.56	NR	n/a
Duration of MS (mean years)	12.6	16.5	!	11.49	NR	!
Duration of SPMS (mean years)	3.8	NR	n/a	3.19	NR	n/a
Normalised brain volume (mean cm3) c	1423	NR	n/a	1421.1	NR	n/a
Proportion of patients with Gd+ lesions of T1-weighted images (%)	21	36	!	45.9	NR	!
Total volume of T2 lesions on T2-weighted images (mean mm3)	15,321	NR	n/a	17,659	NR	n/a
Proportion of patients without previous use of a DMT (%)	22	NR	n/a	23.4	NR	n/a
Mean Timed 25-Foot Walk Test (seconds)	16.7	14.5	!	16.92	NR	!
Time since most recent relapse (months)	59	44.4	!	30.53	NR	!
Proportion of patients relapse-free in prior year (%)	78	61	!	54.6	NR	!
Proportion of patients relapse-free in prior 2 years (%)	64	NR	n/a	24.1	NR	n/a
Number of relapses per patient in the prior year (mean)	0.2	0.6	!	0.5	NR	!
Number of relapses per patient in the previous 2 years (mean)	0.7	NR	n/a	1.4	NR	n/a

✓ = Both studies report the characteristic and the values are similar (within 10%); ! = Both studies report the characteristic and the values are dissimilar (by >10%). A 10% threshold for similarity was subjectively selected to qualitatively assess heterogeneity; choice of the 10% threshold was supported by a quantitative analysis using estimated standardized mean differences.
DMT, disease-modifying treatment; EDSS, expanded disability status scale; Gd+, gadolinium-enhancing; MS, multiple sclerosis; NR, not reported; SPMS, secondary progressive multiple sclerosis.

Placebo-arm Outcomes

The placebo-arm outcomes for ARR and discontinuation in IMPACT were >10% different than values reported by EXPAND (Table 129). ARR and annualised discontinuation rate were not reported for the active SPMS subgroup in the IMPACT study.

Table 129: Pairwise Comparison of Placebo-Arm Outcomes – EXPAND vs. IMPACT

Study ID	Placebo Administration	ARR	Annualised Rate of Discontinuation
Total Population			
EXPAND	PO QD	0.16	0.084
IMPACT	IM QW	0.30	0.142
Comparability		!	!
Active SPMS Population			
EXPAND	PO QD	n/a – not reported in IMPACT study	n/a – not reported in IMPACT study
IMPACT	IM QW		
Comparability			

✓ = Outcome value is similar (within 10%) compared to EXPAND; ! = Outcome value is dissimilar (>10% different) compared to EXPAND. A 10% threshold for similarity was subjectively selected to qualitatively assess heterogeneity; choice of the 10% threshold was supported by a quantitative analysis using estimated standardized mean differences.
ARR, annualised relapse rate; IM, intramuscular; PO, oral; QD, once daily; QW, once weekly.

Conclusion

Like all aforementioned comparisons (arguably aside from ASCEND), the presence of significant clinical heterogeneity between IMPACT and EXPAND undermines the validity of ITCs based on summary-level data. Again, failure to account for these differences can lead to misleading comparisons of treatment effect. The requirements for conducting MAICs between IMPACT and EXPAND (i.e., similar study design, similar or broader inclusion criteria in EXPAND, and similar outcome definitions) were all considered to be met, with the caveat that not all differences in study populations could be accounted for during the matching and adjusting process. Despite this, MAICs would still have the advantage over Bucher ITCs because they consider a combination of IPD and aggregate data to adjust for observed differences in characteristics among trials, thereby providing a more robust and valid indirect comparison than Bucher ITC.

As neither baseline characteristics nor relevant outcomes were not reported for the active SPMS subgroup in the IMPACT study, a MAIC for this subgroup was not deemed feasible.

6.3.3 Methods of analysis of studies included in the indirect or mixed treatment comparison

Prior to running the analysis, the inclusion and exclusion criteria were aligned between the two studies (or arms) being compared. For example, if the EXPAND trial had males and the ASCEND trial did not, it was possible to use the IPD to remove male patients from the EXPAND trial to match the inclusion and exclusion criteria of the ASCEND trial. However, it would not be possible to remove males from ASCEND trial given that there is no access to IPD for that trial. After matching on inclusion and exclusion criteria, the patients in the EXPAND trial were adjusted by re-weighting using IPD so that the most important baseline characteristics (e.g., mean EDSS at baseline) match those reported in the competitor trials. A form of propensity score weighting was used, in which patients in one treatment group (in this case, the EXPAND trial for which IPD are available) are weighted by the inverse odds of being in that group compared to the other treatment group (derived from the competitor trial for which only aggregate data are available. The propensity score model was estimated using the generalised method of moments based on the aggregate data and IPD.[136]

After matching and adjusting, it was expected that the average baseline characteristics would be similar between the comparator trials, and treatment outcomes were compared across balanced trial populations. The impact of re-weighting (i.e., adjusting) on the available statistical information in the IPD was expressed through the calculation of the effective sample size (i.e., N_{eff}). N_{eff} was computed as the square of the summed weights divided by the sum of the squared weights. The maximum effective sample size occurs when all patients have equal weight.[136] The occurrence of a small effective sample size can indicate that some patients are receiving extreme weights and that there may be little statistical power to detect differences between treatments.

The adjustment process of the MAIC was first conducted using all the available clinically relevant baseline characteristics as selected and ranked by medical experts. Notably, a perfect alignment of all baseline variables is rarely achieved in MAIC, especially when a larger number of variables are included in the process. Including many variables in the adjusting process will also affect the effective sample size: the more variables that need to be adjusted, the smaller the effective sample size will become. In the proposed analysis, baseline characteristics were ordered according to their relevance to the outcome and were dropped one-by-one from the adjusting process to investigate the impact of each factor. The final results were the most thorough and conservative result (i.e. fully matched and adjusted, no excluded adjustment factors from the pool of available factors). All scenarios, as well as univariate adjustment scenarios, were reported for all comparisons conducted.

6.3.3.1 Siponimod vs Rebif® 22 µg TIW

Only SPECTRIMS evaluated Rebif® 22 µg administered TIW. SPECTRIMS reported time to 3-month CDP and ARR.

Matching

It was possible to match the EXPAND IPD to some but not all differences in the inclusion/exclusion criteria for SPECTRIMS, as summarised below:

Able to Match to Comparator Trial	
• Adults with SPMS	→ Identical criteria
• No previous IFN treatment	→ Removed patients with prior IFN
• Age range (18-55)	→ Removed patients aged >55
• Baseline EDSS range (3.0-6.5)	→ Removed patients with EDSS <3.0 and >6.5
• Documented progression within specified time-frame (progression in prior 24 months, progression for at least 6 months)	→ Very similar criteria, did not require matching (EXPAND: 6 months in past 2 years)
Unable to Match to Comparator Trial	
• No recent relapse in prior 2 months	→ Broader than EXPAND (3 months): allowed more recent relapse

Adjustment: Confirmed Disability Progression

It was possible to adjust the EXPAND IPD to some but not all of the selected adjustment factors (i.e., baseline patient characteristics), as summarised below:

Able to Adjust to Comparator Trial

• Age • EDSS score at screening • Duration of MS since diagnosis • Duration of SPMS • Number of relapses in the two years prior to study • Sex		
Unable to Adjust to Comparator Trial		
• Total volume of T2 lesions on T2-weighted images	→	Not reported in comparator trial
• Gd+ lesions on T1 weighted images	→	Not reported in comparator trial
• Normalised brain volume	→	Not reported in comparator trial

Adjustment: Annualised Relapse Rate

It was possible to adjust the EXPAND IPD to some but not all of the selected adjustment factors (i.e., baseline patient characteristics), as summarised below:

Able to Adjust to Comparator Trial		
• Number of relapses per patient in the two years prior to study		
Unable to Adjust to Comparator Trial		
• Time since onset of most recent relapse	→	Not reported in comparator trial
• Number of relapses in year prior to study	→	Not reported in comparator trial
• Gd+-enhancing lesions on T1-weighted images	→	Not reported in comparator trial
• Total volume of lesions on T2-weighted images	→	Not reported in comparator trial

6.3.3.2 Siponimod vs. Rebif® 44 µg TIW

Only SPECTRIMS evaluated Rebif® 44 µg TIW. SPECTRIMS reported time to 3-month CDP and ARR.

Matching

It was possible to match the EXPAND IPD to some but not all differences in the inclusion/exclusion criteria for SPECTRIMS, as summarised below:

Able to Match to Comparator Trial		
• Adults with SPMS	→	Identical criteria
• No previous IFN treatment	→	Removed patients with prior IFN
• Age range (18-55)	→	Removed patients aged >55
• Baseline EDSS range (3.0-6.5)	→	Removed patients with EDSS <3.0 and >6.5
• Documented progression within specified time-frame (progression in prior 24 months, progression for at	→	Very similar criteria, did not require matching (EXPAND: 6 months in past 2 years)

least 6 months)	
Unable to Match to Comparator Trial	
• No recent relapse in prior 2 months	→ Broader than EXPAND (3 months): allowed more recent relapse

Adjustment: Confirmed Disability Progression

It was possible to adjust the EXPAND IPD to some but not all of the selected adjustment factors (i.e., baseline patient characteristics), as summarised below:

Able to Adjust to Comparator Trial	
• Age • EDSS score at screening • Duration of MS since diagnosis • Duration of SPMS • Number of relapses in the two years prior to study • Sex	
Unable to Adjust to Comparator Trial	
• Total volume of T2 lesions on T2-weighted images	→ Not reported in comparator trial
• Gd+ lesions on T1 weighted images	→ Not reported in comparator trial
• Normalised brain volume	→ Not reported in comparator trial

Adjustment: Annualised Relapse Rate

It was possible to adjust the EXPAND IPD to some but not all of the selected adjustment factors (i.e., baseline patient characteristics), as summarised below:

Able to Adjust to Comparator Trial	
• Number of relapses per patient in the two years prior to study	
Unable to Adjust to Comparator Trial	
• Time since onset of most recent relapse	→ Not reported in comparator trial
• Number of relapses in year prior to study	→ Not reported in comparator trial
• Gd+-enhancing lesions on T1-weighted images	→ Not reported in comparator trial
• Total volume of lesions on T2-weighted images	→ Not reported in comparator trial

6.3.3.3 Siponimod vs. Betaferon® 250 µg Q2D

Two studies evaluated 250 µg Betaferon® (SC IFNβ-1b) administered Q2D: The North American Study and the European Study. Of these two trials, only the North American Study reported time to 6-month CDP, and only the European Study reported time to 3-month CDP. Both studies reported ARR. As a result, the matching and adjusting process differed between 3-month CDP, 6-month CDP, and ARR to account for the different bases of evidence for each outcome in the context of this comparator.

Matching to the North American Study for 6-month CDP

It was possible to match the EXPAND IPD to some but not all differences in the inclusion/exclusion criteria for the North American Study, as summarised below:

Able to Match to Comparator Trial		
• Adults with SPMS	→	Identical criteria
• No previous IFN treatment	→	Removed patients with prior IFN treatment
• Duration of MS ≥ 2 years	→	Removed patients with duration of MS <2 years
• Baseline EDSS range (3.0-6.5)	→	Removed patients with EDSS <3.0 and >6.5
• Documented progression within specified time-frame (progression in prior 24 months, progression for at least 6 months)	→	Very similar criteria, did not require matching (EXPAND: progression in 2 years prior to screening for at least 6 months)
Unable to Match to Comparator Trial		
• Age range (18-65)	→	Broader than EXPAND (18-60): allowed older patients

Adjustment to the North American Study for 6-month CDP

It was possible to adjust the EXPAND IPD to some but not all of the selected adjustment factors (i.e., baseline patient characteristics), as summarised below:

Able to Adjust to Comparator Trial		
• Age		
• EDSS score at screening		
• Duration of MS since diagnosis		
• Duration of SPMS		
• Number of relapses per patient in prior two years to study		
• Sex		
Unable to Adjust to Comparator Trial		
• Total volume of T2 lesions on T2-weighted images	→	Not reported in comparator trial
• Gd+ lesions on T1 weighted images	→	Not reported in comparator trial
• Normalised brain volume	→	Not reported in comparator trial

Matching to the European Study for 3-month CDP

It was possible to match the EXPAND IPD to some but not all differences in the inclusion/exclusion criteria for the European Study, as summarised below:

Able to Match to Comparator Trial		
• Adults with SPMS	→	Identical criteria
• No previous IFN treatment	→	Removed patients with prior IFN
• Age range (18-55)	→	Removed patients aged >55
• Baseline EDSS range (3.0-6.5)	→	Removed patients with EDSS <3.0 and >6.5
• Documented progression in specified	→	Criteria were considered similar to

timeframe (≥2 relapses or disability increase in prior 2 years)		EXPAND (progression in prior 24 months; progression for at least 6 months), although European Study was slightly broader than EXPAND.
• Duration of SPMS (≥6 months)	→	Identical criteria
Unable to Match to Comparator Trial		
• No recent relapse in specified time frame (<1 month)	→	Cannot match because European study's criteria on relapses within a time-frame is broader than EXPAND (<3 months). The European Study required no relapse-related neurological deterioration within one month prior to study (not reported in EXPAND IPD)

Adjustment to the European Study for 3-month CDP

It was possible to adjust the EXPAND IPD to some but not all of the selected adjustment factors (i.e., baseline patient characteristics), as summarised below:

Able to Adjust to Comparator Trial		
• Age • EDSS score at screening • Duration of MS since diagnosis • Duration of SPMS • Proportion of patients relapse-free in the two years prior to study • Sex		
Unable to Adjust to Comparator Trial		
• Total volume of T2 lesions on T2-weighted images	→	Not reported in comparator trial
• Gd+ lesions on T1-weighted images	→	Not reported in comparator trial
• Normalised brain volume	→	Not reported in comparator trial

Matching to the North American and European Studies for ARR

It was possible to match the EXPAND IPD to some but not all differences in the inclusion/exclusion criteria for the North American and European Studies, as summarised below:

Able to Match to Comparator Trials		
• Adults with SPMS	→	Identical criteria
• Duration of SPMS (European Study: ≥6 months)	→	Identical criteria
• No previous IFN treatment	→	Removed patients with prior IFN
• Baseline EDSS range (3.0-6.5)	→	Removed patients with EDSS <3.0 and >6.5
• Documented progression in specified time-frame (Disability increase in prior 2 years [European study: or ≥2 relapses])	→	Criteria were considered similar to EXPAND (progression in prior 24 months; progression for at least 6 months), although European Study was slightly broader than EXPAND and North American Study
Unable to Match to Comparator Trials		

• No recent relapse in prior 1 month (European)	→	Cannot match because European study's criteria on relapses within a time-frame is broader than EXPAND (<3 months). The European Study required no relapse-related neurological deterioration within one month prior to study (not reported in EXPAND IPD)
• Age Range (North American: 18-65)	→	Broader than EXPAND (18-60)
• Age Range (European: 18-55)	→	Conflicts with North American

Adjustment to the North American and European Studies for ARR

For the adjustment stage, the EXPAND IPD would be adjusted to align with the average baseline patient characteristics of the available trials for this comparator. However, the European Study did not report any of the ranked baseline patient characteristics identified for adjustment in the context of ARR. As a result, adjustment could not be performed for this DMT.

6.3.3.4 Siponimod vs. Tysabri® 300 mg Q4W

Only ASCEND evaluated Tysabri® (natalizumab), using a dosing regimen of 300 mg Q4W.

Although ASCEND reported "Time to 6-month CDP," the definition of this outcome differed between ASCEND and EXPAND in such a way that prevented meaningful comparison. In lieu of a suitable time-to-event outcome pertaining to 6-month CDP, the proportion of patients who experienced 6-month CDP by the end of the 96-week period in ASCEND was compared to that in EXPAND instead. To make this comparison, the analogous outcome was calculated from the EXPAND IPD (OR = 0.77, 95% CI: 0.61 to 0.97). Calculating the proportion of patients who experienced 6-month CDP in the EXPAND IPD required an assumption to be made regarding patients who were censored at or before 96 weeks. It was conservatively assumed that all patients who were censored at or before 96 weeks in EXPAND experienced a 6-month CDP event. Note that the handling of censored data is not described in ASCEND or related supplemental materials to our knowledge, ergo it is unknown if the data were similarly imputed, or if the censored patients were excluded from the reported outcome.

ASCEND also reported the outcome of ARR.

Matching

It was possible to match the EXPAND IPD to some but not all differences in the inclusion/exclusion criteria for the ASCEND trial, as summarised below:

Able to Match to Comparator Trial		
• Adults with SPMS	→	Identical criteria
• Baseline EDSS range (3.0-6.5)*	→	Removed patients with EDSS <3.0 and >6.5
• SPMS onset (≥2 years)	→	Removed patients with SPMS onset <2 years
• MS severity score (≥4)	→	Removed patients with MS severity score <4
• No recent relapses in prior 3 months	→	Removed patients with most recent relapse within 3 months
• Timed T25FW (≤30s)	→	Removed patients with >30s T25FW
• Age range (18-58)	→	Removed patients >58 years old
Unable to Match to Comparator Trial		
• No IFNβ therapy in prior 4 weeks	→	Time since IFNβ therapy not captured in

		EXPAND IPD
• No relapse-related neurological deterioration within 1 month prior to study	→	Not captured in EXPAND IPD
• Required disability progression not related to relapses within the prior year	→	Although EXPAND was broader (required disability progression within prior two years), time since disability progression was not captured in EXPAND IPD, ergo this criterion could not be matched

Adjustment: Confirmed Disability Progression

It was possible to adjust the EXPAND IPD to all of the selected adjustment factors (i.e., baseline patient characteristics), as summarised below:

Able to Adjust to Comparator Trial
• Age
• EDSS score at screening
• Duration of MS since diagnosis
• Treatment experience (IFN or DMT history)
• Normalised brain volume
• Gd+ lesions on T1-weighted images
• Duration of SPMS
• Total volume of T2 lesions on T2-weighted images
• Number of relapses in prior 2 years
• Sex

Adjustment: Annualised Relapse Rate

It was possible to adjust the EXPAND IPD to some but not all of the selected adjustment factors (i.e., baseline patient characteristics), as summarised below:

Able to Adjust to Comparator Trial		
• Time since most recent relapse		
• Gd+-enhancing lesions on T1-weighted images		
• Total volume of lesions on T2-weighted images		
Unable to Adjust to Comparator Trial		
• Number of relapses per patient in prior two years to study	→	Not reported in comparator trial
• Number of relapses per patient in prior one year to study	→	Not reported in comparator trial

6.3.3.5 Siponimod vs. Avonex® 60 µg QW

Only IMPACT evaluated Avonex®. IMPACT reported time to 3-month CDP and ARR.

The matching and adjustment process for this pairwise comparison is summarised below.

Matching

It was possible to match the EXPAND IPD to some but not all differences in the inclusion/exclusion criteria for the IMPACT trial, as summarised below:

Able to Match to Comparator Trial		
• Adults with SPMS	→	Identical criteria
• No prior IFNβ therapy	→	Removed patients with prior IFNβ therapy
• Baseline EDSS range (3.0-6.5)	→	Removed patients with EDSS <3.0 and >6.5
• Age range (18–60)	→	Identical criteria
Unable to Match to Comparator Trial		
• Disease progression required over the previous year	→	IMPACT requires disease progression over the previous year; although EXPAND was broader, the IPD did not include data required to match

Adjusting: Confirmed Disability Progression

It was possible to adjust the EXPAND IPD to some but not all of the selected adjustment factors (i.e., baseline patient characteristics), as summarised below:

Able to Adjust to Comparator Trial		
• Age		
• EDSS score at screening		
• Duration of MS since diagnosis		
• Gd+ lesions on T1-weighted images		
• Number of relapses in prior 2 years		
• Sex		
Unable to Adjust to Comparator Trial		
• Duration of SPMS	→	Not reported in comparator trial
• Total volume of T2 lesions on T2-weighted images	→	Not reported in comparator trial
• Normalised brain volume	→	Not reported in comparator trial

Adjusting: Annualised Relapse Rate

It was possible to adjust the EXPAND IPD to some but not all of the selected adjustment factors (i.e., baseline patient characteristics), as summarised below:

Able to Adjust to Comparator Trial		
• Time since most recent relapse		
• Number of relapses per year in 1 year prior to study		
• Gd+-enhancing lesions on T1-weighted images		
Unable to Adjust to Comparator Trial		
• Total volume of lesions on T2-weighted images	→	Not reported in comparator trial
• Number of relapses per patient in prior two years to study	→	Not reported in comparator trial

6.3.4 Bucher ITCs and Network meta-analysis

6.3.4.1 Methods

Bucher ITCs

Bucher ITCs were conducted using published summary or aggregate data of siponimod and the comparator DMTs. Due to this, the validity of Bucher ITCs each rely on the similarity of trial design and patient population since they do not allow for adjusting for sources of heterogeneity. A Bucher ITC calculator[137] authored by Tobías, Catalá-López and Roqué [137] was used to perform the calculations according to the methodology by Bucher, Guyatt, Griffith and Walter [138].[138]

Network Meta-Analysis

All NMAs using summary level data were performed using a Bayesian framework.[139-141] The chosen reference treatment for all analyses was placebo, given that it was the only common comparator between any studies. Only fixed-effect models were used for the NMAs due to the sparse network populated by almost exclusively single-study connections. Vague or flat priors, such as $N(0, 100^2)$, were assigned for basic parameters throughout, although informative priors were also considered.[142, 143] A binomial or normal likelihood model which accounts for the use of multi-arm trials was used for analyses, depending on the outcome. Standard ITC/NMA methodology based on National Institute for Health and Care Excellence (NICE) Decision Support Unit (DSU) Technical Support Documents (TSD) was followed.[139, 144]

As a measure of the association between each treatment and its efficacy, Markov Chain Monte Carlo methods were used to model point estimates and 95% credible intervals for each pairwise comparison of outcomes of interest. Measures of effect that are commonly presented for Bayesian NMAs were generated, including mean rank with 95% credible intervals (where values closer to 1 are preferred), and probability of best (p-best).[145] Additionally, Surface Under the Cumulative RAnking curve (SUCRA) values were generated as an additional measure to reflect ranking and uncertainty. This measure, expressed as a percentage, shows the relative probability of an intervention being among the best options.[145] To assess whether fixed- or random-effects models had adequate fit to the data, the posterior mean of the residual deviance from each NMA was compared to the corresponding number of unconstrained data points (approximately equal if the fit is adequate), as well as the deviance information criterion (DIC).

All analyses were conducted using R (R Core Team, Vienna, Austria) and WinBUGS software (MRC Biostatistics Unit, Cambridge, UK) based on the WinBUGS code outlined in the NICE DSU TSD.[139, 144] Three chains were fit in WinBUGS for each analysis, with a burn-in of ≥60,000 iterations and subsequent sampling of ≥60,000 iterations.

6.3.4.2 Results

Bucher ITCs

The results from the Bucher ITCs are presented below in Table 130, Table 131 and Table 132. There are major limitations in these results, which are biased and unreliable; large heterogeneity in the patient characteristics between studies, several of which are treatment effect modifiers, which break the assumptions required to appropriately conduct an ITC.

Table 130: Bucher ITC Results – Time to 6-month CDP

Comparator	Dose and Regimen	Study ID(s)	HR [a] vs. PBO (95% CI)	Siponimod vs. Comparator (Bucher ITC)			
				HR [a] Effect Size	Lower 95% CI	Upper 95% CI	p-value
Siponimod (PO)	2 mg qd	EXPAND	0.74 (0.60 to 0.92)				
Betaferon® (SC IFNβ-1b)	250 µg q2d	North American Study	0.92 (0.71 to 1.20) [a]	0.80	0.57	1.12	0.1953

An effect size of <1 indicates siponimod has a favourable outcome relative to the treatment that is being compared in the ITC. [a]The relevant HR and/or CI were not reported. Missing values were estimated based on the presented HR, CI, p-value, Kaplan-Meier curve, and/or IPD as necessary.
CDP, confirmed disability progression; CI, confidence interval; HR, hazard ratio; IFN-β, interferon-beta; IPD,individual patient data; ITC, indirect treatment comparison; PBO, placebo; PO, oral; qd, once daily q2d, every other day; SC, subcutaneous.

Table 131: Bucher ITC Results – Time to 3-month CDP

Comparator	Dose and Regimen	Study ID(s)	HR vs. PBO (95% CI)	Siponimod vs. Comparator (Bucher ITC)			
				HR Effect Size	Lower 95% CI	Upper 95% CI	p-value
Siponimod (PO)	2 mg qd	EXPAND	**0.79 (0.65 to 0.95)**				
Rebif® (SC IFN-β1a)	22 µg tiw	SPECTRIMS	0.88 (0.69 to 1.12) [a]	0.90	0.66	1.22	0.4919
Rebif® (SC IFN-β1a)	44 µg tiw	SPECTRIMS	0.83 (0.65 to 1.07)	0.95	0.70	1.30	0.7573
Betaferon® (SC IFN-β1b)	8 MIU (250 µg) q2d	European Study	**0.74 (0.60 to 0.91) [a]**	1.07	0.81	1.41	0.6460
Avonex® (IM IFN-β1a)	60 µg qw	IMPACT	0.98 (0.68 to 1.41)	0.81	0.53	1.23	0.3107

An effect size of <1 indicates siponimod has a favourable outcome relative to the treatment that is being compared in the ITC. Statistically significant values are bolded. [a] The relevant HR and/or CI were not reported. Missing values were estimated based on the presented HR, CI, p-value, Kaplan-Meier curve, and/or IPD as necessary.
CDP, confirmed disability progression; CI, confidence interval; HR, hazard ratio; IFN-β, interferon-beta; IM, intramuscular; IPD, individual patient data; ITC, indirect treatment comparison; PBO, placebo; PO, oral; qd, once daily; q2d, every other day; SC, subcutaneous; tiw, three times weekly.

Table 132: Bucher ITC Results – ARR

Comparator	Dose and Regimen	Study ID(s)	RR vs. PBO (95% CI)	Siponimod vs. Comparator (Bucher ITC)			
				RR Effect Size	Lower 95% CI	Upper 95% CI	p-value
Siponimod (PO)	2 mg qd	EXPAND	**0.45 (0.34 to 0.59)**				
Tysabri® (IV natalizumab)	300 mg q4w	ASCEND	**0.45 (0.32 to 0.63)**	0.99	0.64	1.54	0.9761

Rebif® (SC IFN-β1a)	22 µg tiw	SPECTRIMS	**0.69 (0.56 to 0.84)**	**0.65**	**0.46**	**0.92**	**0.0143**
Rebif® (SC IFN-β1a)	44 µg tiw	SPECTRIMS	**0.69 (0.56 to 0.85)**	**0.65**	**0.46**	**0.92**	**0.0154**
Betaferon® (SC IFNβ-1b)	250 µg q2d	North American Study European Study †	**0.65 (0.48 to 0.88)**	0.69	0.46	1.04	0.0734
Avonex® (IM IFN-β1a)	60 µg qw	IMPACT	**0.67 (0.49 to 0.90)***	0.68	0.45	1.01	0.0586

An effect size of <1 indicates siponimod has a favourable outcome relative to the treatment that is being compared in the ITC. Statistically significant values are bolded. * Error was calculated with RR and p-value reported in study publication. † Error has been estimated using the CI from the North American SG 160 µg/m2 treatment arm which has a similar effect size and sample size. The Handling Continuous Outcomes in Quantitative Synthesis (Fu et al., 2013) guide recommends that studies only missing error should not be excluded as this can lead to a biased combined estimate. The body surface area arm of the North American Study is not shown.
ARR, annualised relapse rate; CI, confidence interval; IFN-β, interferon-beta; IM, intramuscular; ITC, indirect treatment comparison; IV, intravenous; PBO, placebo; PO, oral; qd, once daily; qw, once weekly; q2d, every other day; q4w, every 4 weeks; RR, rate ratio; SC, subcutaneous; tiw, three times weekly.

Network Meta-Analysis

The results of the NMAs are presented as league tables below. There are major limitations in the results of the network meta-analyses presented, which are biased and unreliable; large heterogeneity in the patient characteristics between studies, several of which are treatment effect modifiers, which break the assumptions required to conduct an NMA appropriately.

All results are presented as RR (95% CI) or HR (95% CI), as appropriate. An RR or HR < 1 indicates that the intervention to the upper left had a more favourable outcome than the intervention to the lower right. Statistically significant results are bolded.

Figure 49: League Table for Time to 6-month CDP

Siponimod PO 2 mg qd	Fixed Effect Consistency Model: resdev, 3.001 vs. 3; DIC = -0.533	
0.80 (0.57 to 1.13)	**Betaferon® 250 µg q2d**	
0.74 (0.60 to 0.92)	0.92 (0.71 to 1.20)	**Placebo**

Note: Results are HR (95% CI). HR < 1 suggests upper left intervention is better.
Betaferon® = SC IFN-beta-1b; Rebif® = SC IFN-beta-1a; Tysabri® = IV Natalizumab.
CDP, Confirmed disability progression; DIC, deviance information criterion; HR, hazard ratio; IFNβ-1a, interferon beta-1a; IFNβ-1b, interferon beta-1b; IV, intravenous; NMA, network meta-analysis; PO, oral; qd, once daily; qw, once weekly; q2d, every other day; q4w, once every 4 weeks; resdev, residual deviance; SC, subcutaneous; tiw, three times weekly.

Figure 50: League Table for Proportion with 6-month CDP at 96 Weeks (Sensitivity Analysis)

Fixed Effect Consistency Model: resdev, 8.007 vs. 8; DIC = 64.635

Siponimod PO 2 mg qd			
1.02 (0.66 – 1.55)	**Betaferon® 250 µg q2d**		
0.78 (0.63 – 0.98)	0.77 (0.54 – 1.11)	**Placebo**	
0.74 (0.48 – 1.14)	0.73 (0.44 – 1.22)	0.94 (0.65 – 1.36)	**Tysabri® 300 mg q4w**

Note: Calculating the proportion of patients who experienced CDP-6 in the EXPAND IPD required an assumption to be made regarding patients who were censored at or before 96 weeks. We conservatively assumed that all patients who were censored at or before 96 weeks in EXPAND experienced a CDP-6 event.
Abbreviations: CDP, confirmed disability progression; ITC, indirect treatment comparison; OR, odds ratio; PO, oral; NMA, network meta-analysis; qd, once daily; q2d, every other day; q4w, every 4 weeks.

Figure 51: League Table for Time to 3-month CDP

Fixed Effect Consistency Model: resdev, 5.003 vs. 5; DIC = -1.665

Betaferon® 250 µg q2d					
0.94 (0.71 to 1.24)	**Siponimod PO 2 mg qd**				
0.89 (0.65 to 1.23)	0.95 (0.70 to 1.30)	**Rebif® 44 µg tiw**			
0.84 (0.61 to 1.15)	0.90 (0.66 to 1.22)	0.94 (0.67 to 1.33)	**Rebif® 22 µg tiw**		
0.76 (0.50 to 1.15)	0.81 (0.54 to 1.22)	0.85 (0.55 to 1.32)	0.90 (0.58 to 1.40)	**Avonex® 60 µg qw**	
0.74 (0.60 to 0.91)	**0.79 (0.65 to 0.96)**	0.83 (0.65 to 1.06)	0.88 (0.69 to 1.12)	0.98 (0.68 to 1.41)	**Placebo**

Note: Results are HR (95% CI). HR < 1 suggests upper left intervention is better.
Avonex® = IM IFN-beta-1a; Betaferon® = SC IFN-beta-1b; Rebif® = SC IFN-beta-1a.
CDP, confirmed disability progression; DIC, deviance information criterion; HR, hazard ratio IFNβ-1a, interferon beta-1a; IFNβ-1b, interferon beta-1b; IM, intramuscular; NMA, network meta-analysis; PO, oral; qd, once daily; qw, once weekly; q2d, every other day; resdev, residual deviance; SC, subcutaneous; tiw, three times weekly.

Figure 52: League table for ARR

Fixed Effect Consistency Model: resdev, 7.722 vs 8; DIC = -0.471

Siponimod PO 2 mg qd						
0.99 (0.64 to 1.53)	**Tysabri® 300 mg q4w**					
0.69 (0.46 to 1.04)	0.70 (0.44 to 1.09)	**Betaferon® 250 µg q2d**				
0.67 (0.45 to 1.01)	0.68 (0.43 to 1.07)	0.98 (0.64 to 1.49)	**Avonex® 60 µg qw**			
0.65 (0.46 to 0.92)	**0.66 (0.44 to 0.97)**	0.94 (0.66 to 1.35)	0.97 (0.67 to 1.39)	**Rebif® 22 µg tiw**		
0.65 (0.46 to 0.92)	**0.66 (0.44 to 0.98)**	0.94 (0.66 to 1.35)	0.97 (0.67 to 1.39)	1.00 (0.75 to 1.34)	**Rebif® 44 µg tiw**	
0.45 (0.34 to 0.59)	**0.45 (0.32 to 0.64)**	**0.65 (0.48 to 0.87)**	**0.67 (0.49 to 0.90)**	**0.69 (0.56 to 0.84)**	**0.69 (0.56 to 0.85)**	**Placebo**

Note: Results are RR (95% CI). RR < 1 suggests upper left intervention is better.
Avonex® = IM IFN-beta-1a; Betaferon® = SC IFN-beta-1b; Rebif® = SC IFN-beta-1a; Tysabri® = IV Natalizumab.
ARR, annualised relapse rate; DIC, deviance information criterion; IFNβ-1a, interferon beta-1a; IFNβ-1b, interferon beta-1b; IM, intramuscular; IV, intravenous; NMA, network meta-analysis; PO, oral; qd, once daily; qw, once weekly; q2d, every other day; q4w,every 4 weeks; resdev, residual deviance; RR, rate ratio; SC, subcutaneous; tiw, three times weekly.

Table 133: NMA Results – Sample Size, P-Best, and SUCRA for All Outcomes

Intervention (administration)	Study ID(s)	Sample Size	Mean P-best (%)	Mean SUCRA (%)
Time to 6-month CDP				
Placebo	All studies in network [24, 42, 118]	1032	0	35
Siponimod (PO 2 mg qd)	EXPAND[24]	1099	89	96
IFNβ-1b (SC 250 µg q2d)	North American Study[118]	317	10	56
Proportion with 6-month CDP at 96 Weeks (Sensitivity Analysis)				
Placebo	All studies in network[24, 42, 118]	1,480	0	28
Siponimod (PO 2 mg qd)	EXPAND[24]	1,099	37	78
Tysabri® Natalizumab (IV 300 mg q4w)	ASCEND[42]	439	3	23
Betaferon® IFNβ-1b (SC 250 µg q2d)	North American Study[118]	317	45	77
Time to 3-month CDP				
Placebo	All studies in network[24, 103, 104, 113, 114, 117]	1328	0	14
Siponimod (PO 2 mg qd)	EXPAND[24]	1099	22	71
IFNβ-1a (SC 22 µg tiw)	SPECTRIMS[103, 117]	209	7	46
IFNβ-1a (SC 44 µg tiw)	SPECTRIMS[103, 117]	204	15	59
IFNβ-1b (SC 250 µg q2d)	European Study[113, 114]	360	51	84
IFNβ-1a (IM 60 µg qw)	IMPACT[104]	217	5	27
ARR				
Placebo	All studies in network[24, 42, 103, 104, 113, 114, 117, 118]	2262	0	4
Siponimod (PO 2 mg qd)	EXPAND[24]	1099	50	92
Natalizumab (IV 300 mg q4w)	ASCEND[42]	439	48	91
IFNβ-1a (SC 22 µg tiw)	SPECTRIMS[103, 117]	209	0	46
IFNβ-1a (SC 44 µg tiw)	SPECTRIMS[103, 117]	204	0	46
IFNβ-1b (SC 250 µg q2d)	North American Study[118] European Study[113, 114]	677	1	54
IFNβ-1a (IM 60 µg qw)	IMPACT[104]	217	1	51

ARR, annualised relapse rate; CDP, confirmed disease progression; IFN, interferon; IM, intramuscular; IV, intravenous; PO, oral; qw, once weekly; q2d, twice daily; q4w, four times weekly; SC, subcutaneous; tiw, three times weekly

6.3.5 Simulated treatment comparison (STC)

STCs were conducted as sensitivity analyses to the MAICs, using the methods outlined in the NICE DSU TSD18.[103] Similar to the MAIC method, the STC method is designed to reduce cross-trial differences in baseline patient characteristics and reduce sensitivity to effect measures. In an STC, regression models are applied to individual patient data from one trial (i.e. EXPAND) and the fitted model is used to simulate or predict the effect of a treatment (i.e. siponimod) in designated populations of interest. The regression models were specified to incorporate

prognostic effects and treatment effect modifiers. As with MAICs, when the treatments of interest share a common comparator (i.e. placebo), STCs produce anchored ITCs that are adjusted via the common comparator for all known and unknown prognostic factors that may differ between trials.

An STC was conducted for each pairwise comparison for CDP and ARR outcomes. For each comparison, the EXPAND dataset was used to fit a Cox proportional-hazard regression (for time-to-event CDP outcomes), a logistic regression (for 6-month CDP response evaluated at 96-weeks), or a negative binomial regression (for ARR). All regressions included ranked prognostic factors (see below) and a binary treatment indicator (siponimod versus placebo) as predictors. Additionally, effect modifiers were incorporated as interactions between each prognostic factor and the binary treatment indicator. Ranked factors were included in the regression only if they were reported in the comparator trial and available in the EXPAND dataset. All continuous covariates (e.g. age) were standardised to the covariate's mean and standard deviation in the EXPAND dataset.

After fitting a regression model, the effect of siponimod versus placebo was simulated on an additive (log) scale by setting covariate values equal to the published mean for the comparator population of interest. Published means of continuous variables were standardised using the means and standard deviations of corresponding variables in the EXPAND trial. The point estimate of the ITC of interest was calculated as the difference between the simulated effect of siponimod versus placebo and the published effect of the comparator treatment versus placebo (transformed to the log scale), followed by back-transformation to a multiplicative scale (e.g., hazard ratio, odds ratio, or rate ratio). Robust standard errors were used to derive 95% confidence intervals on the additive (log scale) prior to back-transformation to the multiplicative scale of interest. Siponimod was considered numerically superior to the comparison treatment if the associated hazard ratio, odds ratio, or rate ratio was less than one. Point estimates were considered statistically significant if their corresponding 95% confidence interval excluded one.

Prognostic factors for CDP outcomes:

- Age
- EDSS score at screening
- Duration of MS since diagnosis
- Treatment experience (IFN or DMT history)
- Normalised brain volume
- Gadolinium-enhancing lesions on T1-weighted images
- Duration of SPMS
- Number of relapses in prior 2 years (or any other relapse variable)
- Sex

Prognostic factors for ARR outcome:

- Treatment experience (IFN or DMT history)
- Time since onset of most recent relapse
- Number of relapses in prior 1 year
- Number of relapses in prior 2 years
- Gadolinium-enhancing lesions on T1-weighted images
- Total volume of lesions on T2-weighted images

6.3.6 Programming language for the indirect or mixed treatment comparison

MAICs were conducted using methods outlined in the NICE DSU Technical Support Documents (TSDs). As the matching-adjusting process is conducted on the IPD from the EXPAND trial to produce a re-weighted outcome, there is no code to present for the ITC.

6.3.7 Risk of bias of studies included in indirect or mixed treatment comparisons

Table 134: Quality assessment results for included trials

Study name	Randomisation	Allocation concealment	Baseline characteristics	Blinding	Withdrawals	Outcome selection and reporting	Statistical methodology
EXPAND trial (Kappos et al., 2018)	LR	LR	LR	LR	LR	LR	LR
ASCEND trial (Kapoor et al., 2018)	LR	LR	LR	LR	LR	LR	LR
European Study (Kappos et al., 1998)	LR	LR	LR	Unclear	LR	LR	LR
North American Study (Panitch et al., 2004)	LR	LR	LR	LR	LR	LR	LR
SPECTRIMS trial (Francis, 2001)	LR	LR	LR	LR	LR	LR	LR
IMPACT study (Cohen et al., 2002)	LR	LR	LR	Unclear	LR	LR	LR

Randomisation: Was randomisation carried out appropriately? Concealment grade: Was the concealment of treatment allocation adequate? Blinding: Were the care providers, participants, and outcome assessors blind to treatment allocation? Baseline comparability: Were the groups similar at the outset of the study in terms of prognostic factors? Follow-up: Were there any unexpected imbalances in drop-outs between groups? Selective reporting and other sources of bias: Is there any evidence to suggest that the authors measured more outcomes than they reported?; Analysis: Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?
LR, low risk