NICE National Institute for Health and Care Excellence

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Contains no AIC data

Siponimod for treating secondary progressive multiple sclerosis [ID1304]

Lead team presentation

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Key issues

- To whom would siponimod be offered in the NHS?
  - what treatment would otherwise have been offered – what are the comparators?
- Are the baseline characteristics of the participants in EXPAND (company's key trial and main source of evidence) generalisable to patients with active secondary progressive multiple sclerosis seen in the NHS?
- What is the best way to compare siponimod to other treatments indirectly?
  - matching-adjusted indirect comparison or network meta-analysis?
- Is the siponimod treatment effect likely to remain constant over time?

Clinical effectiveness

Disease background: multiple sclerosis (MS)

- Chronic, lifelong, neurological disease with no cure, resulting in progressive, irreversible disability
- Affects central nervous system:
  - immune system mistakenly attacks myelin sheath (layer that surrounds and protects nerves), disrupting signals travelling along the nerves
- Associated with pain, chronic fatigue, unsteady gait, speech problems, incontinence, visual disturbance and cognitive impairment
- Onset typically between 25 and 35 years of age
- Secondary progressive MS characterised by more persistent or gradually increasing disability
  - associated with lower mobility, higher levels of depression/anxiety and greater dependence on caregivers than relapsing-remitting MS
- Approximately 110,000 people in UK have MS, 43,000 have secondary progressive
  - 2/3 with relapsing-remitting transition to secondary progressive over 30 years

Types and diagnosis of multiple sclerosis

Primary progressive MS

- Gradual disability progression from onset with no obvious relapses or remission

Relapsing-remitting MS (RRMS)

- 85% of people at diagnosis
- Treatment strategy: patient choice, number of relapses, MRI activity and response to previous treatment

2/3 within 30 years

Secondary progressive MS (SPMS)

- Steady progressive neurological damage +/- relapses
- Company defined SPMS as progressive increase in disability over 6 months

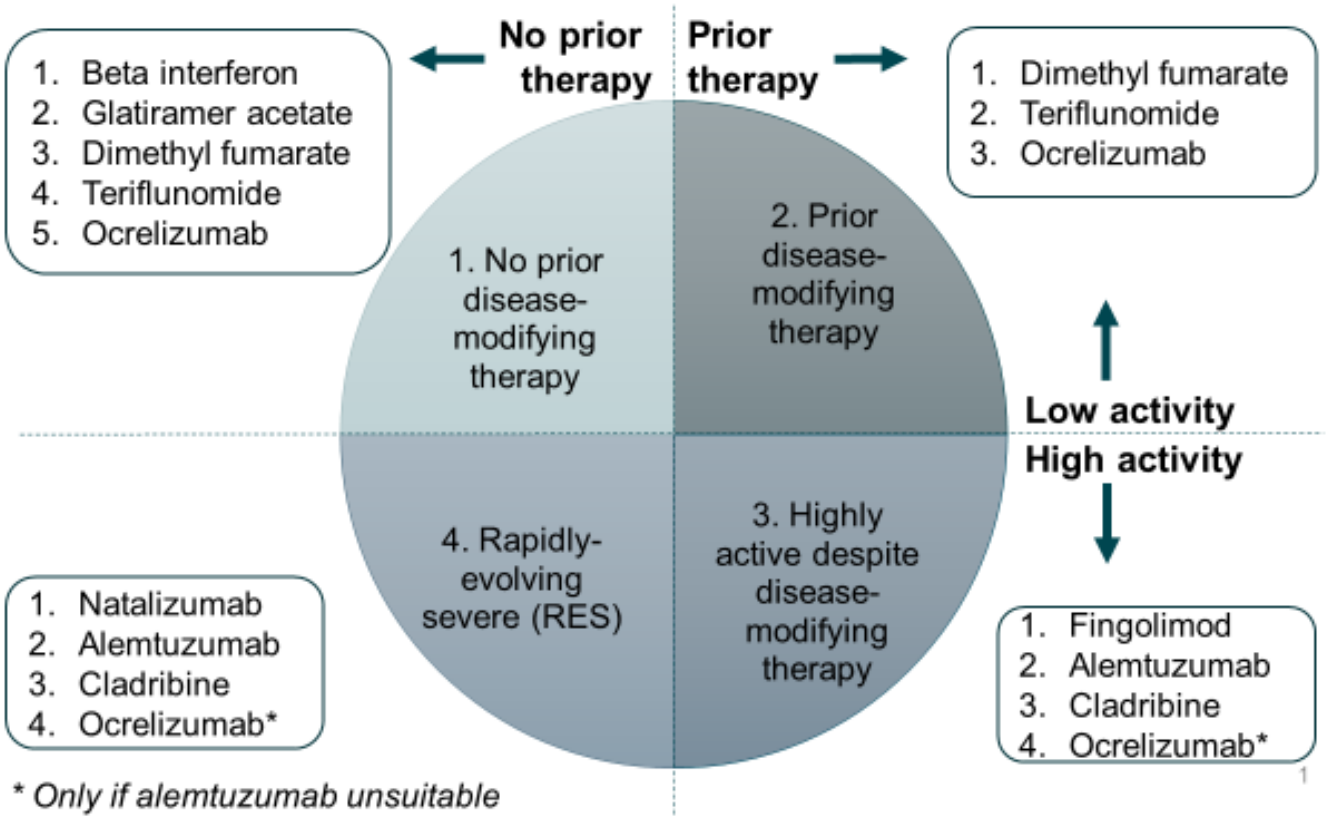
NICE Abbreviations: MRI, magnetic resonance imaging.

NICE recommended treatments for MS

Primary progressive MS
Ocrelizumab TA585

Relapsing- remitting MS (figure)

Secondary progressive MS
- Interferon beta-1b licensed for SPMS with active disease
- Extavia recommended TA527



NHS England criteria

NHS England stopping criteria for disease-modifying therapies:

1. No reduction in frequency or severity of relapses
2. Intolerable adverse effects of the drug
3. Inability to walk (EDSS 7.0), persistent for more than 6 months
4. Confirmed secondary progressive disease with observable increase in disability for >12 months, in the absence of relapse activity
   - secondary progressive disease usually only diagnosed at EDSS ≥6.0

NHS England starting criteria for interferon beta-1b (Extavia)

All of the following criteria must be met:

- ≥2 disabling relapses in 2 years
- able to walk 10m or more (EDSS <7.0)
- minimal increase in disability due to progression over the past 2 years
- aged over 18 years
- has no contra-indications.

Patient and carer perspective

Transitioning from RRMS to SPMS is traumatic

- People perceive there is no effective disease-modifying treatment for SPMS
- People have reduced access to services (e.g. neurology appointments or MS nurses) because they are no longer on disease-modifying therapy
- People with SPMS lose independence and some are reluctant or unable to leave home, leading to social isolation and loss of self-confidence
- Employment rates are low and costs high in people with more severe forms of MS

Health and wellbeing of carers of people with SPMS is greatly affected

- Carers often have to give up work or reduce their hours
- Watching the health of loved ones deteriorate without hope of treatment is very distressing

Needs of people with progressive MS have been forgotten

- Number of treatments available for RRMS have grown, but not for SPMS
- Rates of interferon beta-1b (Extavia) prescribing are low due to difficulties with administration, so the oral formulation of siponimod would be convenient

Abbreviations: RRMS, relapsing–remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis

Siponimod (Mayzent)

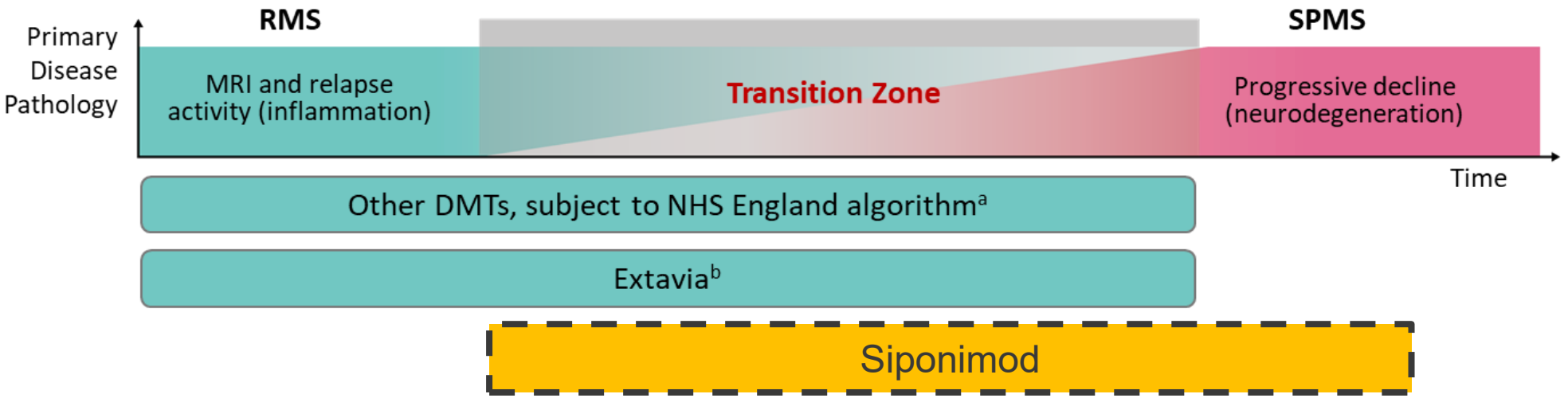
Marketing authorisation	Adults with secondary progressive MS with "active disease evidenced by relapses or imaging features of inflammatory activity" • Company defines 'active disease' in its trial as relapses in 2 years prior to study or gadolinium-enhanced T1 lesions at baseline • Original submission and key trial include broader population "secondary progressive MS" i.e. some did not have active disease
	No marketing authorisation for RRMS
Mechanism	Selective sphingosine 1-phosphate modulator; binds to lymphocytes prevents them leaving lymph nodes; reduces disease activity
Administration and dose	Oral administration Dose titration: 6 days Maintenance: 2 mg once daily
Additional tests	• Genotyping to determine whether metabolises cytochrome P450 2C9 • Certain genotypes may require a lower maintenance dose or may mean siponimod is not suitable
Cost of treatment	• List price ~£1,644 per 28 tablet pack • Patient access scheme (discount) agreed • Company to meet costs of additional genotyping tests

Decision problem

	Final scope	Company submission	Notes
Population	• Secondary progressive MS		• Marketing authorisation is for **"active disease"**
Subgroups	• Active secondary progressive MS, evidenced by relapses		• **Subgroup analysis aligns with marketing authorisation**
Comparators	• Established clinical management, including treatments licensed for relapsing-remitting MS used outside their marketing authorisations • Interferon β-1b (Extavia) for patients with active disease	• Matches final scope	• Company **base case** compares siponimod to interferon β-1b (Extavia) ○ Company states: because Extavia is the lowest-cost interferon, this will lead to conservative estimates of cost-effectiveness • Company compares siponimod with treatments licensed for relapsing-remitting MS in **scenario analyses**

Company's positioning of siponimod

Company positioning of siponimod: EDSS between 3.0 and 6.5, SPMS defined as **progressive increase in disability over 6 months**



- *Is SPMS a continuum of RRMS?*
- *Is company's definition of SPMS accepted?*
- *When, if ever, are treatments started in RRMS carried through to SPMS?*
- *Does this include interferon beta-1b?*
- *When would treatment start and stop in SPMS?*

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Abbreviations: DMT: disease-modifying therapy; MRI: magnetic resonance imaging; RRMS, relapsing–remitting MS; SPMS: secondary progressive MS.

Comparators

Company: interferon beta-1b (Extavia) is appropriate comparator

Comparators need to be used, but not necessarily licensed, for SPMS

Background

- Transition period in which people with RRMS suspected of having SPMS but not diagnosed – people may continue RRMS disease-modifying therapy
- **Company:** interferon beta-1b (Extavia) is the only option licensed for SPMS – so, it is the most relevant comparator

Stakeholder responses to technical engagement

- Mixed views on whether patients would use siponimod in same position as interferon beta-1b (Extavia); agreement that there is some overlap
- Few people with **active** SMPS use interferon beta-1b (Extavia)
  - neurologists not convinced of its benefits, difficulties with preparing injections
- Mixed views whether doctors would diagnose SPMS earlier if siponimod available
- Agree that siponimod could displace RRMS treatments used in transition period

- *Does treatment differ between 'suspected' and 'diagnosed' SPMS?*
- *Are there some people with active SPMS who do not receive any treatment?*
- *Which are appropriate comparators: interferon beta-1b (Extavia), disease-modifying therapies for RRMS, best supportive care?*

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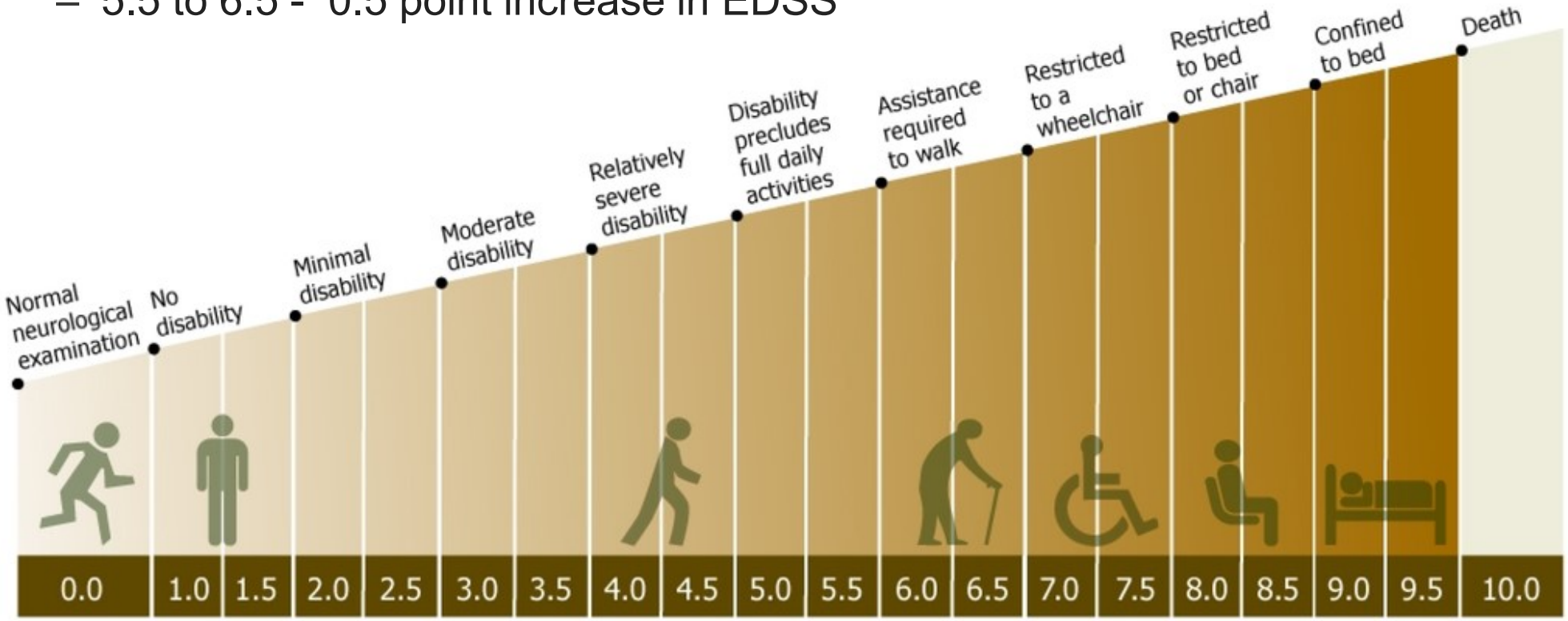
Abbreviations: RRMS, relapsing–remitting MS; SPMS: secondary progressive MS.

Definition of outcomes in trials

Treatments offered to ambulatory patients only EDSS ≤6.5

- Relapse: new or recurrent neurological symptoms lasting ≥24 hours without fever or infection; separate events are at least 30 days apart
- Disability assessed using **Expanded Disability Status Scale (EDSS)**
- Disability that lasts for 3 or 6 months is ‘confirmed disability progression’ CDP3/6M
- Defined as for baseline score of:
  - 3.0 to 5.0 - 1-point increase in EDSS
  - 5.5 to 6.5 - 0.5 point increase in EDSS



Source: *http://www.msunites.com/understanding-the-expanded-disability-status-scale-edss-scale/*

EXPAND trial and open-label extension

Double-blind, randomised, placebo controlled, but no active comparator

Eligibility:
Adults 18 to 60 years with SPMS

- EDSS 3.0 to 6.5
- EDSS progression in 2 years before study
- No relapses 3 months before randomisation
- Not CYP2C9*3/*3 genotype

R 2:1

Siponimod
Maintenance dose: 2 mg once daily (**n=1,105**)

Placebo
Once daily (**n=546**)

Reassignment: Patients with **CDP6M** could continue double-blind treatment, switch to open-label siponimod or stop treatment

1º endpoint

- Time to CDP3M

2º outcomes

- Time to 3 month worsening ≥20% in timed 25-foot walk
- Change in T2 lesion volume
- **Time to CDP6M**
- **Annualised relapse rate**
- **EQ-5D**

Bold = used in company's model

Open-label extension: following trial, all patients switched to open-label siponimod. Long-term efficacy and safety recorded for up to 10 years (ongoing)

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Abbreviations: CDP3M/6M, confirmed disability progression at 3/6 months; CYP2C9, cytochrome P450 2C9; EDSS, Expanded Disability Status Scale; SPMS, secondary progressive multiple sclerosis.

EXPAND: baseline characteristics of subgroup with active disease

Definition: relapses in 2 years prior to study or gadolinium-enhanced T1 lesions at baseline

	Siponimod n=516	Placebo n=263
Age, mean years (SD)	[redacted]	[redacted]
Female (%)	[redacted]	[redacted]
Years since MS diagnosis, mean (SD)	[redacted]	[redacted]
Years since conversion to SPMS, mean (SD)	[redacted]	[redacted]
Number of relapses prior to screening		
- relapses in previous 2 years, mean (SD)	[redacted]	[redacted]
- no relapses in previous 2 years, %	[redacted]	[redacted]
- relapses in previous year, mean (SD)	[redacted]	[redacted]
- no relapses in previous year, %	[redacted]	[redacted]
EDSS, mean (SD)	[redacted]	[redacted]
≥1 Gadolinium-enhancing T1 lesions, %	[redacted]	[redacted]
Previous treatment with disease modifying therapy %	[redacted]	[redacted]

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Abbreviations: EDSS, Expanded Disability Status Scale; SD, standard deviation; SPMS, secondary progressive multiple sclerosis.

Do baseline characteristics in EXPAND reflect patients in the NHS with active SPMS?

Background

- EXPAND trial enrolled participants across 31 countries, including the UK (10 centres, number of patients unknown)
- **Company**: expect trial to be generalisable to NHS SPMS population
- **ERG**: company has not provided sufficient evidence of generalisability. Outcomes and clinical practice may vary across countries in the trial

Stakeholder responses to technical engagement

- Agree that baseline characteristics broadly generalisable
  - NHS population may be slightly older and have more comorbidities vs the trial population
  - In clinical practice, people may be diagnosed with SPMS at higher EDSS scores (EDSS 5 or greater)

- ⊙ *Does the number of relapses at baseline in the trial reflect the NHS?*
- ⊙ *Is it likely that effect of treatment would differ between populations?*

 Abbreviations: EDSS, Expanded Disability Status Scale; SPMS, secondary progressive multiple sclerosis.

EXPAND: key results active SPMS subgroup

Siponimod delays disability progression vs. placebo

Comparing siponimod to an active drug requires an indirect comparison

	Siponimod n=516	Placebo n=263	Siponimod vs placebo	In base-case?
Confirmed disability progression (CDP) [a]				
People with 3-month CDP - *1º endpoint*	[redacted]	[redacted]	[redacted]	X
People with 6-month CDP - *2º endpoint*	[redacted]	[redacted]	[redacted]	✓
Relapse rate [b]				
Adjusted annualised relapse rate – *2º endpoint*	[redacted]	[redacted]	[redacted]	✓

- *Is annualised relapse rate adjusted for treatment switching to siponimod?*
- *What is preferred endpoint for modelling: 3 month or 6 month disability?*

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a. Cox proportional hazards models; b. Negative binomial regression.
Abbreviations: HR, hazard ratio; SPMS, secondary progressive multiple sclerosis.

Comparator trials

	EXPAND	NA study	EU study	ASCEND	SPECTRIMS	IMPACT
Intervention	Siponimod	IFN β-1b	IFN β-1b	Natalizumab	IFN β-1a	IFN β-1a
Comparator	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo
% with relapses in 2 years prior to study (proxy for active SPMS)	[redacted]	45%	68%	69%	47%	NR
Mean age (yrs)	48	46.8	41	47.2	42.8	47.6
Mean EDSS	5.4	5.1	5.1	5.6	5.4	5.2
Duration of MS / SPMS (yrs)	12.6 / 3.8	14.7 / 4.0	13.1 / 2.2	12.1 / 4.8	13.3 / 4.0	16.5 / not reported
Treatment history	Prior IFN allowed	No prior IFN use	No prior IFN use	Prior IFN allowed [a]	No prior IFN use	No prior IFN use
CDP6M	Yes	Yes [b]	No	Yes [b,c]	No	No
CDP3M	Yes	No	Yes [b]	No	Yes	Yes [b]
ARR	Yes	Yes	Yes	Yes	Yes	Yes

[a] Allowed but not within the prior 4 weeks; [b] Definition differs vs EXPAND; [c] Matching vs EXPAND not possible.

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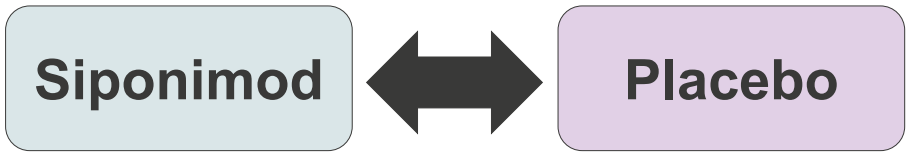
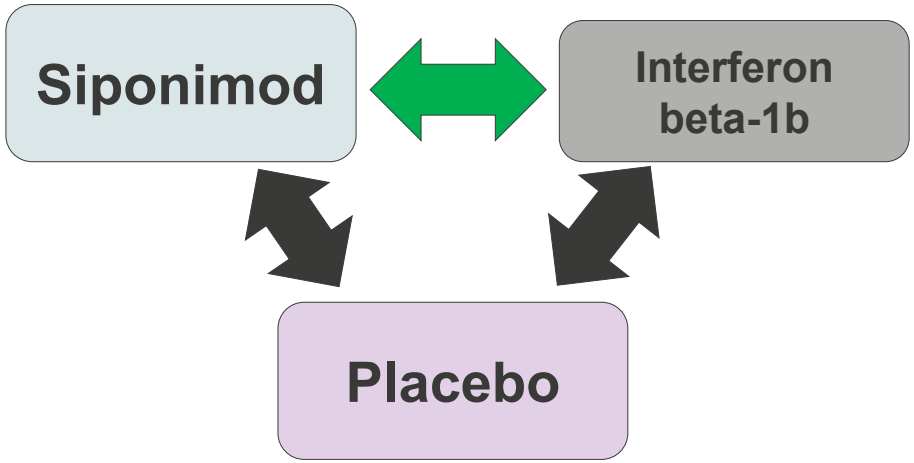
Abbreviations: ARR, annualised relapse rate; CDP6M/3M, 6-month/3-month confirmed disability progression; DMT, disease modifying therapy; EDSS, Expanded Disability Status Scale; IFN, interferon; NA, North American; RRMS, relapsing remitting MS; SPMS, secondary progressive MS.

Indirect comparison approaches

Direct comparison

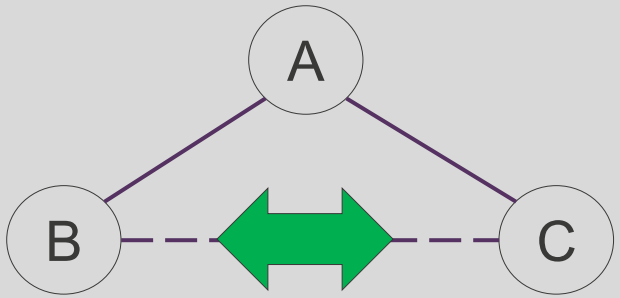


Indirect comparison



Effect of interest (not available from head-to-head trials)

Network meta-analysis (NMA)



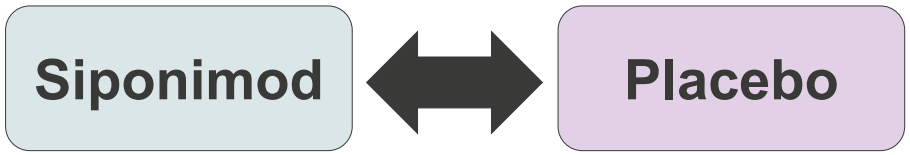
- Relies on '**constancy of relative effects**' assumption
  - AB effect in AB study is the same as the hypothetical AB effect in the AC study *if it had included a B arm*
- **Issue:** biased estimate if there are differences in effect-modifying variables[a] between trials

Company: cannot accurately infer treatment effect using NMA – trials are heterogeneous and there are imbalances in effect modifiers

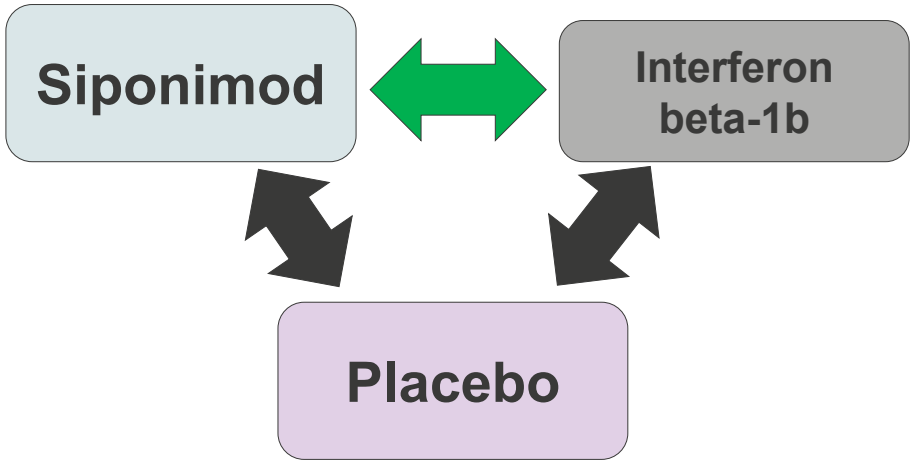
[a]An 'effect modifying variable' alters the effect of treatment **relative to control**.

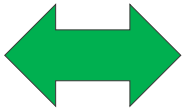
Indirect comparison approaches

Direct comparison



Indirect comparison




Effect of interest (not available from head-to-head trials)

Matching-adjusted indirect comparison (MAIC)

- 'Anchored (by placebo) MAIC' similar to NMA
- Adjusts for differences in effect modifiers between studies:
  - uses individual patient data (IPD) for siponimod adjusted to 'study level' data for comparators
  - more weight given to people in siponimod trial who are more similar to comparator trial
- **Issues:**
  - reduces sample size
  - may not match on all confounders/effect modifiers

ERG: company MAIC has small sample size, not matched for all important inclusion/exclusion criteria and not all relevant effect modifiers included

Company's matching-adjusted indirect comparison

- EXPAND and all comparator trials connected by placebo (anchored MAIC)
- Company did **not** limit to active disease
- **Matching step:**
  - to align EXPAND inclusion / exclusion criteria with comparator trials
  - if inclusion broader in EXPAND (e.g. males and females) than comparator (e.g. female only), company excluded males from EXPAND IPD
- **Adjustment step:**
  - Company reweighted patients in EXPAND to match distribution of important baseline characteristics (namely, treatment effect modifiers) to comparator trials

- Unmatched EXPAND sample size: [redacted]
- Effective sample size for CDP after matching and adjusting to comparator trials: [redacted]
  - vs. IFN beta-1b (Extavia): [redacted]

Identified treatment effect modifiers	
CDPM6	**ARR**
• Age • EDSS at screening • Duration of MS • Prior interferon/DMT • Normalised brain volume • Gd+ lesions on T1-weighted images • Duration of SPMS • Volume of T2 lesions • Relapses in prior 2 yrs • Sex	• Time since onset of most recent relapse • Relapses in prior 1 yr • Relapses in prior 2 yrs • Gd+ lesions on T1-weighted images • Volume of T2 lesions

- *Is a network meta-analysis inappropriate?*
- *Is this list of effect modifiers complete? Is disease 'activity' represented?*

Indirect treatment comparisons

Company argues network meta-analysis not appropriate

Company: did a matching adjusted indirect comparison (MAIC)

- Company: differences between comparator trials means network meta-analysis not feasible
- **Company believes MAIC not feasible in active subgroup so used full population**
- Argued MAIC produces results that are more generalisable to the active SPMS population than full population before matching and adjusting; preferable to an unadjusted comparison

ERG: preferred network meta-analysis (NMA) in full population

- MAIC has a small effective sample size, not matched for all important inclusion / exclusion criteria and not all relevant effect modifiers included
- MAIC results appear optimistic, and effect estimates for disability progression and relapse rates were statistically non-significant and inconclusive
- **Exploratory NMAs for 3/6-month confirmed disability progression and ARR outcomes**

Additional company analysis: NMA in active subgroup

- **Company:** if unadjusted NMA is appropriate, it should use data for active SPMS subgroup
- **ERG:** Full population NMA preferable because active NMA relies on the active SPMS subgroup data from EXPAND only; the input data for other trials still use the full populations

⊙ *Is it appropriate to do an indirect comparison on whole population when licence is limited to active disease?*

 Abbreviations: ARR, annualised relapse rate; SPMS, secondary progressive MS.

Results of indirect comparisons

Is MAIC or NMA the better source of efficacy data?

Siponimod vs. Interferon beta-1b	Trial population used		6-month CDP, HR	Annualised relapse rate, RR
	EXPAND	Comparators		
MAIC (company)	Full	Full	[redacted]	[redacted]
NMA (ERG)	Full	Full	0.80 (0.57 to 1.13)	0.65 (0.46 to 1.04)
NMA (company)	Active	Full	[redacted]	[redacted]

Used in company base case

Statistically significant results are in bold.

⊙ ***If an NMA is preferred, should it use data from the full population in the EXPAND trial, or the subgroup on which marketing authorisation based?***

- Company also conducted MAIC for siponimod vs. other treatments for relapsing-remitting MS (**see next slide**)
- Not used in model; company argue comparison with interferon beta-1b (Extavia) more conservative

Abbreviations: CDP: confirmed disability progression; HR: hazard ratio; ITT, intention-to-treat; MAIC: matching adjusted indirect comparison; NMA: network meta-analysis; RR: rate ratio; SPMS: secondary progressive MS.

MAIC and NMA results for all comparators

Siponimod vs comparator	Company MAIC	Company active SPMS NMA	ERG ITT NMA
Time to CDP-6, HR (95% CI / 95% CrI)			
Interferonβ-1b (Extavia)	[redacted]	[redacted]	0.80 (0.57–1.13)
Proportion with CDP-6 by 96 weeks (95% CI / 95% CrI)			
Natalizumab (Tysabri)	[redacted]	Not reported	0.73 (0.47, 1.12)
Time to CDP-3, HR (95% CI / 95% CrI)			
Interferonβ-1b (Extavia)	[redacted]	[redacted]	1.07 (0.81–1.41)
Interferonβ-1a (Rebif 44 µg)	[redacted]	[redacted]	**0.79 (0.66–0.95)**
Interferonβ-1a (Rebif 22 µg)	[redacted]	[redacted]	0.90 (0.66–1.22)
Interferonβ-1a (Avonex)	[redacted]	[redacted]	0.81 (0.54–1.22)
ARR ratio, RR (95% CI / 95% CrI)			
Interferonβ-1b (Extavia)	[redacted]	[redacted]	0.65 (0.46–1.04)
Interferonβ-1a (Rebif 44 µg)	[redacted]	[redacted]	0.67 (0.45–1.00)
Interferonβ-1a (Rebif 22 µg)	[redacted]	[redacted]	**0.65 (0.47–0.91)**
Interferonβ-1a (Avonex)	[redacted]	[redacted]	**0.65 (0.46–0.92)**
Natalizumab (Tysabri)	[redacted]	[redacted]	0.99 (0.65, 1.52)

Statistically significant results are in bold.

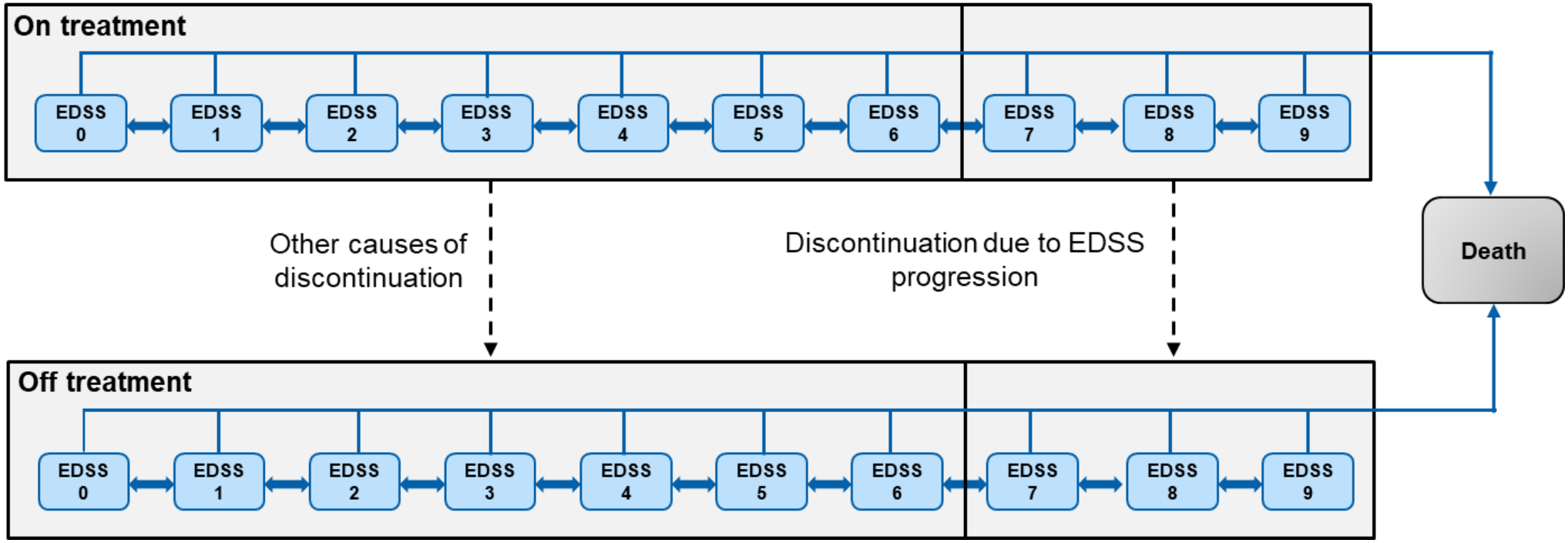
[a]Calculated by the NICE technical team based on the RR for natalizumab versus siponimod reported in Novartis technical response appendix A. Abbreviations: ARR: annualised relapse rate; CDP-3/6: 3/6-month confirmed disability progression; CI: confidence interval; CrI: credible interval; HR: hazard ratio; IM: intramuscular; MAIC, matching adjusting indirect comparison; NMA: network meta-analysis; RR: rate ratio; SPMS: secondary progressive multiple sclerosis.

Clinical perspective

- Treatment aims to reduce progression of disability and relapses
- A treatment that reduces disability progression represents a step change in managing secondary progressive multiple sclerosis
- There is great unmet need. There are no effective treatments; siponimod would be the first of its kind
- Introducing siponimod would require education and training; it would impact clinic time e.g. for monitoring
  - existing services may need additional support
  - should not underestimate the additional demand on resources to treat and monitor patients

Cost effectiveness

Company's model



- Markov cohort model
- 10 EDSS health states (on/off treatment)
- Annual cycle, lifetime horizon
- Starting age 48 years; 40% men
- On-treatment effects (annualised relapse rates, disability progression) from MAIC
- Treatment stops after at EDSS ≥7
- After stopping treatment, patients follow natural disease course based on placebo arm of EXPAND and the London Ontario MS data set (preferred to British Columbia as has separate data for SPMS)

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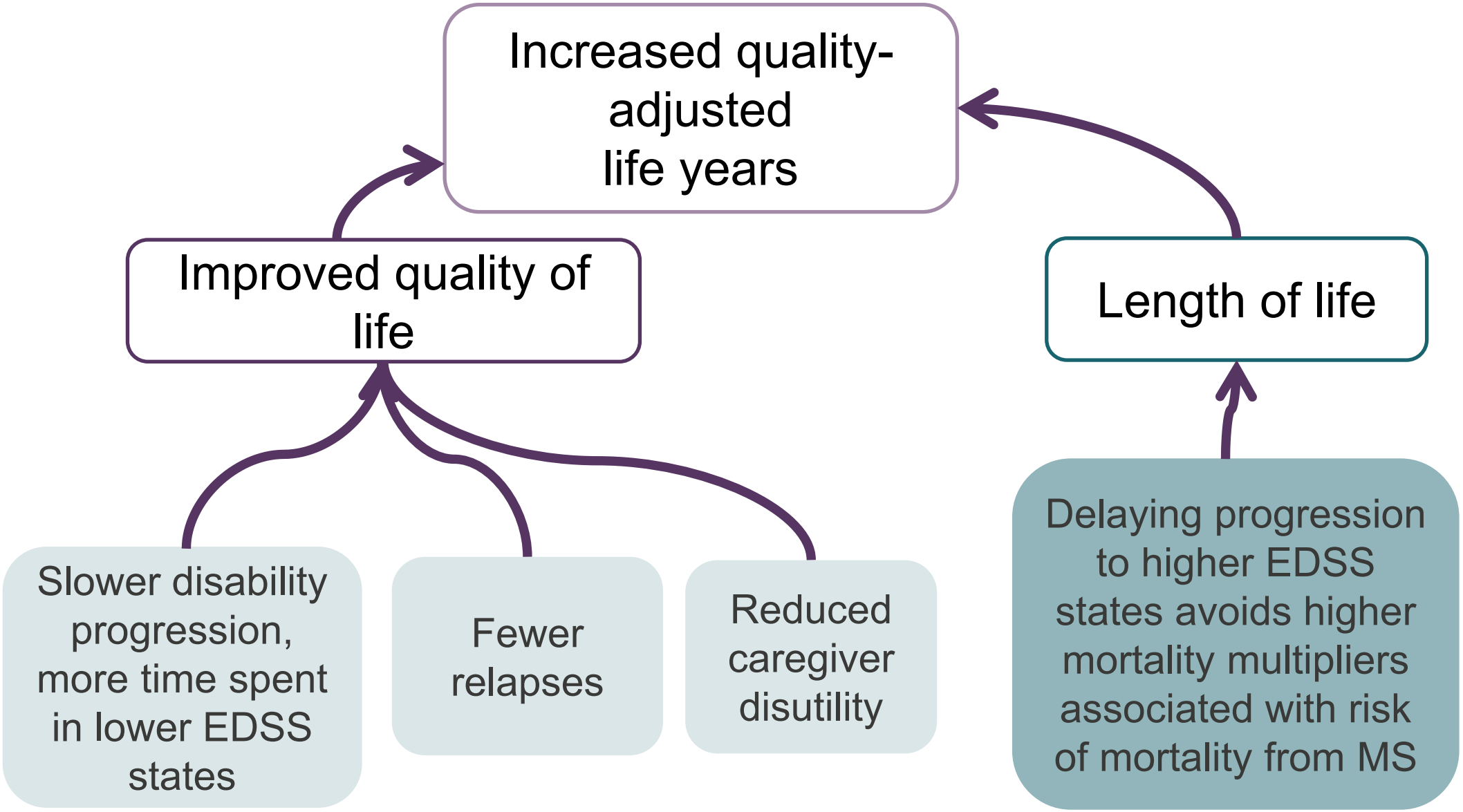
Abbreviations: EDSS, Expanded Disability Status Scale; MAIC, matching adjusted indirect comparison; SPMS: secondary progressive MS.

Overview of how quality-adjusted life years accrue in the model



NICE Abbreviations: EDSS, Expanded Disability Status Scale.

Key model assumptions

	Base-case assumption	Justification
Disability progression	Relapses have no residual effect on EDSS	Impact of relapses included through costs and disutility according to severity
	Treatment does not have impact on severity or duration of relapses	Little evidence, less frequent relapses in SPMS than RRMS→ impact on results negligible
	Treatments has indirect effect on the risk of mortality	Delaying progression to higher EDSS levels avoids higher mortality multipliers associated with risk of mortality from MS
	After stopping treatment, patients follow the natural disease course	In line with previous NICE Technology appraisals
Treatment discontinuation	Applied in a time-dependent manner using exponential distribution fitted to EXPAND data: • [redacted] stopped siponimod 5 at yrs • [redacted] stopped siponimod at 10 yrs	Exponential and Weibull most appropriate fit to data, exponential preferred by ERG and technical team
Health state costs	EDSS state costs from UK MS survey (as reanalysed in TA320 and inflated to 2017/18 prices)	In line with previous NICE Technology appraisals

Abbreviations: EDSS, Expanded Disability Status Scale; RRMS, relapsing–remitting MS; SPMS: secondary progressive MS.

Natural history data

Some people's disability improved in trial, should model reflect this?

Company

- Used placebo group from EXPAND supplemented with London Ontario registry to model transition probabilities between EDSS states (i.e. natural disease history)
- **Means people can regress (improve) to less severe EDSS states**
  - n.b treatment effect only applied to progression, not regression

ERG

- In the short-term people could improve before they worsen again, e.g. if they have a relapse from which they recover
- Timeframe for improving and worsening is 2–3 months; as modelled transitions are yearly, EDSS regressions would be rare
- Previous MS appraisals have used the London Ontario natural history dataset – **does not allow improvements in EDSS**
- More appropriate than trial data because data were collected over 25 years compared with 2 years in EXPAND trial

Stakeholder responses to technical engagement

- No clear consensus, however most think there is the possibility to improve, albeit rarely

⊙ ***Is it appropriate to model improving EDSS state in untreated secondary progressive MS? If so, which is the best source of data to reflect this?***

Treatment effect of siponimod over time

Company assumes effect remains constant over time

Previous appraisals for relapsing-remitting MS have modelled a waning of treatment effect

Company:

- Model includes stopping rule at EDSS >7.0 to reflect NHS England treatment algorithm
- Stopping for any reason is a suitable proxy for treatment effect waning – this assumption was accepted in NICE TA533 ***ocrelizumab for treating relapsing-remitting MS***
- Evidence of maintained treatment effect at 6 years (see graph on next slide)
- Also submitted scenarios modelling a decrease in treatment effect

Stakeholder responses to technical engagement

- If siponimod's main action is against the active inflammatory component:
  - efficacy is likely to reduce as inflammation becomes less of a contributing factor to disability worsening as disease progresses
- No clear consensus on whether people would stop siponimod if efficacy is reduced
  - some people would stay on siponimod
  - people who have disease progression without relapses/MRI activity more likely to stop

- ***Would the efficacy of siponimod be expected to diminish over time?***
- ***Would people (who do not meet the stopping criteria in NHS England algorithm) continue treatment if it stopped working as well over time?***

Abbreviations: EDSS, Expanded Disability Status Scale; MRI, magnetic resonance imaging.

Treatment effect of siponimod over time

Open-label study suggests treatment effect maintained at 6 years

EXPAND extension study:

- People in placebo arm switched to siponimod
- Company uses rank-preserving structural failure time (RPSFT) method to model disability in placebo arm as if there was no switching

RPSFT-adjusted HR: [redacted] vs **0.74** (95% CI: 0.60–0.92) in the end of core part of trial

⊙ ***Is the company's choice of RPSFT appropriate?***

[redacted]

Abbreviations: CDP: confirmed disability progression; CI: confidence interval; HR: hazard ratio.

Health state utility values

Company uses EQ-5D values from trial + Orme et al. (2007)

- **Company:** EQ-5D 3L utility values from EXPAND supplemented with Orme et al (2007) for EDSS states 0,1, 2, 8 and 9 because few people in the trial had these EDSS values
- **ERG:** EXPAND EQ-5D values uncertain and may not be generalisable. Prefer to use Orme data only – based on more patients and consistent with previous appraisals
- Value for EDSS 3 lower (0.529) than EDSS 4 (0.565) in the Orme data – lacks face validity

EDSS	Company: EXPAND and Orme et al.	ERG: Orme et al.
0	0.825	0.825
1	0.754	0.754
2	0.660	0.660
3	[redacted]	0.529
4	[redacted]	0.565
5	[redacted]	0.473
6	[redacted]	0.413
7	[redacted]	0.252
8	-0.094	-0.094
9	-0.240	-0.240

Stakeholder responses to technical report

- EQ-5D values from EXPAND measures study population so should use them supplemented by Orme et al.
- Should use Orme et al. data alone for consistency with previous appraisals

- ⊙ ***Which source, if either, of health state utility values is more appropriate?***
- ⊙ ***Does Orme et al. reflect secondary progressive disease?***

Abbreviations: EDSS: Expanded Disability Status Scale

Cost effectiveness results: company + ERG

	Company base case	ERG base case
Comparative Effectiveness	Matching adjusted indirect comparison (full population)	Network meta-analysis (full population)
Baseline characteristics	Active population	Full population
Natural history	EXPAND + London Ontario	London Ontario
Utility values	EXPAND + Orme et al.	Orme et al.

Key company scenarios – treatment effect waning

- **Scenario 1: 50% decrease in effectiveness from year 11**
  - company rationale: aligned with TA527 - beta interferons and glatiramer acetate for treating multiple sclerosis
- **Scenario 2: 25% decrease in effectiveness from year 7, 50% from year 10**
  - company rationale: long-term trial data show no evidence of treatment waning for up to 6 years after adjusting for treatment switching)

Because of confidential commercial arrangements for siponimod and some comparators, all cost-effectiveness results presented in private part 2 of committee meeting

Innovation

Company considers siponimod innovative.
It notes that there are additional benefits not captured within the QALY calculation, including:

- improved cognitive processing speed, disability regression and reduced relapse severity, which are not modelled in the economic analysis
- siponimod is administered orally, so avoids infusions or injections, and provides greater convenience

Abbreviations: QALY, quality-adjusted life-year.

Equalities

People with SPMS are likely to have difficulties with their hands, vision or cognition

- may struggle with interferon beta-1b (Extavia) as it is a solvent and powder, which patients (or carers) must mix each time they take it
- some may find oral siponimod easier to take

Abbreviations: SPMS, secondary progressive MS.

Back-up slides

EXPAND: baseline characteristics

ITT population

	Siponimod n=1,105	Placebo n=546
Age, mean years (SD)	48.0 (7.8)	48.1 (7.9)
Female (%)	669 (61)	323 (59)
Years since MS diagnosis, mean (SD)	12.9 (7.9)	12.1 (7.5)
Years since conversion to SPMS, mean (SD)	3.9 (3.6)	3.6 (3.3)
Number of relapses prior to screening		
- relapses in previous 2 years, mean (SD)	0.7 (1.2)	0.7 (1.2)
- no relapses in previous 2 years, %	64%	63%
- relapses in previous year, mean (SD)	0.2 (0.5)	0.3 (0.6)
- no relapses in previous year, %	79%	76%
EDSS, mean (SD)	5.4 (1.1)	5.4 (1.0)
≥1 Gadolinium-enhancing T1 lesions, %	237 (21)	114 (21)
Previous treatment with disease modifying therapy, %	78%	79%

NICE

Abbreviations: EDSS, Expanded Disability Status Scale; SD, standard deviation; SPMS, secondary progressive multiple sclerosis.

NHS England treatment algorithm for relapsing progressive multiple sclerosis

Stopping Criteria

- One or more of the following criteria are met:
  - No reduction in frequency or severity of relapses compared with pre-treatment phase following a minimum 6 month period of beta interferon treatment
  - Intolerable adverse effects of the drug
  - Development of inability to walk, persistent for more than 6 months, unless unable to walk for reasons other than MS