NICE National Institute for Health and Care Excellence

Version for public
Contains no ACIC data

Siponimod for treating secondary progressive multiple sclerosis [ID1304]

2nd committee meeting

Lead team: Mark Glover, Nick Latimer, Nigel Westwood

Chair: Amanda Adler

Evidence Review Group (ERG): Warwick Evidence

Technical team: Hannah Nicholas, Carl Prescott, Ross Dent,
Company: Novartis

9th September 2020

Virtual meeting

Siponimod not recommended

Why the committee made these recommendations

- Interferon beta-1b (Extavia) only disease-modifying treatment available for people with active secondary progressive multiple sclerosis

  – few people take it; most do not have any treatment

- Clinical trial results show siponimod reduces number of relapses and slows disability progression compared with placebo
- Uncertain how effective siponimod is compared with interferon beta-1b (Extavia) - no evidence directly comparing them
- Limited clinical evidence means cost-effectiveness estimates are uncertain and no analyses reflect committee's preferred assumptions

Siponimod (Mayzent)

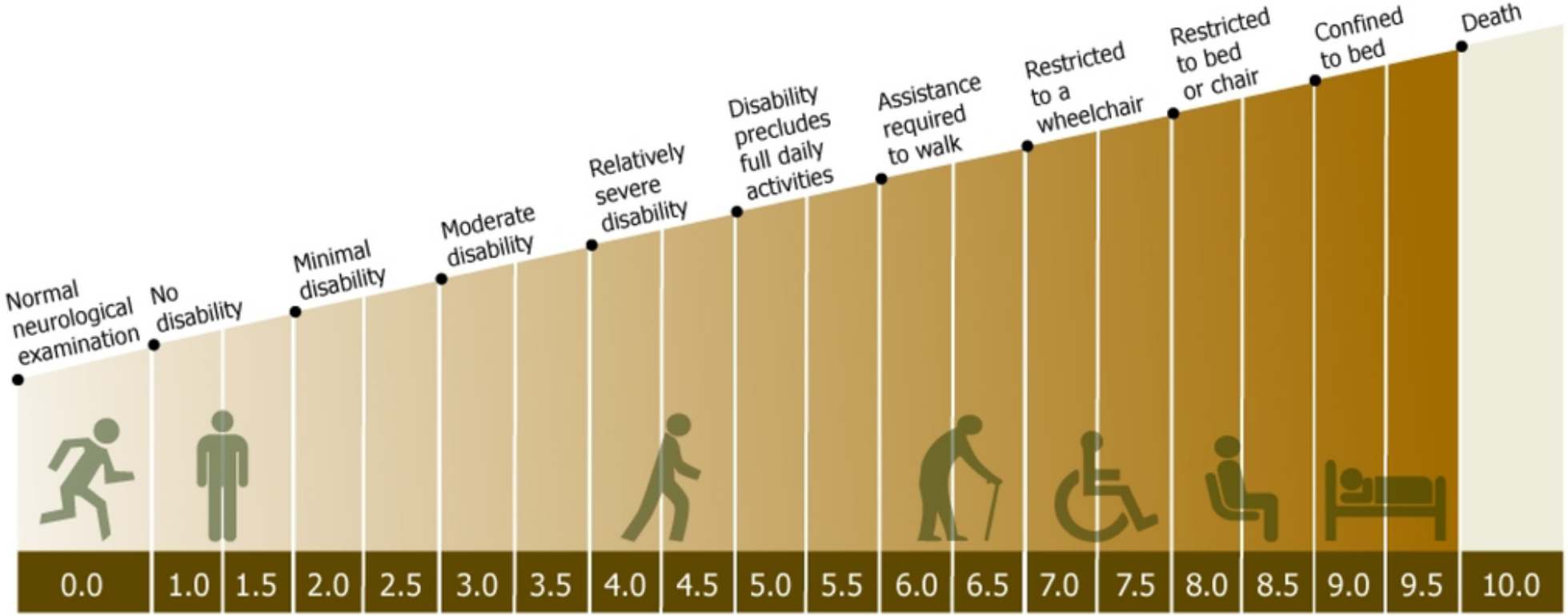
Marketing authorisation	Adults with secondary progressive MS and active disease evidenced by relapses or imaging features of inflammatory activity
	• Company defines 'active disease' in its trial as:
	  • relapses in 2 years prior to study **or**
	  • gadolinium-enhanced T1 lesions at baseline
	• Key trial include broader population 'secondary progressive MS'; some did not have active disease

Administration and dose	• Oral administration • Dose titration: for 6 days then maintenance at 2 mg daily
Additional tests	• 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 – xxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxx • Company to meet costs of additional genotyping tests

Expanded Disability Status Scale (EDSS)

Treatments offered to ambulatory patients only EDSS ≤6.5

- Disability that lasts for 3 or 6 months is ‘confirmed disability progression’ CDP3/6M
- Key trial ‘EXPAND’ placebo controlled outcome was CDP3M
- Differs from relapse: new or recurrent neurological symptoms lasting ≥24 hours without fever or infection; separate events are at least 30 days apart



NICE

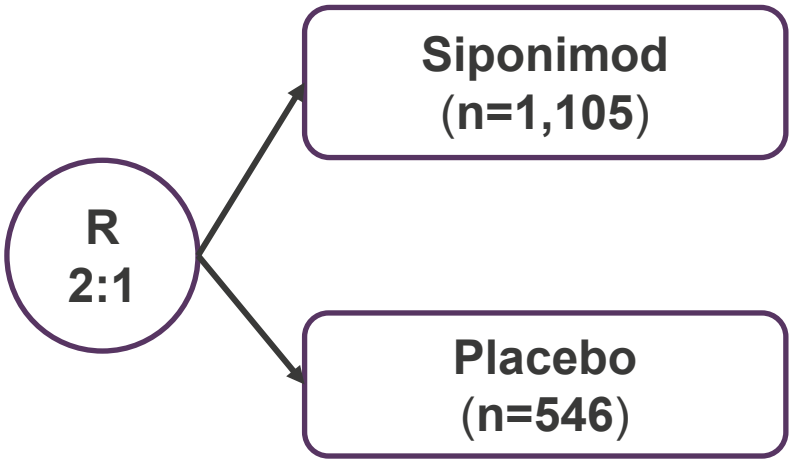
Source: *http://www.msunites.com/understanding-the-expanded-disability-status-scale-edss-scale/*

EXPAND trial and open-label extension

Double-blind, randomised, no active comparator

Eligibility:
Adults 18 to 60 years with SPMS

- EDSS 3.0 to 6.5
- EDSS progression in 2 yrs before study
- No relapses 3 months before randomisation



1º endpoint

- Time to CDP3M

Selected 2º outcomes

- **Time to CDP6M**
- **Annualised relapse rate**
- **EQ-5D**

Bold = used in model

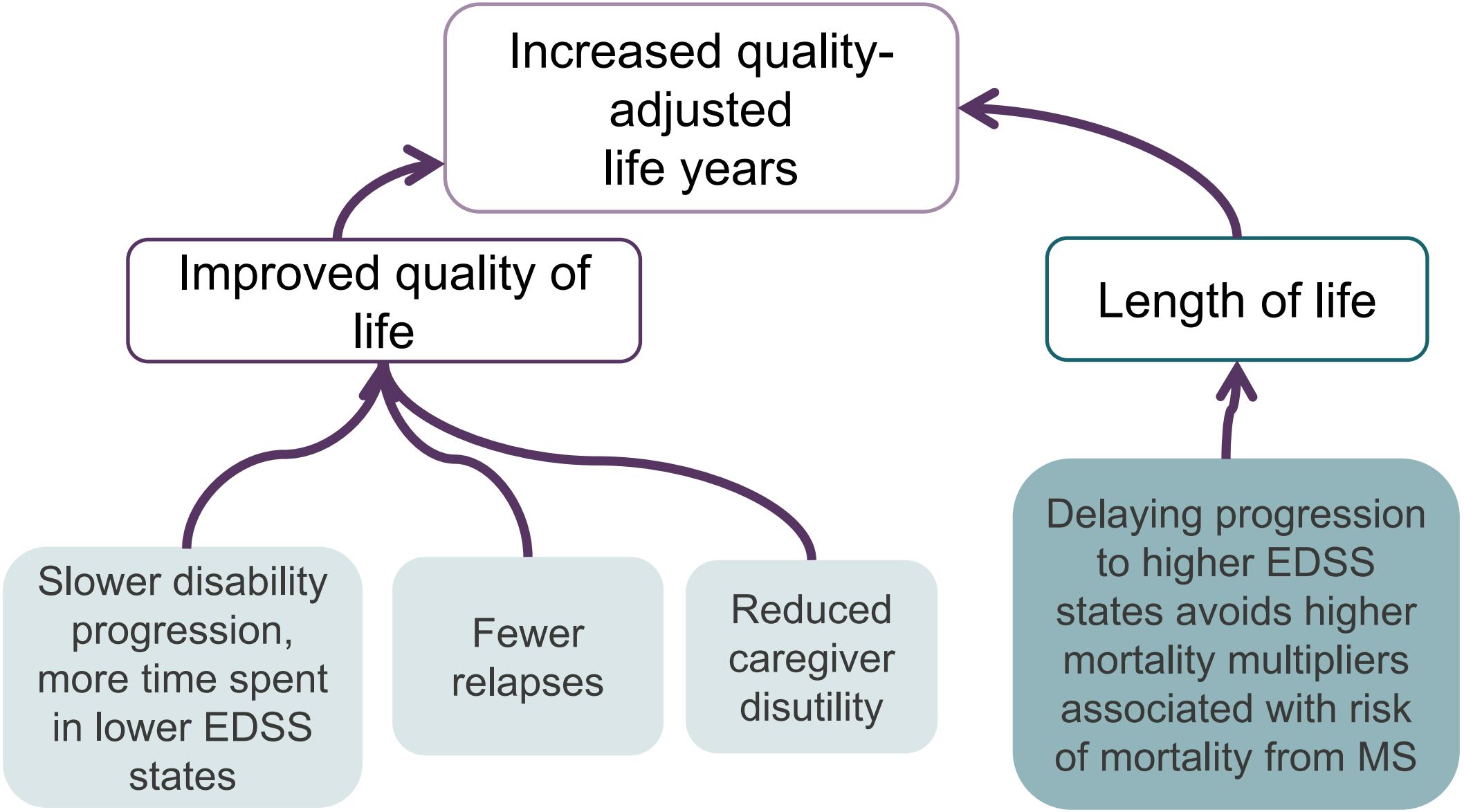
Reassignment: Patients with **CDP6M** could continue double-blind treatment, switch to open-label siponimod or stop treatment

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

NICE

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

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



NICE Abbreviations: EDSS, Expanded Disability Status Scale.

Appraisal consultation document (ACD) conclusions + uncertainties (1)

Diagnosing secondary progressive MS	• Neurologists reluctant to diagnosis 2º progressive MS without effective treatments • If siponimod available, diagnosis could be at EDSS 4, not 6 • Diagnosis would involve MRI scan to confirm active disease
Comparators	• Interferon beta-1b only licensed treatment; ~75 people take it • Note: Extavia is only interferon beta-1b brand recommended by NICE (TA527), so is comparator in this appraisal • NHS commissioner: NHS does not commission other disease modifying therapies for 2º progressive - not comparators • Most people have no disease-modifying treatment; company should provide comparison with best supportive care
Clinical effectiveness vs best supportive care	• 'EXPAND' key trial: randomised, placebo controlled, 1º outcome confirmed disability progression 3 months + single arm follow-on • Siponimod effective compared with placebo • Uncertain whether siponimod has same effect in disease with and without imaging features of inflammatory activity

Appraisal consultation document (ACD) conclusions + uncertainties (2)

Indirect comparison vs. interferon beta-1b (Extavia)	• Company uses 'full' trial not active subgroups from 2 interferon trials (n.b. siponimod licence is for active disease) • Matching-adjusted indirect comparison using data from 'European trial' of interferon beta-1b may be better estimate
Utility values	• Company uses utility values from whole EXPAND population • Should use utility values from subgroup with active disease
Costs	• Company should include costs of additional neurology visits and MRI scans associated with starting siponimod
Waning of siponimod treatment effect	• Efficacy of siponimod may diminish over time • Hard to estimate relative treatment effect from long-term data as no comparator in EXPAND extension study • Should include waning of effect of treatment with siponimod
Stopping siponimod	• Unclear whether company used data on trial discontinuation or treatment discontinuation to model rate people stop siponimod • Treatment discontinuation would provide better estimate of numbers stopping siponimod in clinical practice
Cost-effectiveness	• No analyses reflected committee's preferences

Consultation responses

Responses received from:

- Novartis (company)
- Association of British Neurologists
- MS Society
- MS Trust
- UK MS Specialist Nurse Association
- Public comments - web

Patients and patient organisations

Themes of comments:

- **Significant unmet need; with no treatment options, less care**
  - SPMS impacts “on all aspects of life – physical, emotional, social and economic”
  - “Transitioning to SPMS is frightening...this represents the point at which current treatments are withdrawn, contact with MS specialist health professionals is significantly reduced while increasing disability and loss of independence become major concerns”
  - “Since progressing from relapsing-remitting I have (not) been offered and so not received any treatment, care or consideration”
- **Diagnosis of SPMS and treatment options are linked**
  - “A survey of UK MS neurologists and nurses revealed that the most common reason for reluctance to diagnose SPMS was withdrawal of disease modifying drugs”
- **Cognitive benefits** – models do not capture possible benefits of preventing cognitive decline
- **Increase in need for MRI scans** - not a pre-requisite.

Summary of company ACD response

Issue	Committee preferences	Company response
Comparators	• Compare siponimod with best supportive care (as well as interferon-beta-1b [Extavia])	✓
Comparison with interferon-beta-1b	• Scenario based on matching-adjusted indirect comparison using European trial	X
Number who stop siponimod	• Use treatment discontinuation from trial	✓
Utility values	• Use values for active subgroup from EXPAND	✓
Costs	• Include costs of neurology appointments and MRI scans when starting siponimod	✓
Waning of treatment effect	• Include waning of treatment effect in model	✓

XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX

EXPAND: key results active SPMS subgroup

Siponimod delays disability progression vs. placebo

	Siponimod n=516	Placebo n=263	Siponimod vs placebo	In base-case?
Confirmed disability progression (CDP)				
People with 3-month CDP	XXXXX	XXXXX	HR: XXXX 95% CI: XXXXXXXXXXX p=XXXXXX	X
People with 6-month CDP	XXXXX	XXXXX	HR: XXXXX 95% CI: XXXXXXXXXXX p=XXXXXX	✓
Relapse rate				
Adjusted annualised relapse rate	XXXX	XXXXX	Ratio: XXXXX 95% CI: XXXXXXXXXXX p=XXXXXX	✓

NICE Abbreviations: HR, hazard ratio; SPMS, secondary progressive multiple sclerosis.

Comparators

New base case includes best supportive care as comparator

Company submission:

- Base case compared with interferon beta-1b (Extavia)
- Scenarios using disease-modifying therapies for relapsing–remitting disease (RRMS) outside marketing authorisations

Committee's conclusions

- Disease modifying therapies for RRMS not commissioned for 2º progressive MS and not comparators
- Comparators are interferon beta-1b (Extavia) and best supportive care

Company response to ACD:

- New base case analysis considers best supportive care as a relevant comparator
- Although NHS England does not commission therapies other than Extavia, a pharmaco-epidemiology study shows XXX with active SPMS had active therapy showing that disease modifying therapies are used outside licensed indications
- Company presents scenario analysis using 'weighted comparator': XXX of people have a disease modifying therapy[a] and the remainder best supportive care

[a] Company assumes all people on disease-modifying therapy in weighted comparator get Extavia. Rationale: conservative approach because it is comparatively low cost.

Trials of interferon beta 1-b

No trials directly compare siponimod and interferon beta 1-b

	EXPAND	North American study	European study
Intervention	Siponimod	IFN beta-1b	IFN beta-1b
Comparator	Placebo	Placebo	Placebo
Relapses in 2 yrs before study	36%	45%	68%
CDP6M	Yes	Yes [a]	No
CDP3M	Yes	No	Yes [a]
Annualised relapse rate	Yes	Yes	Yes

Company submitted a matching-adjusted indirect comparison using EXPAND and North American study, ERG submitted a network meta-analysis of same studies

Committee conclusion:

- Substantial uncertainties in both the company's matching-adjusted indirect comparison and ERG's network meta-analysis
- In the European trial, about 70% of people had relapses, indicating probable active disease
  - Matching-adjusted indirect comparison using only this trial data may provide a more reliable result than the other indirect comparisons

NICE

[a] Definition differs vs EXPAND.

Company and ERG differ on which approach to use

Company's ACD response:

- Acknowledge EU study has larger proportion of relapsing patients than North American study but concerned that:
  - population younger (mean 41 yrs) than North American and EXPAND trials (both 47 yrs)
  - 6-month CDP not available in EU study – committee prefers 6-month CDP
  - effective sample size=140 for comparison with EU study, 410 for North American study
- Results of MAIC for siponimod vs. interferon beta-1b 3-month CDP based on EU study presented in original company submission

ERG's ACD response:

- Baseline patient characteristics of EXPAND study and EU study similar
- Results of EU study more relevant and generalisable to NHS population with active SPMS compared to North American study

Results of indirect comparisons with interferon beta-1b

	Trial population used		6-month CDP, HR	Annualised relapse rate
	EXPAND	Comparators		
North American study				
MAIC (company)	Full	Full	**0.55 (0.33 to 0.91)**	0.90 (0.51 to 1.59)
NMA (ERG)	Full	Full	0.80 (0.57 to 1.13)	0.65 (0.46 to 1.04)
NMA (company)	Active	Full	XXXX XXXXXXXXX	XXXX XXXXXXXXX
EU study			**3-month CDP, HR**	
MAIC (company)	Full	Full	0.82 (0.42 to 1.63)	0.90 (0.51 to 1.59)

company base case

MAIC, matching-adjusted indirect comparison; NMA, network meta-analysis

◉ *Which is best estimate of effectiveness of siponimod vs. interferon beta-1b?*

NICE

Subgroups based on MRI activity

ACD conclusion:

- Committee interested in whether siponimod is of more benefit in disease with imaging features of inflammatory activity than without

Company's ACD response: subgroup results presented for:

- **Relapsing SPMS with MRI activity** - patients with relapses in 2 years before study and with gadolinium-enhanced T1 lesions at baseline
- **Relapsing SPMS without MRI activity** - patients with relapses in 2 years prior before study but without gadolinium-enhanced T1 lesions at baseline
- **Non-relapsing SPMS with MRI activity -** patients with gadolinium-enhanced T1 lesions at baseline but without relapses in the 2 years prior to the study

Company conclusion:

- XXXXXXXXXXXXXXXXXXXXXXXXX between the subgroups in effectiveness
- Overall, siponimod is an effective treatment for all patients with active SPMS

Treatment effect of siponimod over time

Company assumes in base case effect remains constant over time

Company submission:

- 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 – accepted in NICE TA533 ***ocrelizumab for treating relapsing-remitting MS***
- Evidence of maintained treatment effect at 6 years in extension study

Committee's conclusions

- No comparator arm in extension study - cannot estimate long-term relative treatment effect
- Company's approach (stopping for any reason as proxy) may overestimate the benefits of siponimod if people remain on treatment even if its efficacy decreases over time
- Appraisals for relapsing-remitting MS (e.g. fingolimod) modelled waning of treatment effect

Company response to ACD:

- Base case includes treatment waning of 50% from Year 11 in line with TA527, MTA of beta-interferons and glatiramer acetate in relapsing-remitting MS
- Scenario analysis: waning of 25% from Year 7, followed by 50% from Year 10
  - rationale: longest follow-up in EXPAND extension is 6 years

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

Health state utility values

Company's updated base case uses EQ-5D values for active subgroup

Original submission: 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

Committee's conclusions

- EXPAND supplemented with Orme et al. appropriate
- Would prefer to see values for active subgroup from EXPAND

Company response to ACD: updated base case uses utility values for active subgroup

EDSS	Original: Full trial population	ACD response: active subgroup
0	0.825	0.825
1	0.754	0.754
2	0.660	0.660
3	XXXXX	XXXXX
4	XXXXX	XXXXX
5	XXXXX	XXXXX
6	XXXXX	XXXXX
7	XXXXX	XXXXX
8	-0.094	−0.094
9	-0.240	−0.240

Additional costs: neurology visits and MRIs

Company includes cost of MRI scan in updated base case

Committee conclusion:

- Before starting siponimod, people would attend a neurology clinic and have an MRI scan that they would not normally have been offered
- Clinical expert: costs would apply only to people already diagnosed with secondary progressive MS, not to people transitioning from relapsing–remitting to secondary progressive disease who have regular MRI scans
- Committee: costs of additional neurology visits and scans should be included

Company response to ACD:

- Model already included 2 neurology appointments for siponimod each year, including both a higher cost of a 1st appointment as well as a follow-up appointment in Year 1
  - 3rd appointment included in revised model as scenario analysis
- Updated model includes cost of an additional MRI scan for siponimod
- Company argues this overestimates expected cost to NHS:
  - licence wording means active disease could be evidenced by relapses alone
  - people transitioning from relapsing-remitting disease would already be having MRI scans

Benefits not captured in model (1)

Company and consultees: benefits on cognition not captured

ACD: some evidence siponimod benefits cognitive processing speed; EQ-5D may not capture

- Committee considered that such benefits could be important but company had not included them in its model, nor presented sufficient evidence of these benefits

Company response to ACD:

- Symbol digit modalities test (SDMT) score preferred test for assessing cognitive processing speed by the Multiple Sclerosis Outcome Assessments Consortium
- Score improved with siponimod at months 12 and 24 in EXPAND (i.e. improved cognitive processing speed over time), compared with worsening in placebo group
- Sustained clinically meaningful improvement (≥4 points from baseline) in SDMT greater for siponimod vs. placebo (HR: 1.28; 95% p=0.0131)
- In active subgroup, siponimod significantly reduced the risk of 6-month confirmed deterioration in SDMT of ≥4 points by 27%
- Statement from neuropsychologist - work focuses on cognitive aspects of MS
- Cost-effectiveness results do not account for additional, important patient benefits

Benefits not captured in model (2)

Company and consultees: benefits on cognition not captured

ERG ACD response:

- EQ-5D does not capture cognitive processing speed – not accounted for in economic model

Patient group comments:

- Survey of people with SPMS (n=235) 56% reported cognitive problems.
- Improving function would greatly benefit people allowing work + family/social relationships

Innovation and equality

Company ACD response:

- Siponimod an innovative treatment for people with very limited treatment options
  - that committee consider best supportive care a comparator highlights this
- No other disease-modifying therapy slows disability progression or cognitive impairment
- ACD states "*committee concluded that people may be formally diagnosed with secondary progressive multiple sclerosis earlier if siponimod is available*."
  - availability of siponimod would result in a step-change in disease management Siponimod taken orally so avoids infusions or injections
  - In TA527 committee concluded interferon β-1a was a cost-effective use of NHS resources despite ICERs >£30,000, by accounting for "*equality considerations… for the group of people who will find the preparation and administration of Extavia challenging*."

Patient group comments:

- Patients report "losing control of hand" and "crooked fingers" along with severe and painful spasms and cramps so can't administer injections
- Patients report lesions and skin problems at injection sites and fear running out of sites
- No available treatment options has psychological impact

Company updated base case

- Company updated base case continues to source efficacy data vs. interferon beta 1-b from matching-adjusted indirect comparison.
- Updated base case includes:
  - Additional cost for MRI scan for people starting siponimod
  - Utility values for active population
  - Treatment discontinuation as opposed to study discontinuation
  - Treatment waning of 50% from Year 11 (in line with assumptions in TA527)
  - Increased patient access scheme discount
  - Fully incremental probabilistic analyses including best supportive care

Company considers cost-effectiveness results confidential because of commercial arrangements for siponimod and Extavia so they are presented in private part 2 of committee meeting