Siponimod for treating secondary progressive multiple sclerosis [ID1304]

Lead team presentation

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Company: Novartis
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Avonmouth House, 6 Avonmouth St, London
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

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

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
<table>
<thead>
<tr>
<th><strong>Siponimod (Mayzent)</strong></th>
</tr>
</thead>
</table>
| **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 |
| **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

<table>
<thead>
<tr>
<th>Population</th>
<th>Final scope</th>
<th>Company submission</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Secondary progressive MS</td>
<td></td>
<td>• Marketing authorisation is for “active disease”</td>
</tr>
<tr>
<td>Subgroups</td>
<td>• Active secondary progressive MS, evidenced by relapses</td>
<td></td>
<td>• Subgroup analysis aligns with marketing authorisation</td>
</tr>
</tbody>
</table>
| Comparators        | • Established clinical management, including treatments licensed for relapsing-remitting MS used outside their marketing authorisations  | • Matches final scope | • Company **base case** compares siponimod to interferon β-1b (Extavia)  
  o 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?

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?
Definition of outcomes in trials

Treatments offered to ambulatory patients only EDSS $\leq 6.5$

- Relapse: new or recurrent neurological symptoms lasting $\geq 24$ 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/](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

Sipimod
Maintenance dose:
- 2 mg once daily (n=1,105)

Placebo
Once daily (n=546)

1° endpoint
- Time to CDP3M

2° 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

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

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

NICE
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*

<table>
<thead>
<tr>
<th></th>
<th>Siponimod n=516</th>
<th>Placebo n=263</th>
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</thead>
<tbody>
<tr>
<td><strong>Age, mean years (SD)</strong></td>
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<tr>
<td><strong>Female (%)</strong></td>
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<tr>
<td><strong>Years since MS diagnosis, mean (SD)</strong></td>
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</tr>
<tr>
<td><strong>Years since conversion to SPMS, mean (SD)</strong></td>
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<tr>
<td><strong>Number of relapses prior to screening</strong></td>
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<td></td>
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<tr>
<td>- relapses in previous 2 years, mean (SD)</td>
<td></td>
<td></td>
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<tr>
<td>- no relapses in previous 2 years, %</td>
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<td></td>
</tr>
<tr>
<td>- relapses in previous year, mean (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- no relapses in previous year, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>EDSS, mean (SD)</strong></td>
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</tr>
<tr>
<td><strong>≥1 Gadolinium-enhancing T1 lesions, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Previous treatment with disease modifying therapy %</strong></td>
<td></td>
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</tr>
</tbody>
</table>

**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

<table>
<thead>
<tr>
<th></th>
<th>Siponimod n=516</th>
<th>Placebo n=263</th>
<th>Siponimod vs placebo</th>
<th>In base-case?</th>
</tr>
</thead>
</table>
| Confirmed disability progression (CDP)  
People with 3-month CDP - 1º endpoint  |        |               |                     | X            |
| People with 6-month CDP - 2º endpoint  |        |               |                     | ✔            |
| Relapse rate b  
Adjusted annualised relapse rate – 2º endpoint |        |               |                     | ✔            |


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

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

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

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

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**

- Siponimod ↔ Placebo

**Indirect comparison**

- Siponimod ↔ Interferon beta-1b ↔ Placebo

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

Siponimod \(\leftrightarrow\) Placebo

Indirect comparison

Siponimod \(\leftrightarrow\) Interferon beta-1b \(\leftrightarrow\) Placebo

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

**Identified treatment effect modifiers**

<table>
<thead>
<tr>
<th>CDPM6</th>
<th>ARR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Time since onset of most recent relapse</td>
</tr>
<tr>
<td>EDSS at screening</td>
<td>Relapses in prior 1 yr</td>
</tr>
<tr>
<td>Duration of MS</td>
<td>Relapses in prior 2 yrs</td>
</tr>
<tr>
<td>Prior interferon/DMT</td>
<td>Gd+ lesions on T1-weighted images</td>
</tr>
<tr>
<td>Normalised brain volume</td>
<td>Duration of SPMS</td>
</tr>
<tr>
<td>Gd+ lesions on T1-weighted images</td>
<td>Volume of T2 lesions</td>
</tr>
<tr>
<td>Duration of SPMS</td>
<td>Relapses in prior 2 yrs</td>
</tr>
<tr>
<td>Volume of T2 lesions</td>
<td>Sex</td>
</tr>
<tr>
<td>Relapses in prior 2 yrs</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
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</tbody>
</table>

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

**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?

NICE Abbreviations: ARR, annualised relapse rate; SPMS, secondary progressive MS.
Results of indirect comparisons

Is MAIC or NMA the better source of efficacy data?

<table>
<thead>
<tr>
<th>Siponimod vs. Interferon beta-1b</th>
<th>Trial population used</th>
<th>6-month CDP, HR</th>
<th>Annualised relapse rate, RR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EXPAND</td>
<td>Comparators</td>
<td></td>
</tr>
<tr>
<td>MAIC (company)</td>
<td>Full</td>
<td>Full</td>
<td></td>
</tr>
<tr>
<td>NMA (ERG)</td>
<td>Full</td>
<td>Full</td>
<td>0.80 (0.57 to 1.13)</td>
</tr>
<tr>
<td>NMA (company)</td>
<td>Active</td>
<td>Full</td>
<td></td>
</tr>
</tbody>
</table>

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

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

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)

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

Increased quality-adjusted life years

Improved quality of life

- Slower disability progression, more time spent in lower EDSS states
- Fewer relapses
- Reduced caregiver disutility

Length of life

- Delaying progression to higher EDSS states avoids higher mortality multipliers associated with risk of mortality from MS

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

**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?**

NICE
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:

0.60 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?

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.

<table>
<thead>
<tr>
<th>EDSS</th>
<th>Company: EXPAND and Orme et al.</th>
<th>ERG: Orme et al.</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.825</td>
<td>0.825</td>
</tr>
<tr>
<td>1</td>
<td>0.754</td>
<td>0.754</td>
</tr>
<tr>
<td>2</td>
<td>0.660</td>
<td>0.660</td>
</tr>
<tr>
<td>3</td>
<td>0.529</td>
<td><strong>0.565</strong></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>0.473</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>0.413</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>0.252</td>
</tr>
<tr>
<td>8</td>
<td>-0.094</td>
<td>-0.094</td>
</tr>
<tr>
<td>9</td>
<td>-0.240</td>
<td>-0.240</td>
</tr>
</tbody>
</table>

**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?**
### Cost effectiveness results: company + ERG

<table>
<thead>
<tr>
<th></th>
<th>Company base case</th>
<th>ERG base case</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comparative Effectiveness</td>
<td>Matching adjusted indirect comparison (full population)</td>
<td>Network meta-analysis (full population)</td>
</tr>
<tr>
<td>Baseline characteristics</td>
<td>Active population</td>
<td>Full population</td>
</tr>
<tr>
<td>Natural history</td>
<td>EXPAND + London Ontario</td>
<td>London Ontario</td>
</tr>
<tr>
<td>Utility values</td>
<td>EXPAND + Orme et al.</td>
<td>Orme et al.</td>
</tr>
</tbody>
</table>

#### 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)

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

NICE
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
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

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

**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