NICE National Institute for Health and Care Excellence

Public observer slides

Ponesimod for treating multiple sclerosis [ID1393]

Lead team presentation

Lead team: Nigel Westwood, Anna Pracz, Gabriel Rogers,

Chair: Sanjeev Patel

Evidence Review Group (ERG): PenTAG

Technical team: Emily Leckenby, Adam Brooke, Nicole Elliott

Company: Janssen

9th September 2021

Key issues

Issues resolved at technical engagement	Impact on the ICER
1. Uncertainty in the evidence base for the rapidly evolving severe (RES) RRMS population	Company not pursuing RES population HA population defined using NHS definition
Outstanding issues after technical engagement	**Impact on the ICER**
2. Uncertainty in the clinical efficacy of ponesimod and its comparators	ICER highly sensitive to small variations in treatment efficacy
3. Insufficient comparative evidence for the safety of ponesimod	Further safety evidence required to inform most relevant comparators
4. Uncertainty surrounding use of 3-month CDA as the primary measure of disease progression in the economic model	ICER sensitive to using 6-month CDA estimates in RRMS population
5. Uncertainty surrounding the assumption that 100% of people who convert to SPMS will receive best supportive care (BSC)	No significant impact on ICER; better reflects clinical practice

CDA: confirmed disability accumulation; HA: highly active;
RRMS: relapsing remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis
Green: resolved; amber: requires discussion

Questions for committee

- Is the expected positioning of ponesimod appropriate? Would ponesimod be used in the highly active subgroup?
- How should the results of the NMA be interpreted? Is it appropriate to pool the interferon efficacy by class?
- Is the modelled output plausible?
- How should use of siponimod be modelled? Would siponimod be given to people in EDSS health states ≥7?

Background

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
- 85% of MS is relapsing-remitting (RRMS): episodes of relapses (neurological worsening) separated by remission (periods of stability)
- Associated with pain, **chronic fatigue**, unsteady gait, speech problems, incontinence, visual disturbance and cognitive impairment
- Onset typically between 25 and 35 years of age
- Approximately 110,000 people in the UK have MS, and about 5,000 people are newly diagnosed each year
- Treatment (disease-modifying therapies): decrease frequency and severity of relapses, reduce accumulation of lesions, slow accumulation of physical and mental disability, maintain or improve patient quality of life

Types 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

50% to 60% in 15 to 20 years

Secondary progressive MS (SPMS)

- Steady progression of neurological damage with or without relapses
- Treatment might be restricted to secondary progressive disease *with relapses*

Subgroups of RRMS

1. Active RRMS with no prior disease-modifying therapy
2. Active RRMS with prior disease-modifying therapy
3. Highly active (HA), with disease activity on first line therapy
4. Rapidly evolving severe (RES)

NICE

MRI, magnetic resonance imaging.

Patient and carer perspectives

MS impacts daily life for people with MS and carers

- Complex and unpredictable condition that impacts all aspects of life
- Carers also impacted – provide physical and emotional support

Best to treat early, with range of options

- Clinicians don't always offer "treat early" approach; "too well" for treatment
- Essential that there is range of treatment options
  - One treatment will not suit all
  - Treatment availability must be consistent across different centres

Taking ponesimod avoids hospital visits and allows flexibility

- Some treatments require hospital visits; can be disruptive and expensive
- Provides reduction in relapses while maintaining favourable tolerability profile
- Considers fatigue symptoms, which impact quality of life heavily
- Family planning managed more easily; benefits younger patients

Ponesimod (Ponvory)

Marketing authorisation	Adult patients with relapsing forms of multiple sclerosis with active disease as defined by clinical or imaging features **EMA**: May 2021; **MHRA**: July 2021
'Active' disease in ponesimod trial population	≥1 relapse in 1 year, or ≥2 relapses in 2 years, or ≥1 gadolinium-enhancing lesions on the brain on MRI within 6 months prior to baseline EDSS
Mechanism of action	• Sphingosine 1-phosphate receptor-1 ($S1P_1$) modulator • Causes lymphocyte retention in lymphoid tissues • May reduce lymphocyte migration into the central nervous system, thereby modulating immunity
Administration and dose	Oral administration once daily • Starting dose of 2mg on day 1 increasing up to • 10mg on days 12 to 14, then • 20mg thereafter (maintenance dose)
Cost of treatment	• List price: [redacted] per 28-capsule pack (maintenance dose) • Patient access scheme discount agreed

EDSS: Expanded Disability Status Scale; **MRI**: magnetic resonance imaging

Clinical perspectives

Aims to prevent/reduce relapses, and slow accumulation of fixed disability

- Useful addition of moderately effective more specific S1P inhibitor
  - "Need for a safe highly effective oral medication… first line"
- Low burden management/monitoring, unlike existing S1P inhibitors
  - No need to admit for first dose observation in majority of patients

Offers patients earlier access to more effective oral therapy

- When patients start on more efficacious first line disease modifying therapies (DMT) at early stage of disease, disability and some measures of quality of life improved
- "Not innovative" but refinement of existing drug class; short washout useful in patients considering families
- "Step-change" if approved for first line treatment in active disease

Decision problem (1)

	Final scope	Company submission (CS)	Company rationale if CS different from decision problem
P	People with relapsing MS	**Only** people with RRMS (including people with active RRMS and people with highly active RRMS) • SPMS excluded at CS • Rapidly evolving severe MS excluded at TE stage*	• Evidence presented based on a phase 3 RCT (OPTIMUM). At study entry, RRMS = 97.4%. SPMS = 2.6% • Phase 3 data more robust in people with active RRMS/highly active RRMS (35% trial popn)
C	**For people with active RRMS** beta-interferon; dimethyl fumarate; glatiramer acetate; teriflunomide; ocrelizumab; peginterferon β-1a; ozanimod[a]; ofatumumab[b] **For people with highly active RRMS despite previous treatment** alemtuzumab; cladribine; fingolimod; ocrelizumab[c]; ozanimod[a]; ofatumumab[b]	All comparators listed in the scope were included in the company submission, except ozanimod and ofatumumab. Ozanimod and ofatumumab were added at clarification stage following request from NICE • Both TA699 and TA706 were under appraisal at point of company submission	• Cladribine is a comparator but used in tablet form only • Siponimod not relevant - no comparators included for SPMS as company not making a case for this population

NICE

[a] Ozanimod subject to TA706; [b] Ofatumumab subject to TA699; [c] only if alemtuzumab contraindicated/otherwise unsuitable
Note: Final scope also listed comparators for rapidly evolving severe and SPMS
RRMS: relapsing remitting multiple sclerosis, SPMS: secondary progressive multiple sclerosis

Decision problem (2)

	Final scope	Company submission (CS)	Company rationale if CS different from decision problem
O	• Relapse rate • Severity of relapse • Disability (for example, EDSS) • Disease progression • Symptoms of MS (such as fatigue, cognition and visual disturbance) • Freedom from disease activity (for example lesions on MRI scans) • Mortality • Adverse effects of treatment • HRQoL	• Relapse rate *(ARR, time to first confirmed relapse)* • Disability *(change from baseline in EDSS score)* • Disease progression *(3-month CDA, 6-month CDA)* • Symptoms of MS *(change from baseline in FSIQ-RMS score)* • Freedom from disease activity *(CUAL, NEDA-3, NEDA-4)* • Adverse effects of treatment • Mortality • HRQoL *(change from baseline in SF-36 and MSFC-Z scores)*	• Outcomes such as severity of relapse and mortality not included in pharmacoeconomic analyses due to absence of comparative trial data • OPTIMUM did not formally measure severity of relapse; difficult to measure in MS trials

ARR: annualised relapse rate; **CDA**: confirmed disability accumulation; **CUAL**: combined unique active lesions; **EDSS**: Expanded Disability Status Scale; **FSIQ-RMS**: Fatigue Symptoms and Impacts Questionnaire: Relapsing Multiple Sclerosis **Gd+**: gadolinium enhancing; **HRQoL**: health-related quality of life; **MRI**: magnetic resonance imaging; **MSFC**: Multiple Sclerosis Functional Composite; **NEDA**: no evidence of disease activity; **SF-36**: 36-item Short Form Health Survey

NHS England treatment algorithm and company positioning*

RRMS: 1 relapse in last 2 years & radiological activity	RRMS: 2 significant relapses in last 2 years	Rapidly evolving severe MS (RES)
1st line therapy (and alternatives for intolerance to first-line therapy in underline)		
• Interferon beta-1a • Glatiramer acetate • Ocrelizumab • Peginterferon beta-1a • Ofatumumab • **Ponesimod?**	• Beta interferons (1a/1b) • Dimethyl fumarate • Glatiramer acetate • Ocrelizumab • Peginterferon beta-1a • Teriflunomide • Ofatumumab • **Ponesimod?**	• Alemtuzumab or ocrelizumab[b] • Cladribine • Natalizumab • [Fingolimod, only as alternative to natalizumab] • Ofatumumab

NICE

[a] N.B Peginterferon beta-1a presented but not in algorithm because recommended after algorithm published; [b] Only if alemtuzumab contraindicated or otherwise unsuitable.

*N.B since October 2019 alemtuzumab is no longer recommended for RRMS

NHS England treatment algorithm and company positioning*

RRMS: 1 relapse in last 2 years & radiological activity	RRMS: 2 significant relapses in last 2 years	Rapidly evolving severe MS (RES)
1st line therapy (and alternatives for intolerance to first-line therapy in underline)		
• Interferon beta-1a • Glatiramer acetate • Ocrelizumab • Peginterferon beta-1a • Ofatumumab • **Ponesimod?**	• Beta interferons (1a/1b) • Dimethyl fumarate • Glatiramer acetate • Ocrelizumab • Peginterferon beta-1a • Teriflunomide • Ofatumumab • **Ponesimod?**	• Alemtuzumab or ocrelizumab[b] • Cladribine • Natalizumab • [Fingolimod, only as alternative to natalizumab] • Ofatumumab
Second-line therapy, when disease activity on 1st line therapy (highly active [HA] RRMS)		
• Alemtuzumab or ocrelizumab[b] • Cladribine • Fingolimod • Ofatumumab • **Ponesimod?** *Patients developing RES receive second-line therapy for RES*		• Alemtuzumab or ocrelizumab[b] • Cladribine • Natalizumab • Ofatumumab

NICE

[a] N.B Peginterferon beta-1a on slide but not in algorithm because recommended after algorithm published; [b] Only if alemtuzumab contraindicated or otherwise unsuitable.

*N.B since October 2019 alemtuzumab is no longer recommended for RRMS

NHS England treatment algorithm and company positioning*

RRMS: 1 relapse in last 2 years & radiological activity	RRMS: 2 significant relapses in last 2 years	Rapidly evolving severe MS (RES)
1st line therapy (and alternatives for intolerance to first-line therapy in underline)		
• Interferon beta-1a • Glatiramer acetate • Ocrelizumab • Peginterferon beta-1a • Ofatumumab • **Ponesimod?**	• Beta interferons (1a/1b) • Dimethyl fumarate • Glatiramer acetate • Ocrelizumab • Peginterferon beta-1a • Teriflunomide • Ofatumumab • **Ponesimod?**	• Alemtuzumab or ocrelizumab[b] • Cladribine • Natalizumab • [Fingolimod, only as alternative to natalizumab] • Ofatumumab
Second-line therapy, when disease activity on 1st line therapy (highly active [HA] RRMS)		
• Alemtuzumab or ocrelizumab[b] • Cladribine • Fingolimod • Ofatumumab • **Ponesimod?** *Patients developing RES receive second-line therapy for RES*		• Alemtuzumab or ocrelizumab[b] • Cladribine • Natalizumab • Ofatumumab
Third-line therapy		
• Alemtuzumab or ocrelizumab[b] • Cladribine • Autologous haematopoietic stem cell treatment (AHSCT) *Patients developing RES receive third-line therapy for RES*		• Alemtuzumab or ocrelizumab[b] • Cladribine • Natalizumab • AHSCT

NICE

[a] N.B Peginterferon beta-1a on slide but not in algorithm because recommended after algorithm published; [b] Only if alemtuzumab contraindicated or otherwise unsuitable. *N.B since October 2019 alemtuzumab is no longer recommended for RRMS

Treatments for SPMS

Relapsing-remitting MS (RRMS)

Treatment strategy: patient choice, number of relapses, MRI activity and response to previous treatment
* As per NHS England algorithm

50% to 60% in 15 to 20 years

Secondary progressive MS (SPMS) (2.6%)

- Treatment might be restricted to secondary progressive disease *with relapses*

Treatments

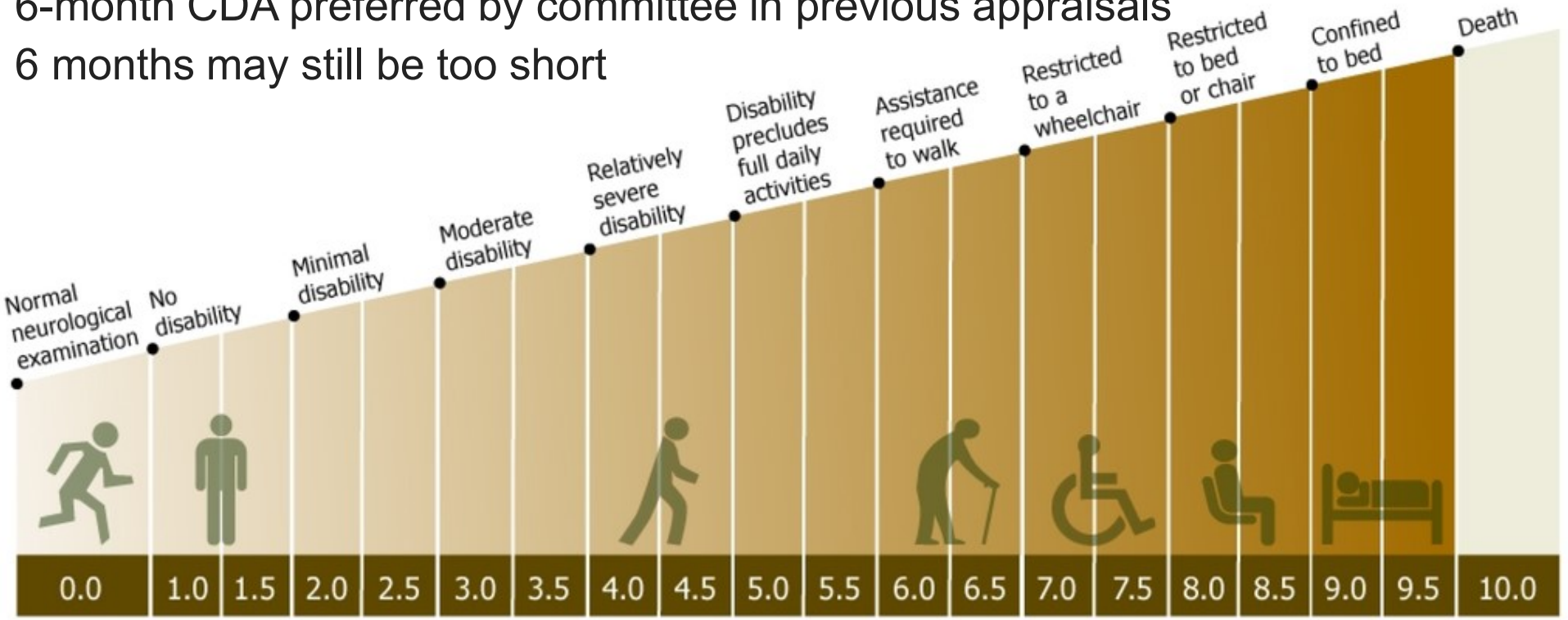
- **Siponimod** recommended for SPMS in Nov 2020; *TA656*
- **Interferon beta-1b** recommended for SPMS in June 2018; *TA527*

Q. Would siponimod be used after ponesimod (S1P1 inhibitor)?

Clinical effectiveness

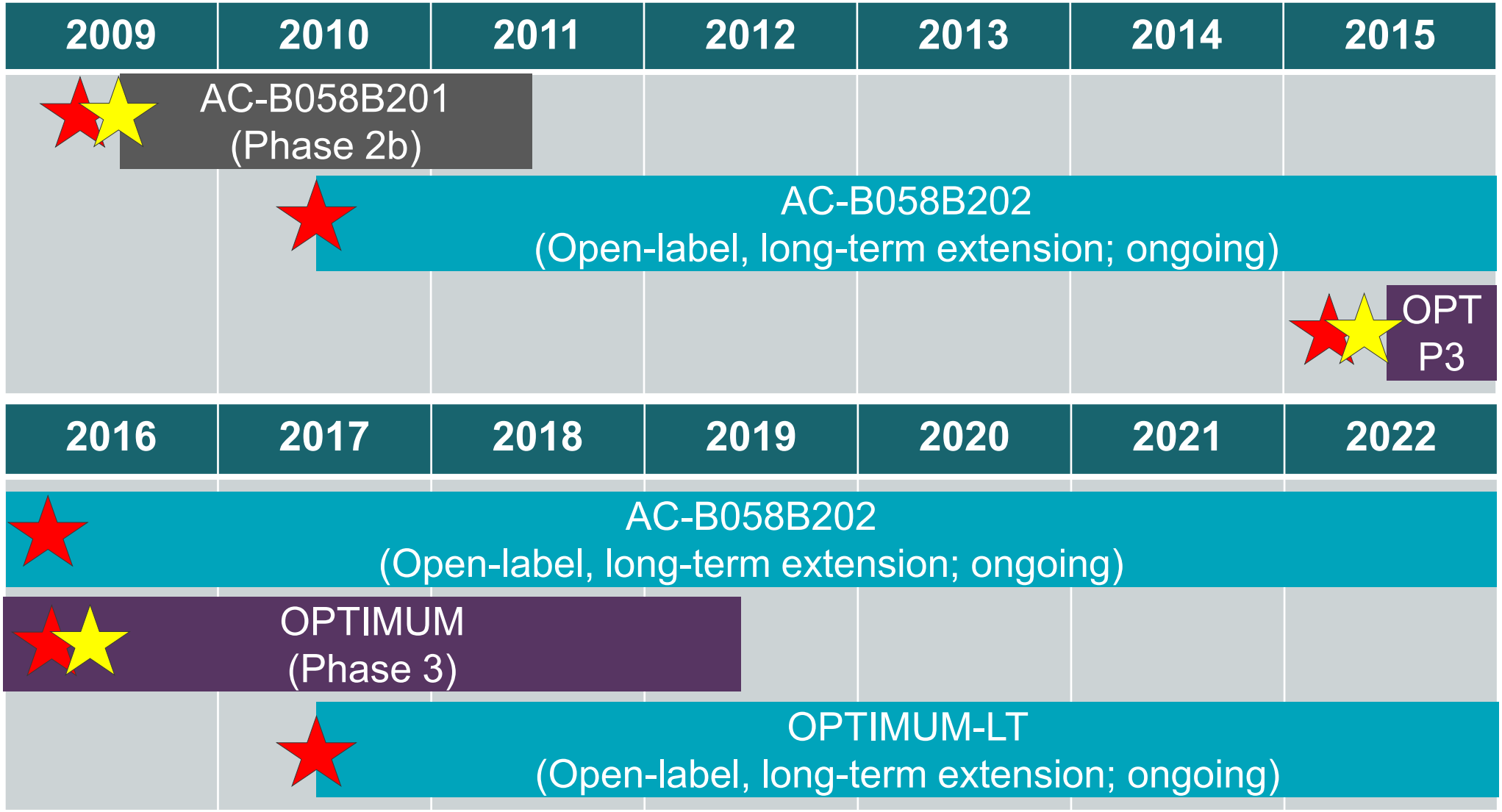
Definition of outcomes in trials

- Relapse: new, worsening, or recurrent neurological symptoms occurring ≥30 days following the onset of a prior relapse and sustained ≥24 hours without fever or infection
- Disability assessed using **Expanded Disability Status Scale (EDSS)**
- Disability that lasts for 3 or 6 months: ‘confirmed disability accumulation’ or CDA
- Defined as a sustained worsening in EDSS score of 1.0 point or more confirmed after 3 or 6 months
- 6-month CDA preferred by committee in previous appraisals
- 6 months may still be too short



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

Ponesimod clinical trial programme in RMS



Included as clinical evidence

Included in NMA (and therefore as clinical efficacy in model)

Phase 3

Phase 2

Open label extension

NICE

Included as clinical evidence

Included in NMA (and therefore as clinical efficacy in model)

OPTIMUM/LT: study design

OPTIMUM: Phase 3 randomised, double-blind, parallel-group, multicentre

Study name and acronym	Study design	Follow-up	Intervention / Comparator	Study objectives
OPTIMUM; AC-058B301 **N = 1,133** *PON 20mg = 567* *Placebo = 566*	Randomised, double-blind, active-controlled parallel trial	108 weeks	Ponesimod 20 mg once daily Teriflunomide 14 mg once daily	Efficacy and safety. Subgroup analyses were conducted in highly active RRMS. *Primary outcome: ARR* *Secondary outcomes Change from baseline in fatigue-related symptoms; 12/24-week CDA (3/6 month); adverse effects*
OPTIMUM-LT; AC-058B303 **N = 877**	Single-group, open-label, non-comparative long-term extension in patients who completed OPTIMUM	Up to 240 weeks	Ponesimod, gradually up-titrated over day 1 to 14 until a maintenance dose of 20 mg is reached on day 15 No comparator	Long-term safety and control of RMS *Primary outcomes: ARR, time to first relapse, time to 12/24-week CDA, change from baseline in EDSS, estimation of incidence rates of adverse events*

ARR: annualised relapse rate; CDA: confirmed disability accumulation; EDSS: expanded disability status scale; RRMS: relapsing-remitting multiple sclerosis; RMS – relapsing multiple sclerosis

Included as clinical evidence

Included in NMA (and therefore as clinical efficacy in model)

B201/B202: study design

Phase 2b randomised, double-blind, placebo-controlled, dose-finding

Study name and acronym	Study design	Follow up	Intervention / Comparator	Study objectives
AC-058B201 **N = 237** *PON 20mg = 116* *Placebo = 121*	Randomised, double-blind, placebo-controlled dose-finding study	24 weeks	Ponesimod 10, 20, or 40 mg once daily Matching unspecified placebo once daily	Efficacy, safety and tolerability of ponesimod at various doses *Primary outcome: cumulative number of new T1 Gd+ lesions from week 12 to 24* *Secondary outcomes: ARR, number of participants with first confirmed relapse from baseline to week 24*
AC-058B202 **(safety population)** **N = 435** *PON 20mg = 145*	Randomised, single arm, double-blind, multiple-dose, uncontrolled long-term extension of AC-058B201 who completed dose-finding study	528 weeks	Ponesimod 10, 20, or 40 mg once daily No comparator	Long-term efficacy, safety and tolerability of ponesimod at various doses *Primary outcome: ARR, time to first relapse, time to 24 weeks CDA* *Secondary outcomes: (serious) adverse events*

ARR: annualised relapse rate; CDA: confirmed disability accumulation; Gd+: gadolinium-enhancing

Ponesimod clinical trials: inclusion/exclusion criteria

OPTIMUM

Key inclusion criteria:

- Adults (aged 18 to 55 years)
- Met McDonald 2010 criteria
- EDSS 0.0–5.5
- ≥1 attacks with onset within 12-1 months prior to baseline EDSS or; ≥2 attacks with onset within 24-1 months prior to baseline EDSS or; ≥1 (Gd+) lesions on an MRI within 6 months prior to baseline EDSS
- Treatment-naïve or treated with IFN beta-1a, IFN beta-1b, glatiramer acetate, natalizumab, DMF

B201

Key inclusion criteria:

- Adults (aged 18 to 55 years)
- Met McDonald 2005 criteria
- EDSS 0.0–5.5
- ≥1 relapse within 12 months prior to screening or; ≥2 relapses within 24 months prior to screening; or ≥1 Gd+ lesion
- No exacerbation in last 30 days

Key exclusion criteria:

- Lactating/pregnant women
- Progressive MS
- Significant medical conditions, or receiving therapies for such conditions (e.g. corticosteroids, immunosuppressants)
- Unlikely to comply

NICE

DMF: dimethyl fumarate; EDSS, Expanded Disability Status Scale; Gd+, gadolinium enhanced; IFN - interferon

Baseline characteristics in OPTIMUM/B201

	OPTIMUM (n=1,113) (108 weeks) ★		B201 (n=237) (24 weeks) ★	
	Ponesimod 20mg (N=567)	Terifluromide 14mg (N=566)	Ponesimod 20mg (N=116)	Placebo (N=121)
Age, years	36.7 (8.74)	36.8 (8.74)	35.5 (8.5)	36.6 (8.6)
Female	64.0%	65.7%	67.5%	70.2%
White	97.2%	97.7%	98.2%	94.2%
EU + UK [UK]	[redacted]	[redacted]	115 study locations over 24 countries, including 3 locations in UK	
Europe non-EU/Russia	[redacted]	[redacted]		
North America	[redacted]	[redacted]		
Rest of world	[redacted]	[redacted]		
EDSS (Median [Q1-Q3])	[redacted]	[redacted]	2.0 (0.0-5.5)	2.0 (0.0-5.5)
Received 1+ prior DMT	[redacted]	[redacted]	35.1%	39.7%
DMT received 2yrs prior	37.6%	37.3%	-	-
Years since first symptoms (SD)	7.63 (6.781)	7.65 (6.782)	7.3(6.25)	6.9(5.7)
Mean relapses in year prior (SD)	1.2 (0.61)	1.3 (0.65)	-	-
Mean months since last relapse (SD)	[redacted]	[redacted]	5.1 (5.51)	5.6 (4.53)
% RRMS subtype	97.0%	98.0%	-	-
Presence of Gd+ T1 lesions	39.9%	45.4%	40.0%	47.4%
Mean BMI kg/m^2 (SD)	[redacted]	[redacted]	-	-
% highly active	35.6%	35.3%	-	-
% RES	[redacted]	[redacted]	-	-

NICE

DMT: disease modifying therapy; EDSS: Expanded Disability Status Scale; Gd+, gadolinium enhanced; RES: rapidly evolving severe; RRMS: relapsing-remitting multiple sclerosis; SD: standard deviation

Key results: OPTIMUM/B201

Whole population

★ Included in NMA (and therefore as clinical efficacy in model)

	OPTIMUM ★		B201 ★	
	Ponesimod	Teriflunomide	Ponesimod	Placebo
Key endpoints associated with relapses				
ARR (mean; 95% CI)	0.20 (0.17, 0.24)	0.29 (0.25, 0.33)	0.42 (0.27, 0.65)	0.53 (0.36, 0.77)
ARR (IRR)	0.70 (0.57, 0.85)		0.79 (0.44, 1.43)	
Key endpoints associated with disability				
% 3-month CDA	[redacted]	[redacted]	NR	NR
HR (95% CI)	0.83 (0.58, 1.18)		NR	
% 6-month CDA	8.1%	9.9%	NR	NR
Risk reduction (95% CI)	0.84 (0.57, 1.24)		NR	
EDSS (mean change from baseline)	[redacted]	[redacted]	[redacted]	[redacted]
Difference in EDSS	[redacted]		[redacted]	

NICE ARR, annualised relapse rate; CDA, confirmed disability progression; CI: confidence interval; EDSS: Expanded Disability Status Scale; IRR: incidence rate ratio; LS: least squared; NR: not recorded. Source: company submission, Document B, trial clinical study report (CSR), Olsson et al., 2014

Indirect treatment comparison: NMA

Network meta-analysis results associated with high degree of uncertainty

Methodology

Company: NMAs submitted for whole population base case, and HA subgroup

- 46 trials with ≥80% RRMS; outcomes: ARR, 3- and 6-month CDA, and treatment discontinuation
  - ≥80% RRMS: ≥80% of trial participants must have RRMS according to OPTIMUM criteria
  - Not all trials had outcomes for 6-month CDA
- Major source of heterogeneity due to variations in treatment effects of interferon beta trials
  - Provided interferon class-based NMA and NMA excluding ADVANCE and INCOMIN trials ('outlier' trials identified in previous appraisals [ofatumumab; TA699])

ERG critique: NMA methods appropriate, however:

- Approach by company does not resolve major limitations with the analyses
  - Extreme heterogeneity in trial design; likely to bias effect estimates
    - Company's feasibility assessment: follow-up duration and previous treatments at baseline
    - ERG report: vast differences in effect of placebo reported across trials for all outcomes
- Agreed that IFNs should be presented as a class to account for outliers without losing data

ARR: annual relapse rate; CDA: confirmed disability accumulation; DMT: disease modifying therapies; NMA: network meta-analysis; RRMS: relapsing remitting multiple sclerosis; TE: technical engagement

Indirect treatment comparison: NMA

Network meta-analyses completed for 4 outcomes

Network for annualised relapse rate

[redacted]

Interferons considered as a class after technical engagement

Company rationale:

- Reduces major source of heterogeneity in the NMA outcomes
- Clinical opinion that interferon treatments have similar clinical efficacy

Q. Is it appropriate to pool results from interferon studies?

RRMS population: NMA outcomes for ponesimod vs. comparator in ≥80% RRMS population* (company base case, interferon as a class)

	ARR, Rate ratio (95% CrI)[a]	3-month CDA[a]	6-month CDA[a]	All-cause discontinuation[b]
Alemtuzumab	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]
Ofatumumab	[redacted]	[redacted]	[redacted]	[redacted]
Fingolimod	[redacted]	[redacted]	[redacted]	[redacted]
Cladribine	[redacted]	[redacted]	[redacted]	[redacted]
Interferon class	[redacted]	[redacted]	[redacted]	[redacted]
Dimethyl fumarate	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide*	[redacted]	[redacted]	[redacted]	[redacted]
Glatiramer acetate, 20mg	[redacted]	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Glatiramer acetate, 40mg	[redacted]	[redacted]	[redacted]	[redacted]

Data are hazard ratios (HRs) (95% credible intervals) [a] fixed effects NMA; [b] random effects NMA

* ≥80% RRMS: ≥80% of trial participants must have RRMS according to OPTIMUM criteria

NICE

***Teriflunomide = trial comparator**

ARR: annualised relapse rate CDA: confirmed disability accumulation; CrI: credible interval; IFN: interferon; NMA; network meta analysis. **Source**: ERG report, table 20

RRMS population: NMA outcomes for ponesimod vs. comparator in ≥80% RRMS* population (company original base case, interferon as individual)

	ARR, Rate ratio (95% CrI)[a]	3-month CDA[a]	6-month CDA[a]	All-cause discontinuation[b]
IFN beta-1a, 22µg	[redacted]	[redacted]	[redacted]	[redacted]
IFN beta-1a, 44µg	[redacted]	[redacted]	[redacted]	[redacted]
IFN beta-1a, 30µg	[redacted]	[redacted]	[redacted]	[redacted]
Peg-IFN beta-1a	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta 1b	[redacted]	[redacted]	‡	[redacted]

NB: Results from the original separate NMA, interferons only presented

‡ Not included in meta-analysis but reported from literature values as **0.34** (0.18-0.63), considered an outlier by the ERG

Data are hazard ratios (HRs) (95% credible intervals) [a] fixed effects NMA; [b] random effects NMA

*≥80% RRMS: ≥80% of trial participants must have RRMS according to OPTIMUM criteria

NICE

*Teriflunomide = trial comparator

ARR: annualised relapse rate CDA: confirmed disability accumulation; CrI: credible interval; IFN: interferon; NMA; network meta analysis. **Source**: ERG report, table 20

HA population: NMA outcomes for ponesimod vs. comparator

	ARR, Rate ratio (95% CrI)[a]	3-month CDA[a]	6-month CDA[a]
Cladribine	[redacted]	[redacted]	[redacted]
Alemtuzumab	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]
Ofatumumab	[redacted]	[redacted]	[redacted]
Fingolimod	[redacted]	[redacted]	[redacted]
Teriflunomide	[redacted]	[redacted]	[redacted]
IFN beta-1a, 44µg	[redacted]	[redacted]	[redacted]
IFN beta-1a, 30µg	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]

[a] fixed effects NMA;

NICE

ARR: annualised relapse rate CDA: confirmed disability accumulation; CrI: credible interval; HA: highly active; IFN: interferon; NMA; network meta analysis. **Source**: ERG report, table 22

Uncertainty in the clinical efficacy of ponesimod and its comparators

Uncertain clinical effectiveness estimates due to limited evidence base

Company: provided NMAs with IFNs considered as a treatment class (slide 28)

ERG: Both NMAs broadly comparable; but ponesimod/comparator evidence heterogeneous:

- Limited evidence for most comparisons in NMAs
- Outcomes of included trials short term; do not capture meaningful change in disease
- Relative treatment effects had wide confidence intervals; uncertain true effect

- Methodology and results validated against previous appraisals; appropriate methodology used:
  - Uncertainty surrounding clinical effectiveness estimates due to limitations of evidence base
    - Treatment effect of DMTs is key issue in multiple RRMS appraisals
- Long-term safety cannot be adequately assessed due to small long term population (146 of long-term data sample were on PON 20mg), plus heterogeneity of evidence within NMAs **(key issue 3)**

Stakeholders: Ponesimod superior to teriflunomide in RRMS, likely equivalence to fingolimod in HA RRMS

- However heterogeneity of condition makes difficult to estimate treatment effect
- Methodology consistent with previous appraisals

Q. Are the results seen in the company's NMAs suitable for decision making?

DMT: disease modifying therapies, HA: highly active, IFN: interferon; NMA: network meta analysis, RRMS: relapsing remitting multiple sclerosis

Safety profile of ponesimod

Insufficient comparative evidence for safety of ponesimod

Company: provided direct safety evidence from OPTIMUM and B201, plus long-term safety set pooling evidence from all participants receiving ponesimod during OPTIMUM, its extension, B201 and its extension B202

ERG: Safety data may be comparable to other DMTs, however elevated risk of SAEs raises concerns

- **Comparisons with most DMTs suggest similar AE safety profile but increased risk of SAEs**
  - 95% CrIs extend on each side of null effect, true difference in AEs and SAEs highly uncertain
  - Associated monitoring has minimal impact on ICER
- **Long term safety not demonstrated in large group**
  - PON 20mg in follow up trial = 145 participants; many years/patients required to detect SAEs
  - Clinical advice to ERG states length of follow up may not be sufficient to detect RAEs
    - e.g. fingolimod appraisal (TA254) in 2012, where trial had short follow up and cases of PML occurred in post-marketing context

***Stakeholders*:** Safety data collected resembles fingolimod, well characterised/acceptable safety profile

- Further investigation needed to understand to establish safety profile of ponesimod
- Would inform positioning in treatment pathway/identification of most relevant comparators
- Suggest review of fingolimod evidence to be considered in absence of long term ponesimod data – safety risks associated with S1P1 modulators include infections, malignancies, bradycardia and heart conduction abnormalities, pulmonary function abnormalities, ophthalmic abnormalities, hepatic abnormalities and dermatological abnormalities.

AE: adverse event, NMA: network meta-analysis; PML: progressive multifocal leukoencephalopathy, RAE: rare adverse event; SAE: serious adverse event

Cost effectiveness

Company's cost utility model structure

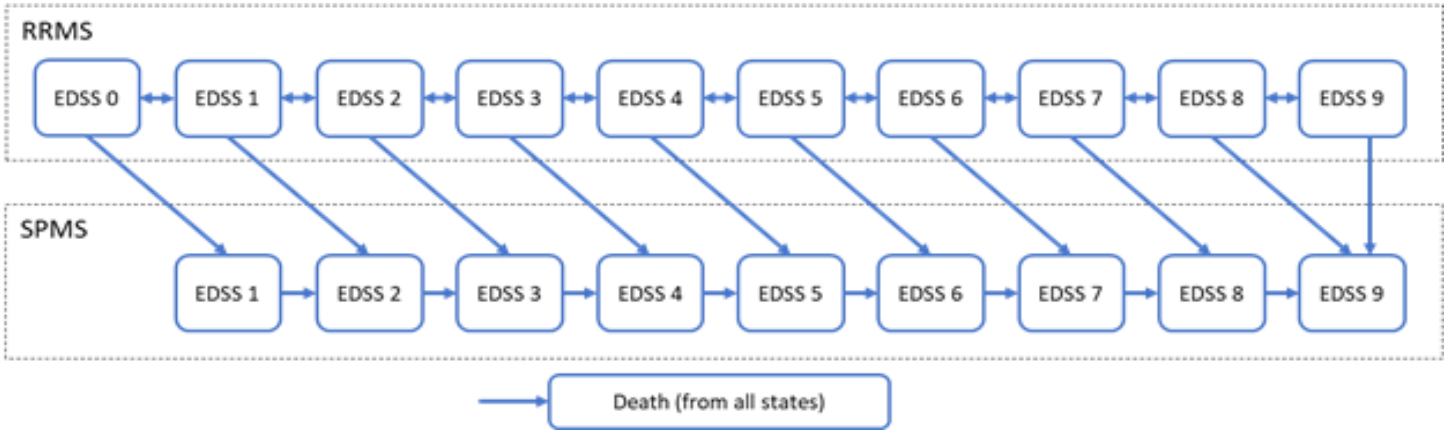
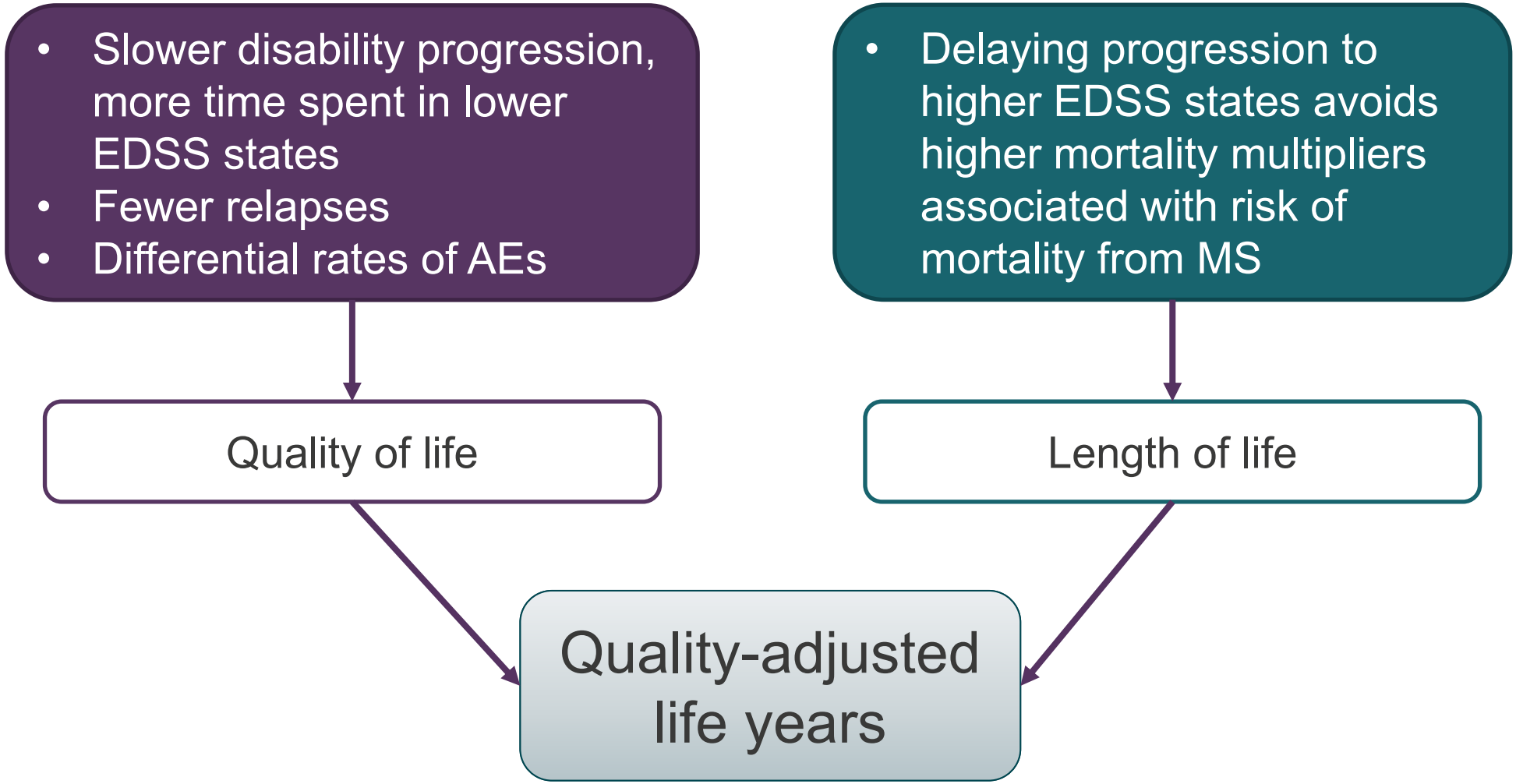


Figure source: ERG report, figure 1

- Markov state transition model
- 20 states
  - 10 EDSS states in RRMS (on/off treatment)
  - 9 EDSS states in SPMS (on/off treatment)
  - Death (equivalent to EDSS 10 for both RRMS and SPMS)
- Annual cycle, 50 year (lifetime) horizon
- Mean age: RRMS: 36 years; 64% women; HA: 37 years, 66% women
- Treatment effects (annualised relapse rates, disability progression, adverse events) from NMAs
- Treatment discontinuation due to:
  - EDSS ≥7
  - Progression from RRMS to SPMS
  - Premature discontinuation for any reason (lack of efficacy, AEs)

AE: adverse event, EDSS: Expanded Disability Status Scale; NMA: network meta analysis, RRMS: relapsing remitting multiple sclerosis: SPMS: secondary progressive multiple sclerosis

Overview: how quality-adjusted life years accrue in the cost utility model



Company's key model assumptions (1)

	Assumption
Population	For the RRMS population, people entered the model based on their baseline EDSS distribution in the OPTIMUM study ([redacted]≤ EDSS 3)
Relapses	Relapses are modelled independently, incurring a utility decrement of -0.071 and associated costs
Disease progression	Natural history of people in RRMS drawn from the British Columbia dataset (898 people followed for 15 years, accepted in previous appraisals). Hazard ratios were applied to natural history based on results of the 6-month CDA NMA. For HA subgroup, natural history drawn from the AFFIRM trial (natalizumab study) for EDSS 0-6 and the British Columbia dataset for EDSS 7-9
Treatment discontinuation	Constant annual treatment discontinuation rates from NMA, also from EDSS score (when EDSS score is ≥ 7), or upon conversion to SPMS
Transition to SPMS	Annual EDSS baseline probability of progressing from RRMS to SPMS was derived from Mauskopf (2016) (DMF study). Annual SPMS conversion probabilities were based on the London Ontario natural history study, Upon progressing to SPMS the company assumed that EDSS would increase by 1

NICE

AE, adverse event; EDSS, Expanded Disability Status Scale; IFN, interferon; RRMS: relapsing remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis.

Company's key model assumptions (2)

	Assumption
Treatment waning	In the base case analysis (for both the active RRMS and HA RRMS populations) treatment waning of 25% decrease in treatment efficacy was applied from years 2 to 5, followed by a 50% decrease in efficacy applied from year 6 onwards applied to all DMTs (as in most of previous submissions)
Patient utility values	Baseline EDSS utility values (EQ-5D) were derived from published literature Orme (2007). SF-36 from OPTIMUM not included
Caregiver utility values	HRQoL impact for caregivers based on a published study by Acaster et al. (2013) – also used in TA527 (IFN and GA) and TA624 (peg-IFN)
Resource use and costs	Drug costs from BNF and administration/monitoring costs from previous appraisals, valued using PSSRU and NHS reference costs
	Health state costs from the UK MS survey in 2005 (subsequently reported by Tyas et al) – used in previous appraisals
	Costs of relapse (£2,243 per relapse, from Tyas) and adverse events also included

NICE

DMT: disease modifying therapies; EDSS, Expanded Disability Status Scale; GA: glatiramer acetate; HA: highly active; IFN, interferon;. RRMS: relapsing-remitting multiple sclerosis

Key model outputs – RRMS health states

Key drivers

- Annual conversion to SPMS from London Ontario dataset as reported in Mauskopf (2016) – ERG notes that rates are higher than those used in the submission for peginterferon (TA624) which also uses London Ontario
- Able to transition into higher and lower EDSS levels
- In base case, transitions within EDSS health states driven by British Columbia dataset natural history with hazard ratio applied for each specific treatment, scenario using London Ontario and placebo arm of DEFINE (DMF trial)

Modelled output (discounted)	
QALY gain	****
Life years gained	****
Carer disutility	****
Number of relapses	****

NICE

Key model outputs – SPMS health states

Key drivers

- London, Ontario database used for transitions between SPMS EDSS states (British Columbia database does not distinguish between RRMS and SPMS)
- All patients converting from RRMS to SPMS have EDSS score increased by 1 point (consistent with TA533 and TA624, ocrelizumab and peg-interferon appraisals)
- Unable to transition to lower EDSS states

Modelled output (discounted)	
QALY gain	[redacted]
Life years gained	[redacted]
Carer disutility	[redacted]
Number of relapses	[redacted]

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

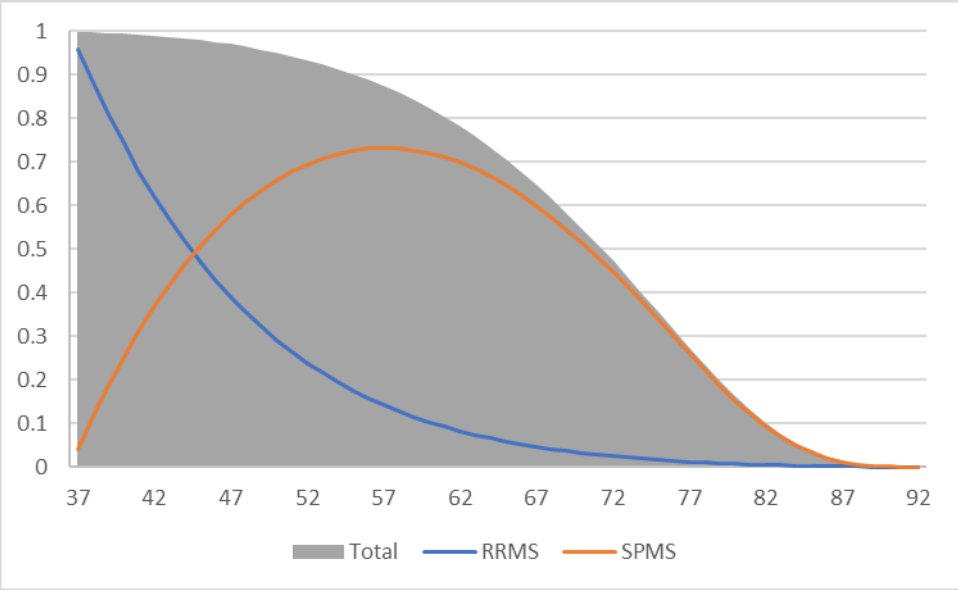
Key model outputs – SPMS health states

[redacted]

- Is it plausible that almost everyone in the model progresses to SPMS before dying?
- Is it plausible that people spend most of their lives in the SPMS state?
- Is it plausible that, once in SPMS, people spend a substantial amount of time in high-EDSS states?

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

Key model outputs – mortality



Relative Risk of Mortality, by EDSS Score					
EDSS score	0	1	2	3	4
RRMS	1.00	1.30	1.60	1.68	1.76
SPMS	NA	1.30	1.60	1.68	1.76
EDSS score	5	6	7	8	9
RRMS	1.84	2.71	3.57	4.44	5.31
SPMS	1.84	2.71	3.57	4.44	5.31

Key drivers

- Relative risk of mortality applied in each health state, taken from Pokorski (1997) which demonstrated risk of death due to MS primarily dependent on disability
- Patients with RRMS and SPMS with same EDSS score have same relative risk of morality (company considers this a conservative assumption)
- Consistent assumptions with previous appraisals (TA624)

NICE

EDSS, Expanded Disability Status Scale; RRMS: relapsing remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis

Disease progression 3-month CDA vs 6-month CDA

ERG consider 6-month CDA to be more robust measure

Company: key driver of clinical effectiveness in model was treatment effects for 3-month CDA:

- Lack of data from trials/missing values result in uncertainty around 6-month CDA
- Evidence network for 3-month CDA more robust than 6-month; more closed loops

ERG: 6-month CDA more robust measure of progression

- 3-month CDA can overestimate progression due to natural fluctuations in disease
- Previous committees show preference for 6-month CDA in RRMS appraisals

Response to technical engagement

Company: conducted additional analyses in model with 6-month values as base case

- Suggest ERG and committee consider both 3-month and 6-month CDA results in model

ERG: still prefers 6-month CDA outcome over 3-month CDA

- Fewer closed loops outweighed by limitations of measuring disability using 3-month CDA

Stakeholders: most view 6-month CDA to be more robust in terms of representing disability

– In line with long-established committee preference across recent appraisals of MS DMTs
– Difficult to demonstrate reduction in CDA in clinical trials due to lagging effect

Uptake and modelling of siponimod

Impact of supply of siponimod remains uncertain

Company: base case analysis assumes 100% of people who discontinue treatment with ponesimod go on to receive BSC; reflective of previous MS appraisals

ERG: aware of siponimod being accepted for use in people with SPMS

- Clinical input to ERG suggests proportion of people likely to receive siponimod = ~25%
- Conducted scenario analysis; assumes 25% converting to SPMS receive siponimod
  - Accounted for **additional costs only**, but not clinical efficacy due to uncertainty

Response to technical engagement

Company: consulted four clinical experts regarding siponimod use in SPMS population

- Anticipated approximately 25% of incident SPMS population will be eligible for treatment
- Not known how widely will be used after COVID-19 and experienced is gained

ERG: findings by company similar to those reported by ERG; limited impact on ICER

- Approach does not account for clinical effect of siponimod, lack of robust long-term data

Stakeholders: Without data on prescribing levels of siponimod, impossible to say which scenarios will most closely match current clinical practice

- Modelling of 25% will use siponimod is plausible

BSC: best supportive care, RRMS: relapsing remitting multiple sclerosis, SPMS: secondary progressive multiple sclerosis

Uptake and modelling of siponimod

Impact of supply of siponimod remains uncertain

Q. Would siponimod be given to people in EDSS health states ≥7?

Summary of changes made to company base case

ERG accepts company changes, no alternative base case

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made by the company in response to technical engagement	Accepted by ERG?
Issue 1: Uncertainty in the evidence base for the rapidly evolving severe (RES) RRMS population	Treatment effects for ponesimod in HA RRMS subgroup based on evidence from prespecified HA RRMS subgroup from OPTIMUM	Treatment effects for ponesimod in the HA RRMS subgroup based on patients with HA RRMS as defined by NICE/NHSE, obtained from post hoc analyses of OPTIMUM	✓
Issue 2: Uncertainty in the clinical efficacy of ponesimod and its comparators	Treatment effects for interferons considered separately for each DMT in RRMS population	Treatment effects for interferons considered as pooled average of class; all considered to have equivalent clinical effectiveness	✓
Issue 4: Uncertainty surrounding use of 3-month CDA as the primary measure of disease progression in the economic model	3-month CDA used as primary measure of disease progression in economic model	6-month CDA used as primary measure of disease progression in economic model, in line with the ERG's preferred assumptions	✓
Issue 5: Uncertainty surrounding the assumption that 100% of people who convert to SPMS will receive BSC	100% of patients that convert to SPMS receive best supportive care (BSC)	25% of patients that convert to SPMS receive siponimod; 75% of patients receive BSC, in line with ERG's preferred assumptions and based on clinical expert feedback to company	✓

BSC: best supportive care, CDA: confirmed disability accumulation, DMT: disease modifying therapies, HA: highly active, RRMS: relapsing remitting multiple sclerosis, SPMS: secondary progressive multiple sclerosis

ERG additional changes – errors identified after technical engagement

Discontinuation base probability calculation:

- Discontinuation rates were calculated by pooling numerators and denominators from a 24-week trial and a 108-week trial - essentially assuming they all come from a single 66-week trial (no weighting for precision)
- Lead team considered that using the 108-week trial was a minor correction but mathematically more accurate than an unweighted mean.
- The ERG considered this had minimal impact but used 108-week trial data in their base case

Hazard ratios used as relative risk:

- The hazard ratios were used directly in the model as if they were relative risks - lead team considered that the hazard ratios should be applied to rates.
- The ERG considered this had minimal impact but applied hazard ratios to rates in their base case

Innovation and equalities

Innovation: company considers ponesimod innovative

- Provides new treatment option for patients with RRMS:
- ***Convenience****:* easy to use with once-daily dosing and oral administration. People with MS can manage treatments without routine hospital appointments: flexibility during COVID-19
- ***Reversibility****:* short half life/rapidly reversible pharmacodynamic effects beneficial for re-establishment of immune system function, pregnancy planning, serious infections, vaccinations – half life of fingolimod is 8 days
- ***Reduced monitoring burden****:* gradual up-titration mitigates first-dose cardiac effects
- ***Concomitant treatment****:* potential for drug-drug interactions is low as no active metabolites
- ***Managing fatigue symptoms****:* validated disease-specific fatigue measure – first DMT to demonstrate stabilisation of fatigue symptoms compared with another oral DMT

No equality issues expected – MS disproportionally affects more women than men

Questions for committee

- Is the expected positioning of ponesimod appropriate? Would ponesimod be used in the highly active subgroup?
- How should the results of the NMA be interpreted? Is it appropriate to pool the interferon efficacy by class?
- Is the modelled output plausible?
- How should use of siponimod be modelled? Would siponimod be given to people in EDSS health states ≥7?

Cost-effectiveness results

All ICERs are reported in PART 2 slides because they include confidential PAS discounts