NICE National Institute for Health and Care Excellence

For public: Contains no confidential information

Ozanimod for treating relapsing–remitting multiple sclerosis [ID1294]

Chair presentation

2nd appraisal committee B meeting

Chair: Sanjeev Patel

Evidence Review Group (ERG): Liverpool Reviews and Implementation Group (LRiG)

Technical team: Hannah Nicholas, Henry Edwards

Company: Celgene

8th April 2020

Key issues

Positioning, population and comparators

- At what position(s) in the pathway would ozanimod be used – 1st line, 2nd, or both?
- Company wish to limit the population to: people 'suitable for or requesting an oral treatment'. Is this appropriate?
- Are oral drugs for relapsing remitting multiple sclerosis the only relevant comparators? Or are injectable and infusion therapies also relevant?

Current treatment patterns

- What proportion of people with active RRMS are treated with oral therapies?

Treatment effect – clinical evidence

- What is ozanimod's likely effect on disability progression?

Treatment effect – economic model

- In the model, should the disability progression hazard ratio for ozanimod be set equal to the interferon beta-1a hazard ratio (company base case), or should ozanimod's own hazard ratio be used?
- Should non-statistically significant differences between treatments be modelled?

N.B. company did not provide new analyses at consultation

RRMS, relapsing–remitting multiple sclerosis.

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)

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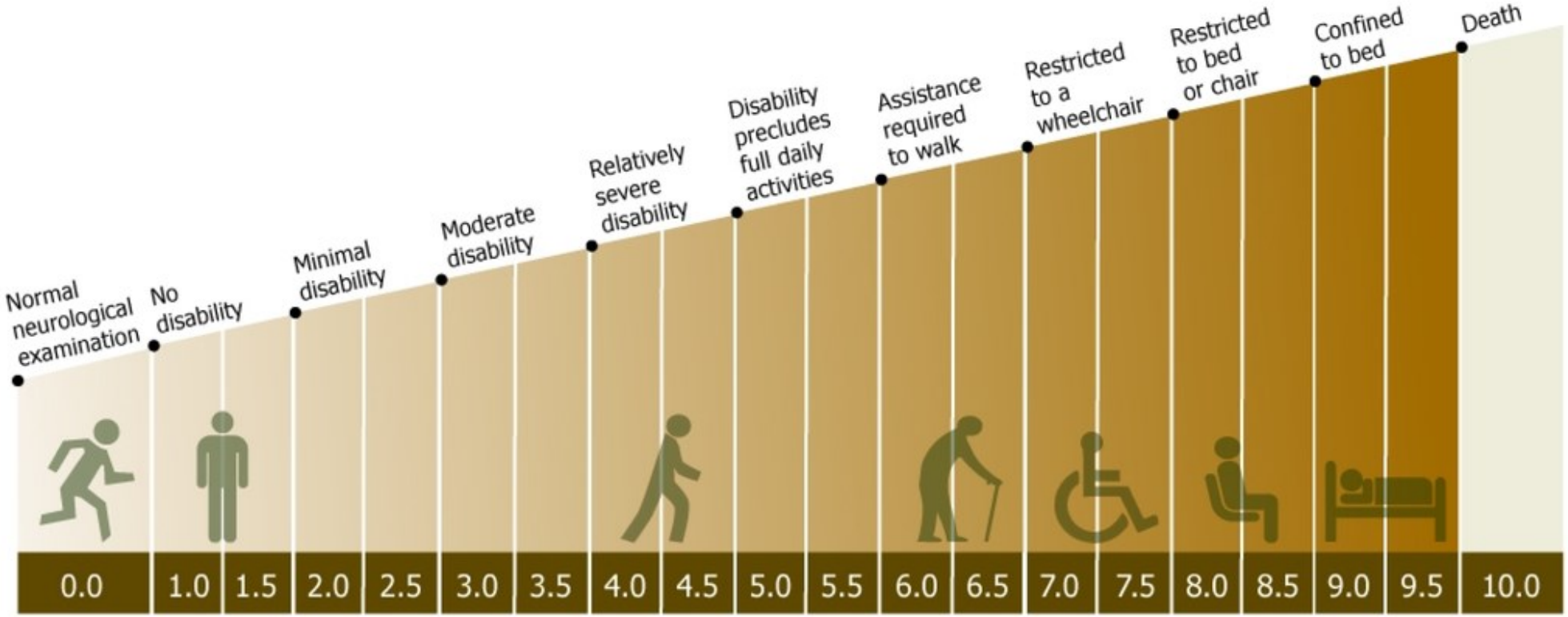
MRI, magnetic resonance imaging.

Definition of outcomes in trials

- Relapse: new or worsening neurological symptoms > 24 hours, preceded by a relatively stable or improving neurological state for at least 30 days
- Disability assessed using **Expanded Disability Status Scale (EDSS)**
- Disability that lasts for 3 or 6 months is ‘confirmed disability progression’ CDP3/6M
- Defined as a sustained worsening in EDSS score of 1.0 point or more confirmed after 3 or 6 months
- CDP6M preferred by committee in previous appraisals



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

Ozanimod (Zeposia)

Marketing authorisation	Adults with relapsing–remitting multiple sclerosis with 'active disease as defined by clinical or imaging features'
'Active' disease in trial population	In ozanimod trials 'active disease' defined as ≥1 relapse within prior year, or 1 relapse within prior 2 years with evidence of at least one gadolinium-enhancing lesion in the prior year
Mechanism of action	• Sphingosine 1-phosphate (S1P) receptor modulator • Causes lymphocyte retention in lymphoid tissues • May reduce lymphocyte migration into the central nervous system, thereby modulating immunity
Administration and dose	Oral administration Dosing: • 0.25 mg on days 1 to 4, then • 0.5 mg on days 5 to 7, then • 1 mg once daily thereafter (maintenance dose)
Cost of treatment	• List price: £1,373 per 28-capsule pack (maintenance dose) • Patient access scheme discount agreed

NHS England treatment algorithm and positioning[a]

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 italics*)		
• *Interferon beta-1a* • *Glatiramer acetate* • Ocrelizumab [b] • Peginterferon beta-1a • **Ozanimod?**	• *Beta interferons (1a and 1b)* • *Dimethyl fumarate* • *Glatiramer acetate* • Ocrelizumab [b] • Peginterferon beta-1a • *Teriflunomide* • **Ozanimod?**	• *Alemtuzumab* • *Cladribine* • Natalizumab • *Ocrelizumab* [b] • *[Fingolimod, only as alternative to natalizumab]*
Second-line therapy, when disease activity on 1st line therapy (highly active [HA] RRMS)		
• Alemtuzumab or ocrelizumab [b] • Cladribine • Fingolimod • **Ozanimod?** *Patients developing RES receive second-line therapy for RES*		• Alemtuzumab or ocrelizumab [b] • Cladribine • Natalizumab
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

[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.

Ozanimod clinical trial programme in RMS: inclusion and exclusion criteria

- Same inclusion and exclusion criteria for RADIANCE Part A, RADIANCE Part B and SUNBEAM

Key inclusion criteria:

- Adults (aged 18 to 55 years) with RMS
- Meet McDonald 2010 criteria
- EDSS 0.0–5.0
- ≥1 relapse within last 12 months, or ≥1 relapse within last 24 months plus ≥1 GdE lesion within last 12 months
- No relapses from 30 days before screening through randomisation

Key exclusion criteria:

- Primary progressive MS
- Disease duration greater >15 years and EDSS ≤2.0
- Previous intolerance to IFN-β
- Specific cardiovascular conditions
- Previous treatment with lymphocyte-depleting therapies or lymphocyte-trafficking blockers

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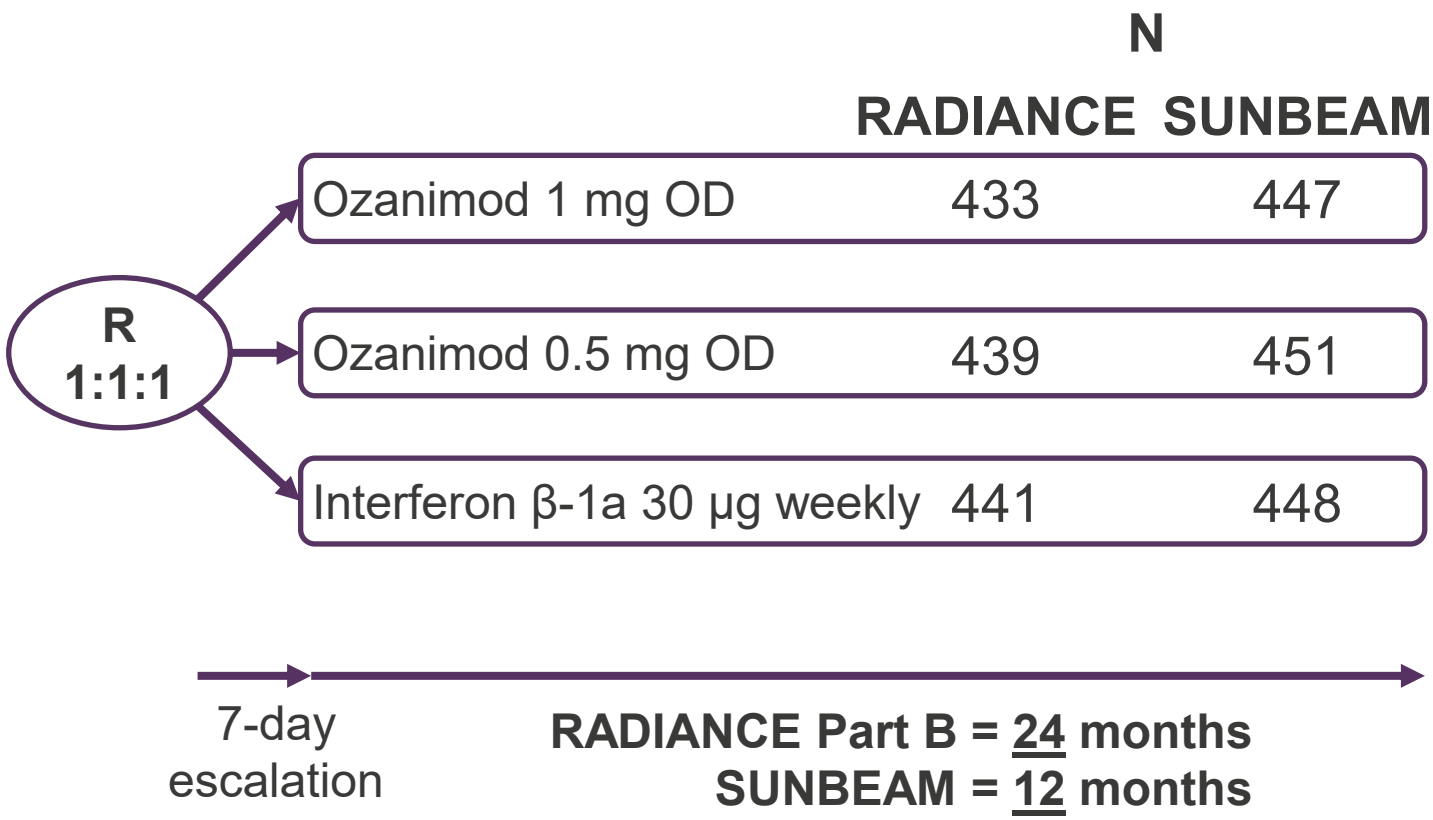
EDSS, Expanded Disability Status Scale; GdE, gadolinium enhanced; RMS, relapsing multiple sclerosis.

RADIANCE Part B and SUNBEAM: study designs

Baseline characteristics generalisable to people in NHS with active RRMS

Phase 3, randomised, double-blind, double-dummy, active-controlled parallel group trials



Primary endpoint

- ARR

Key secondary outcomes

- Time to onset of disability progression after 3 and 6 months
- New or enlarging T2 MRI lesions over 24 months
- Gd-E MRI lesions at month 24
- Adverse events

RADIANCE Part A trial design available as back up slide.

ARR, annualised relapse rate; Gd-E, gadolinium-enhanced; MRI, magnetic resonance imaging; OD, once per day.

Key results from Phase 3 trials

Improvements in relapse rates compared with IFN β-1b

	RADIANCE Part B (24 months)		SUNBEAM (12 months)		Pooled analysis [a] (12 months)	
	IFN β-1a 30 µg (N=441)	Ozanimod 1 mg (N=433)	IFN β-1a 30 µg (N=448)	Ozanimod 1 mg (N=447)	IFN β-1a 30 µg (N=889)	Ozanimod 1 mg (N=880)
Key endpoints associated with relapses (primary outcome)						
Adjusted ARR (95% CI)	0.28 (0.23,0.32)	0.17 (0.14,0.21)	0.35 (0.28,0.44)	0.18 (0.14,0.24)	**** **********	**** **********
Rate ratio (95% CI)	**0.62 (0.51, 0.77)**		**0.52 (0.41, 0.66)**		**********	
Key endpoints associated with disability (secondary outcomes)						
CDP at 3 months, n (%)	50 (11.3)	54 (12.5)	********	********	69 (7.8)	67 (7.6)
HR vs IFN (95% CI)	1.05 (0.71, 1.54)		**********		0.95 (0.68, 1.33)	
CDP at 6 months, n (%)	29 (6.6)	42 (9.7)	********	********	36 (4.0)	51 (5.8)
HR vs IFN (95% CI)	1.44 (0.89, 2.31)		**********		1.41 (0.92, 2.17)	

Statistically significant results in bold. [a] Integrated efficacy analysis aimed to estimate treatment effect (not to test statistical hypotheses), apart from CDP which was used for statistical hypothesis testing for disability progression. ARR, annualised relapse rate; CDP, confirmed disability progression; HR, hazard ratio; IFN, interferon.

Company's NMA: results versus ozanimod

	ARR, Rate ratio	CDP-3M, HR	CDP-6M, HR	CDP-6M combined HR [a]	Discontinuation, HR
Use in model	**Base case**	**Scenario**	**No**	**Base case**	**Base case**
Placebo	**0.5 (0.4, 0.6)**	**********	**********	**********	**********
Interferons					
Beta-1a, 30µg	**0.6 (0.5, 0.7)**	**********	**********	**********	**********
Beta-1a, 22µg	**0.7 (0.5, 0.9)**	**********	–	**********	**********
Beta-1a, 44 µg	**0.7 (0.6, 0.9)**	**********	**********	**********	**********
★ **Beta-1b, 250µg**	**0.7 (0.6, 0.9)**	**********	**********	**********	**********
Others					
DMF	0.9 (0.7, 1.1)	**********	**********	**********	**********
GA 20 mg	**0.7 (0.6, 0.9)**	**********	**********	**********	**********
GA 40 mg[b]	**0.7 (0.6, 0.9)**	–	–	**********	**********
Ocrelizumab[c]	**1.3 (1.0, 1.7)**	**********	**********	**********	**********
Peg-IFN β-1a	0.7 (0.6, 1.01)	**********	–	**********	**********
Teriflunomide	**0.7 (0.6, 0.9)**	**********	**********	**********	**********

★ **Interferon beta-1a 30 µg = trial comparator**

Data are hazard ratios (HRs) (95% credible intervals). Statistically significant results in bold. In favour of ozanimod highlighted green, in favour of comparator highlighted red;

DMF, dimethyl fumarate; GA, glatiramer acetate; [a] Assumes HR of CDP-6M between treatment arms proportional to HR of CDP-3M – conducted so CDP-6M relative efficacy can be estimated for treatments with no CDP-6M data. [b] ERG consider GA 40 mg could be excluded because no CDP-3M or -6M data available (suspect data reported as being CDP-3M from 1 study were actually CDP-12M); [c] Included in appendix to company submission.

Company's cost utility model structure

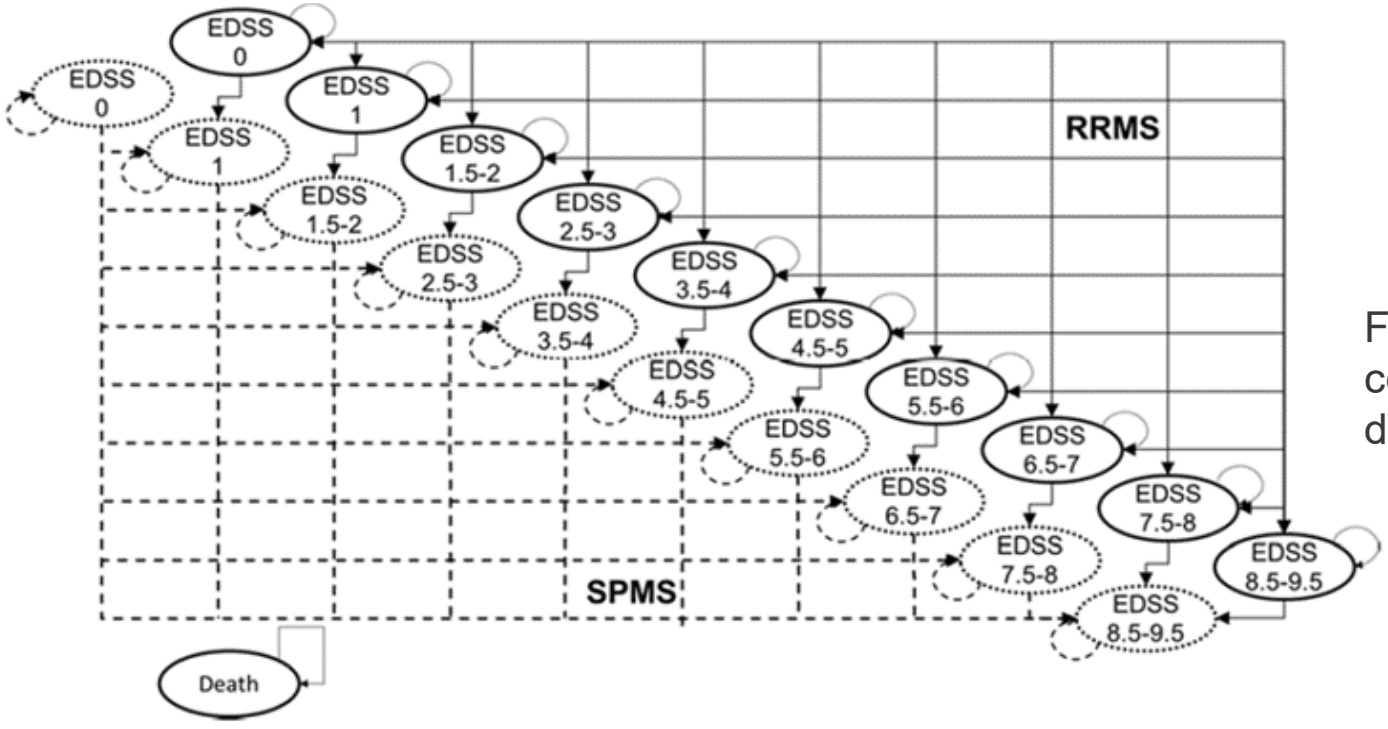
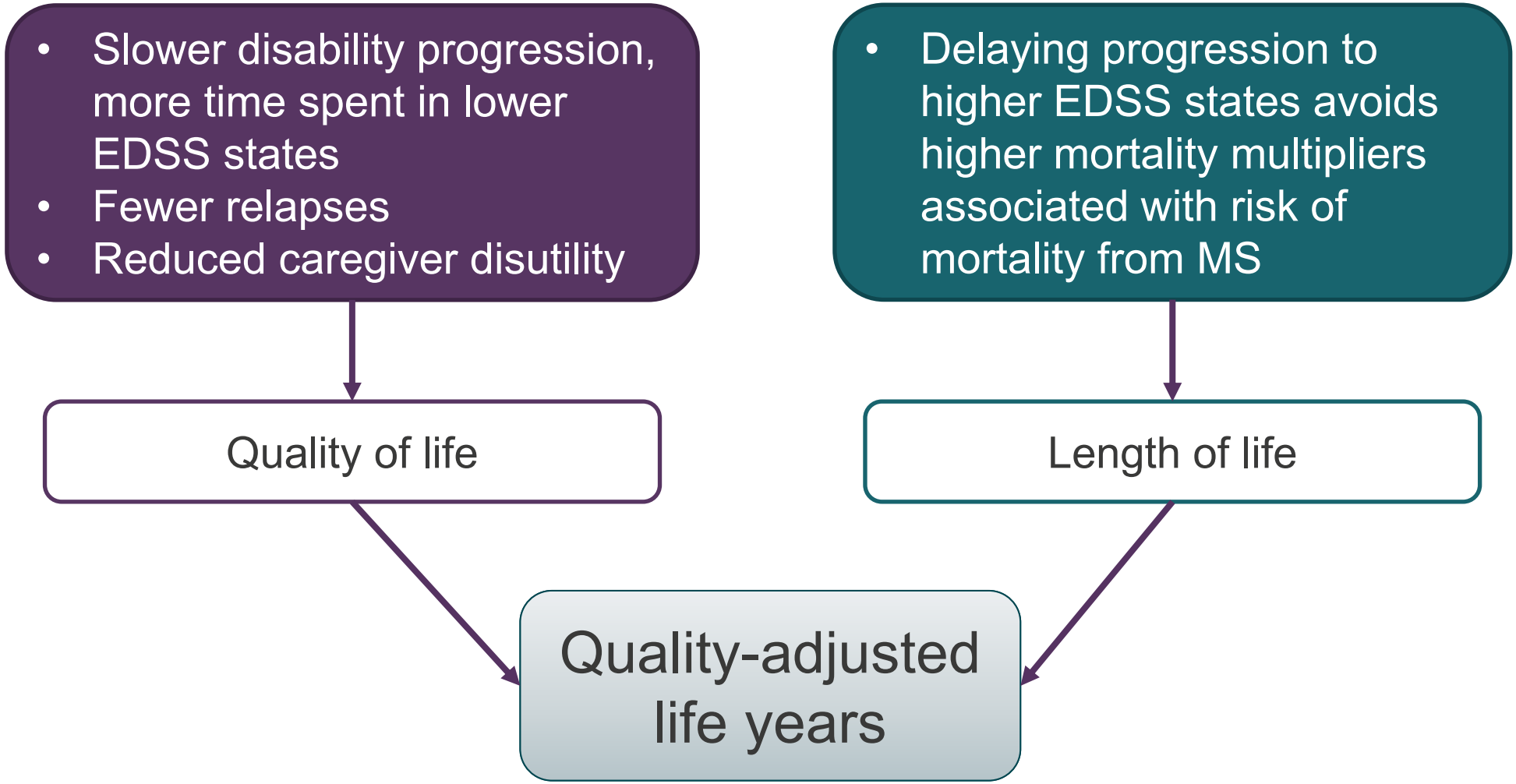


Figure source: company's submission document B, Figure 8

- Markov state transition model
- 21 states
  - 10 EDSS states in RRMS (on/off treatment)
  - 10 EDSS states in SPMS (on/off treatment)
  - Death
- Annual cycle, lifetime horizon
- Mean age 36 years; 67% women

- On-treatment effects (annualised relapse rates, disability progression, adverse events) from NMA
- Treatment discontinuation from NMA
- Treatment stops after at EDSS ≥7
- After stopping treatment people follow natural disease course from British Columbia Multiple Sclerosis registry

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



Summary of appraisal consultation document (ACD) and consultation responses

Recommendation

- *Ozanimod is not recommended, within its marketing authorisation, for treating relapsing–remitting multiple sclerosis in adults with clinical or imaging features of active disease.*

ACD (appraisal consultation document) sent out for consultation January 2021

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

	Committee conclusions	To discuss?	ACD section
Positioning	• Ozanimod likely use as 1st or 2nd line treatment for active RRMS	**Yes**	3.1
Population	• Not appropriate to limit population to people suitable for or requesting oral treatment	**Yes**	3.2
Comparators	• All 1st and 2nd line treatments for active RRMS, including ocrelizumab, are comparators	**Yes**	3.3
Trial characteristics	• Baseline characteristics generalisable to people in NHS with active RRMS	**No**	3.4
Clinical effectiveness	• Ozanimod reduces relapses and brain lesions compared with interferon beta-1a • Effects on disability progression uncertain	**Yes**	3.5
Network meta-analysis (NMA)	• Company's NMA generally well conducted, but should account for variability	**Yes**	3.6

RRMS, relapsing–remitting multiple sclerosis.

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

	Committee conclusions	To discuss?	ACD section
Model	• Company's model generally appropriate and aligns with previous models in MS	**No**	3.7
Disability progression model input	★ Ozanimod's disability progression hazard ratio from NMA should be used, not the interferon beta-1a hazard ratio ★ Modelling non-statistically significant differences (N.B. not discussed in ACD)	**Yes**	3.8
Treatment waning	• Company's model is generally appropriate –waning effect applied for all treatments	**Yes**	3.7
Treatment discontinuation	• Company's and ERG's approaches have limitations	**No**	3.9
Cost-effectiveness estimate	• No analyses reflected committee's preferred assumptions • Outside acceptable range	**Yes**	3.10
Innovation	• No evidence of additional benefits not captured by QALY	**Yes (recap)**	3.11

NICE ★ **Key driver of cost-effectiveness estimates**

RRMS, relapsing–remitting multiple sclerosis.

Consultation responses

- Company
  - Celgene
- Comparator companies
  - Novartis
- Patient and professional groups
  - MS Trust
  - MS Society
  - Multiple Sclerosis Advisory Group as part of the Association of British Neurologists
- Patient and clinical experts

Patients + patient organisations: Common themes

Range of treatments needed, including new oral options

- MS is heterogeneous and highly variable between people so broad range of treatments is important - Oral options currently limited
- Oral route of administration benefits patients: “easy to take and its potential to improve compliance, taking the pressure and stress out of taking the medicine”
- Ozanimod would be a valuable additional oral treatment

Ozanimod’s safety, and effect on relapses and disability, are important

- “Outcomes important to people with MS include a reduction in relapse rate, in disability progression, and a reduction in evidence of active disease”
- Effects on disability progression uncertain, but beneficial effects on relapses and MRI outcomes proven
- Seems to have a good safety profile
- Expected to have fewer side effects than fingolimod and could be offered first line, whereas fingolimod is only 2nd line

Positioning of ozanimod

Background	• Original submission: company positioned ozanimod at 1st line only
	• Response to technical engagement: changed positioning to 1st and 2nd line
	  • 1st line for people unsuitable for infusion / injectables
	  • 2nd line for people who have not responded to ≥1 of infusion / injectable therapies (N.B. often described as 'highly active' MS)

ACD committee conclusion	*"Ozanimod is likely to be used as a first- or second-line treatment for active relapsing–remitting multiple sclerosis"*
Company response to ACD	• Changed preferred positioning – active, not highly active RRMS • Defined in the NHS England MS Treatment Algorithm for RRMS as '2 significant relapses in last 2 years' • Making dimethyl fumarate and teriflunomide key comparators • Ozanimod trial inclusion criteria: at least 1 relapse in last 12 months • 53% of patients (pooled analysis) ≥ 2 relapses in 2 years
Stakeholder response to ACD	• Separating highly active / active MS based on relapses is artificial • Likely use as 1st line therapy • Alternative to fingolimod in people with cardiac concerns • Useful 2nd line alternative for people with relapses but no MRI changes / intermediate disease severity

Recap: NHS England treatment algorithm and positioning [a]

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 italics*)

• *Interferon beta-1a* • *Glatiramer acetate* • Ocrelizumab [b] • Peginterferon beta-1a • **Ozanimod?**	• *Beta interferons (1a and 1b)* • *Dimethyl fumarate* • *Glatiramer acetate* • Ocrelizumab [b] • Peginterferon beta-1a • *Teriflunomide* • **Ozanimod?**	• *Alemtuzumab* • *Cladribine* • Natalizumab • *Ocrelizumab* [b] • *[Fingolimod, only as alternative to natalizumab]*

Second-line therapy, when disease activity on 1st line therapy (highly active [HA] RRMS)

• Alemtuzumab or ocrelizumab [b] • Cladribine • Fingolimod • **Ozanimod?** *Patients developing RES receive second-line therapy for RES*	• Alemtuzumab or ocrelizumab [b] • Cladribine • Natalizumab

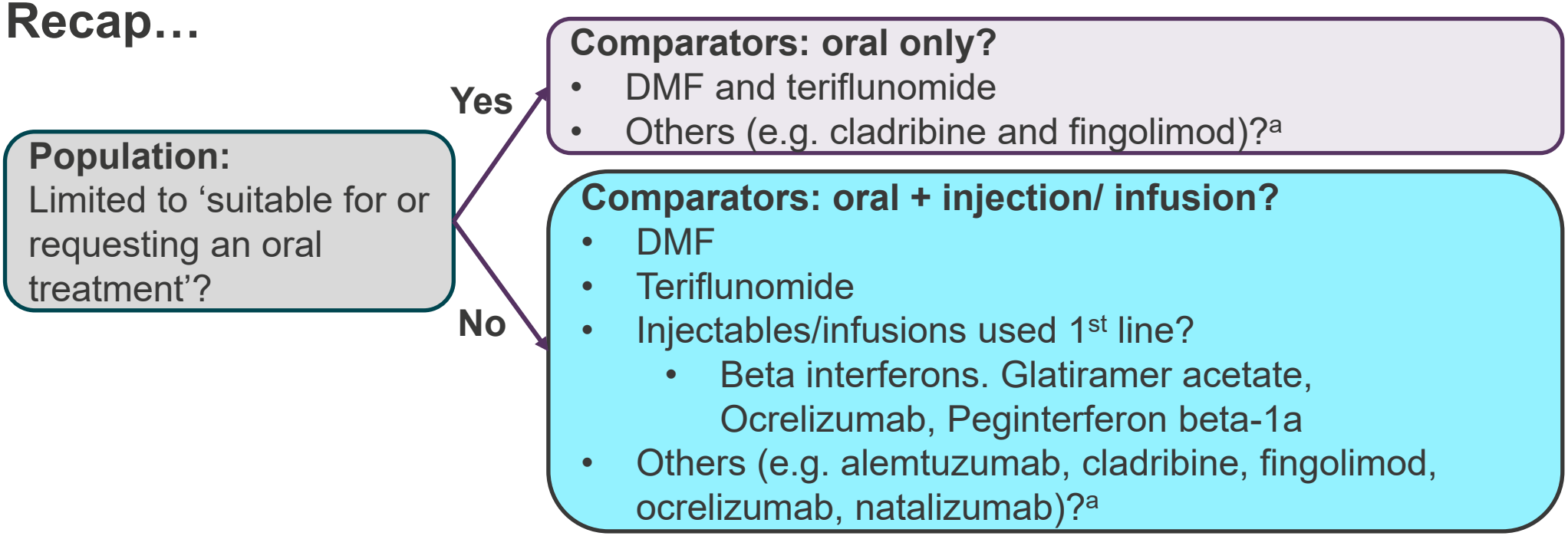
- ***Where in the pathway would ozanimod most likely be used?***
- ***Would it be used as an alternative to fingolimod or other later line treatments?***

[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.

Population and comparators (1)

ACD: company's choice to limit population and comparators not appropriate

Recap…



Background	• Company limited population to 'adults with active RRMS who are suitable for or requesting an oral treatment • Company considered only oral treatments used at first line (dimethyl fumarate and teriflunomide) to be comparators
ACD committee conclusions	• *"It is not appropriate to limit the population to people for whom an oral treatment is suitable or who request an oral treatment"* • *"All first-and second-line treatments used for active relapsing–remitting multiple sclerosis, including ocrelizumab, are comparators"*

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[a] Applicable only if ozanimod's positioning at 2nd line is considered appropriate.

Population and comparators (2)

ACD: company's choice to limit population and comparators not appropriate

Company response to ACD	• NHS algorithm does include injectable DMTs • are not routinely prescribed for this patient group due to perceived lower efficacy • Oral treatments favoured for patients – shift away from injectables to oral treatments in active disease (next slide) • Most appropriate comparators are orals (dimethyl fumarate and teriflunomide)
Stakeholder response to ACD	• People 'suitable for or requesting an oral treatment' not a clinician-defined category, but important for many patients • Risk profile is important factor when picking treatment • Broad range of comparators, including ocrelizumab

- ***Is it appropriate for company to limit population to people 'suitable for or requesting an oral treatment'?***
- ***Based on the positioning and population:***
  - ***Are treatments used at 1st line the only relevant comparators? Or are later line treatments also comparators?***
  - ***Are oral drugs the only relevant comparators? Or are injectable and infusion therapies also relevant?***

Current treatment patterns

Company provided additional information on market share of oral drugs

Background	• Company submission: oral drugs (teriflunomide and dimethyl fumarate) make up ~50% of market share in RRMS • NHS commissioning expert at ACM1: 50% likely a significant overestimate

Company response to ACD	• In clinical practice, oral treatments preferred for active RRMS [a]
	• People only have injectable treatments because of legacy prescribing
	• Provided estimates for percentage share of oral treatments in active RRMS using market share data:
	  • **********
	  • **********
	  • **********
	  • **********
	• Supports estimate: 50% of people with active RRMS have oral treatments

- ***What proportion of people with active RRMS are treated with oral therapies?***
- ***Does this affect the choice of comparators?***

[a] Defined by company as 2 significant relapses in last 2 years.

Key results from Phase 3 trials

Improvements in relapse rates compared with IFN β-1b

	RADIANCE Part B (24 months)		SUNBEAM (12 months)		Pooled analysis [a] (12 months)	
	IFN β-1a 30 µg (N=441)	Ozanimod 1 mg (N=433)	IFN β-1a 30 µg (N=448)	Ozanimod 1 mg (N=447)	IFN β-1a 30 µg (N=889)	Ozanimod 1 mg (N=880)
Key endpoints associated with relapses (primary outcome)						
Adjusted ARR (95% CI)	0.28 (0.23,0.32)	0.17 (0.14,0.21)	0.35 (0.28,0.44)	0.18 (0.14,0.24)	**** **********	**** **********
Rate ratio (95% CI)	**0.62 (0.51, 0.77)**		**0.52 (0.41, 0.66)**		**********	
Key endpoints associated with disability (secondary outcomes)						
CDP at 3 months, n (%)	50 (11.3)	54 (12.5)	********	********	69 (7.8)	67 (7.6)
HR vs IFN (95% CI)	1.05 (0.71, 1.54)		**********		0.95 (0.68, 1.33)	
CDP at 6 months, n (%)	29 (6.6)	42 (9.7)	********	********	36 (4.0)	51 (5.8)
HR vs IFN (95% CI)	1.44 (0.89, 2.31)		**********		1.41 (0.92, 2.17)	

Statistically significant results in bold. [a] Integrated efficacy analysis aimed to estimate treatment effect (not to test statistical hypotheses), apart from CDP which was used for statistical hypothesis testing for disability progression. ARR, annualised relapse rate; CDP, confirmed disability progression; HR, hazard ratio; IFN, interferon.

Effectiveness of ozanimod in clinical trials

ACD: reduces relapses and brain lesions, but uncertain effects on disability progression

Background	• Compared with interferon beta-1a, ozanimod:[a]
	  • reduced relapses and better across MRI outcomes
	  • but no statistically significant differences in disability outcomes[b]

ACD committee conclusion	*"Ozanimod reduces relapses and brain lesions compared with interferon beta-1a, but its effects on disability progression are uncertain"*
Company response to ACD	• Trials not power to detect differences in confirmed disability progression (CDP) endpoints • Few CDP events in both arms – hard to show statistical significance • Trial population had low baseline EDSS scores and ~70% were treatment naïve – low likelihood of disability progression • Other treatments also have not shown statistical significance against active comparators for CDP • Other outcomes important – ozanimod improves 'no evidence for disease activity' (NEDA), relapse rates, brain lesions versus active comparator
Stakeholder response to ACD	• Trial participants had mild disease course and trial had short duration – may explain CDP results • Would expect significant effect on CDP over longer period

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[a] In RADIANCE part B, SUNBEAM and pooled analysis; pooled analysis used 12-month data from trials'
[b]Confirmed disability progression (CDP) at 3 or 6 months.

Company's network meta-analysis (NMA)

Company has not accounted for between-study or between-treatment variability

Background	• Company NMA modelled annualised relapse rate, CDP-3M, CDP-6M, treatment discontinuation, (serious) adverse events • CDP-6M not available for all comparators so company also analysed CDP-3M and -6M combined in a single model • Assumed hazard ratios for CDP-6M between treatments proportional to hazard ratios for CDP-3M between treatments • ERG advised caution when drawing conclusions from the CDP-6M combined analysis
ACD committee conclusions	• *"Company's combined CDP-6M hazard ratios, when these are used, should be from an NMA that accounts for between-study or between-treatment variability, or both"* • *"The committee preferred the CDP-6M NMA estimated from the trial data directly, rather than the combined CDP-6M NMA that was estimated from the CDP-3M data"*
Company response to ACD	• N/A: no comment on these issues, no updated analyses provided
Stakeholder response to ACD (Novartis)	• Inappropriate to infer CDP-6M result from CDP-3M result

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CDP-6M, confirmed disability progression at 6 months; NMA, network meta-analysis.

Company's NMA: results versus ozanimod

	ARR, Rate ratio	CDP-3M, HR	CDP-6M, HR	CDP-6M combined HR [a]	Discontinuation, HR
Use in model	**Base case**	**Scenario**	**No**	**Base case**	**Base case**
Placebo	**0.5 (0.4, 0.6)**	**********	**********	**********	**********
Interferons					
Beta-1a, 30µg	**0.6 (0.5, 0.7)**	**********	**********	**********	**********
Beta-1a, 22µg	**0.7 (0.5, 0.9)**	**********	–	**********	**********
Beta-1a, 44 µg	**0.7 (0.6, 0.9)**	**********	**********	**********	**********
★ **Beta-1b, 250µg**	**0.7 (0.6, 0.9)**	**********	**********	**********	**********
Others					
DMF	0.9 (0.7, 1.1)	**********	**********	**********	**********
GA 20 mg	**0.7 (0.6, 0.9)**	**********	**********	**********	**********
GA 40 mg[b]	**0.7 (0.6, 0.9)**	–	–	**********	**********
Ocrelizumab[c]	**1.3 (1.0, 1.7)**	**********	**********	**********	**********
Peg-IFN β-1a	0.7 (0.6, 1.01)	**********	–	**********	**********
Teriflunomide	**0.7 (0.6, 0.9)**	**********	**********	**********	**********

★ **Interferon beta-1a 30 µg = trial comparator**

Data are hazard ratios (HRs) (95% credible intervals). Statistically significant results in bold. In favour of ozanimod highlighted green, in favour of comparator highlighted red;

DMF, dimethyl fumarate; GA, glatiramer acetate; [a] Assumes HR of CDP-6M between treatment arms proportional to HR of CDP-3M – conducted so CDP-6M relative efficacy can be estimated for treatments with no CDP-6M data. [b] ERG consider GA 40 mg could be excluded because no CDP-3M or -6M data available (suspect data reported as being CDP-3M from 1 study were actually CDP-12M); [c] Included in appendix to company submission.

Modelling disability progression (1)

Committee: not appropriate for company to use interferon beta-1a hazard ratio to model ozanimod

Background	• Company set ozanimod's CDP-6M hazard ratio equal to the CDP-6M hazard ratio for interferon beta-1a in its model • Company considered this conservative assumption – implausible interferon beta-1a better than ozanimod for disability progression
ACD committee conclusions	• *"the committee understood that the ozanimod trials were of high quality"* • *"ozanimod's disability progression hazard ratio from the NMA should be used, rather than the interferon beta-1a hazard ratio"*
Company response to ACD	• CDP inadequate measure for assessing ozanimod benefits • Used same model as previous appraisals – based on CDP • No significant difference between ozanimod and other treatments in CDP NMA – only significant differences should be modelled (next slide) • Clinical input particularly important – clinical experts at 1st meeting "*thought it unlikely that ozanimod would be worse than interferon beta-1a for CDP outcomes*"

NICE

CDP-6M, confirmed disability progression at 6 months; NMA, network meta-analysis.

Modelling disability progression (2)

Company: non-statistically significant differences should not be modelled

Company response to ACD	ERG response to company
• Highlights ERG preferred analysis from original report (January 2020) "*if clinical effectiveness results are not statistically significantly different, then a difference in effect should not be modelled.*"	• Views have changed • Overlapping / wide confidence intervals not sufficient to conclude no difference in effectiveness between treatments

• Other appraisals (TA303, TA320, TA527 and TA624) concluded treatments evaluated in NMAs were similar in absence of non-inferiority evidence [a]
• Should assume ozanimod similar to oral comparators – only consider cost
	• Insufficient evidence to conclude ozanimod and comparators similar
	• Different mechanism of action to relevant first-line comparators
	• Ozanimod not statistically significantly superior to:
	  • DMF for ARR (its main comparator)
	  • any comparator for CDP-6M
	• Insufficient evidence that ozanimod non-inferior to DMF or teriflunomide for CDP-6M

- ***Should non-statistically significant differences between treatments be modelled?***
- ***Is no statistical difference in the NMA sufficient to conclude treatments are similar?***

[a]N.B. In other appraisals quoted by the company, cost–utility analyses were performed modelling all differences between treatments (whether or not statistically significant). Interventions that were recommended were found to be a cost-effective use of NHS resources.

ARR, annualised relapse rate; CDP-6M, confirmed disability progression at 6 months; DMF, dimethyl fumarate; NMA, network meta-analysis.

Economic model

Treatment waning

ACD committee conclusions	• *The company's model is generally appropriate and aligns with previous models in the disease area* • *The company incorporated a treatment waning effect for all treatments* • *The company's model was generally appropriate and in line with previous models in the disease area.*
Stakeholder response to ACD (Novartis)	• This statement ("aligns with…") is inaccurate with respect to waning • Committee has not include waning preference in all previous appraisals – not aligned to TA533 (Ocrelizumab, where all-cause treatment discontinuation was considered a proxy for any waning) • Could bias the ICERs in favour of ozanimod and against all other treatments
Company	• N/A: no comment on these issues

NICE

ICER, incremental cost-effectiveness ratio.

Innovation and equality: recap

Company considers ozanimod innovative

- Addresses unmet need for more options
- Key innovations relate to mechanism of action and safety
- Modulator of the S1P1R pathway – distinct cardiac safety profile compared with other S1P modulators
- Consistent safety profile
- Once daily oral tablet, allowing self-administration at home and minimal disturbance to daily life compared to injectable therapies

Committee's conclusions:

- No evidence to suggest additional benefits not adequately captured by the quality-adjusted life year
- No equality or social value judgement issues identified

NICE S1P, sphingosine 1-phosphate.

Cost-effectiveness results

No new evidence provided by company at consultation

ACD conclusion: Cost-effectiveness estimates for ozanimod outside what NICE normally considers an acceptable use of NHS resources

Committee would have preferred to see a cost–utility analysis that:	Scenario available with preference included?
Use ozanimod's CDP-6M hazard ratio from the NMA, rather than setting ozanimod as equivalent to interferon beta-1a	• **Yes: NICE technical team exploratory scenario** • **Calculated by ERG for ACM1**
Use trials' CDP-6M hazard ratios when possible, and only use the combined CDP-6M hazard ratios for treatments that do not have CDP-6M data available	• **Not provided by company** • **ERG: considers scenario cannot be undertaken[a]**
If combined CDP-6M hazard ratios used, obtain from an NMA that accounts for between-study and/or between-treatment variability	• **Not provided by company** • **Company's NMA does not account for between-study / treatment variability**
Includes comparisons with second-line treatments (alemtuzumab, cladribine, fingolimod and ocrelizumab) if ozanimod is positioned for second-line treatment	• **Yes: Calculated by ERG for ACM2** • **Only models statistically significant differences**

[a] Because 'CDP-6M' and 'CDP-6M combined' hazard ratios have been generated using different NMA models that are based on different input data. ACM, appraisal committee meeting; CDP-6M, confirmed disability progression at 6 months; NMA, network meta-analysis.

Cost-effectiveness results

All incremental cost-effectiveness ratios are reported in PART 2 slides because they include confidential patient access scheme discounts