NICE National Institute for Health and Care Excellence

Version for public
Contains no ACIC data

Ozanimod for treating relapsing–remitting multiple sclerosis [ID1294]

Lead team presentation

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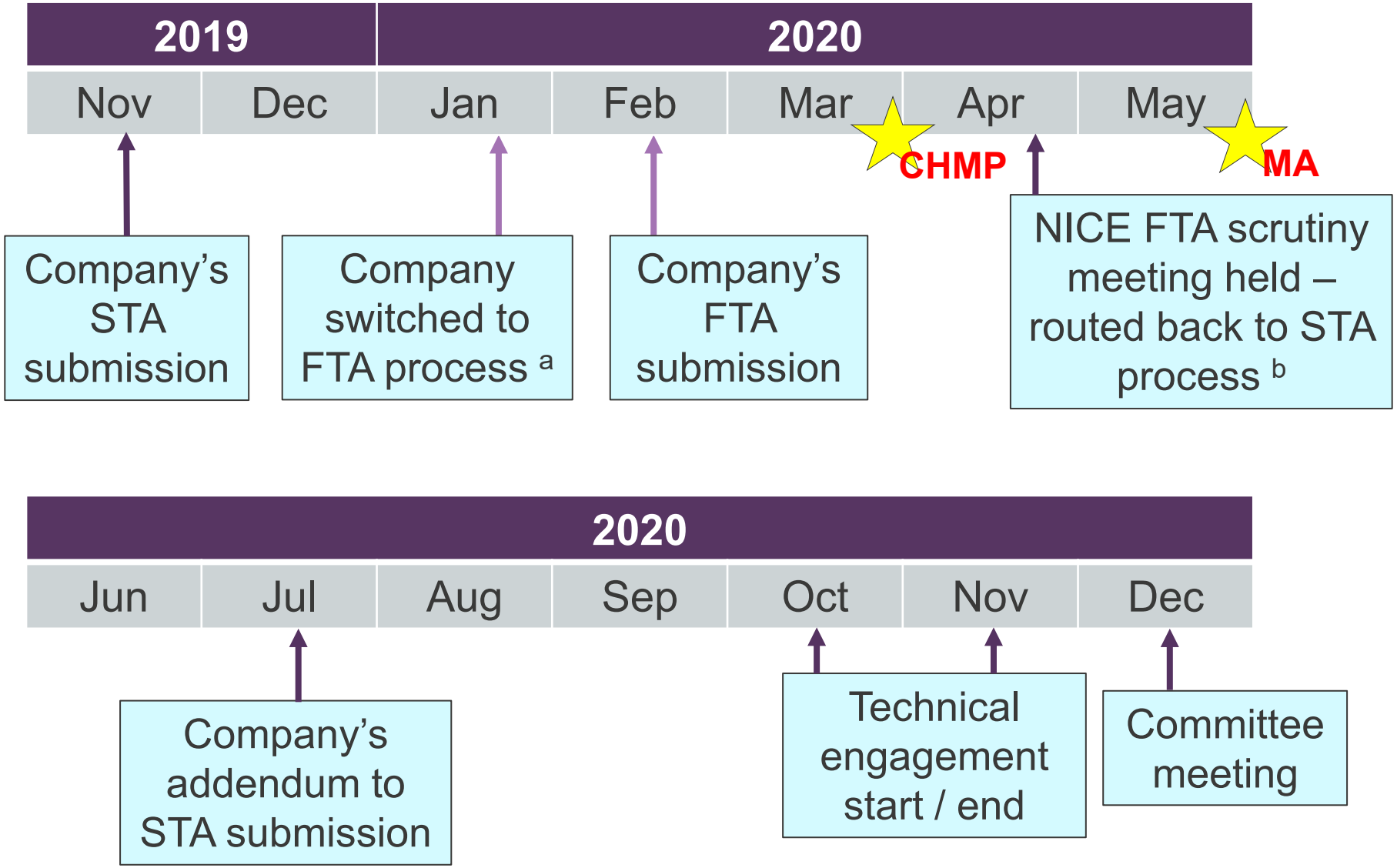
Key issues

- 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?
- At what position(s) in the pathway will ozanimod be used – 1st line, 2nd, or both?
  - If relevant, has enough evidence been presented to consider ozanimod at multiple lines of therapy?
- Are RADIANCE Part B and SUNBEAM trials generalisable to NHS practice?
- 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?
- How should treatment discontinuation be applied in the model?

Background

Appraisal timeline



[a] Cost comparison case; [b] Not suitable for lower scrutiny FTA process so original STA submission / model to be used. CHMP, Committee for Medicinal Products Human Use; FTA, fast track appraisal; MA, marketing authorisation; STA, single technology appraisal.

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

Early treatment, with range of options

- Early proactive treatment essential to prevent future disability
- Essential that there is range of treatment options – “one size does not fit all”
- “There should always be choice, an option to change your mind and confidence in alternative treatments should your disease course change”

Ozanimod benefits form oral administration and acceptable safety profile

- Oral route of administration means better compliance than injectables, can be taken at home, less pressure on NHS
- Seems to have acceptable safety profile
  - “Do not underestimate the tough decision patients have to make when weighing up the risk profile of some of the medicines for MS”

Clinical perspectives

- Aim of treatment is to reduce relapses and risk of long term disability
- Ozanimod will offer another option as 1st line oral therapy
  - "Not a step change, but valuable additional therapy"
  - Likely used similarly to dimethyl fumarate and teriflunomide
- Current S1P inhibitor (fingolimod) only available 2nd line and requires hospital admission to monitor for bradyarrhythmias – adds to patient inconvenience and healthcare costs
- Ozanimod is intended as 1st line therapy offering a potentially more effective oral therapy to patients with earlier disease
- Overall safety profile appears to be favourable
- Oral treatment usually more acceptable to patients than injectables, less resource-intensive than the infusion treatments, and low monitoring burden

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

Decision problem (DP) (1)

	Final scope	Company submission (CS)	Company rationale if CS different from DP
P	People with RRMS	**Nov 19:** As per scope **Jul 20:** People with RRMS: 1) With active disease as defined by clinical or imaging features 2) Suitable for or requesting an oral treatment	1) To reflect licence 2) To reflect where company expect will be used in NHS
C	For people with active RRMS: [a] • Alemtuzumab[b] • Beta-interferons • Dimethyl fumarate • Glatiramer acetate • Teriflunomide • Ocrelizumab • Peginterferon β-1a	**Nov 19:** All comparators in scope relevant apart from alemtuzumab and ocrelizumab[c] **Jul 20:** • Dimethyl fumarate • Teriflunomide	Alemtuzumab limited to highly active RRMS, and ocrelizumab recommended for use after alemtuzumab Injectable treatments not relevant comparators (also see 'population')

[a] Only drugs for active RRMS from scope listed. Other comparators for highly active and rapidly evolving severe RRMS were in scope (cladribine, fingolimod, natalizumab); [b] Alemtuzumab marketing authorisation restricted to highly active RRMS since scope issued; [c] Ocrelizumab not comparator but comparison was provided in appendix.

Decision problem (DP) (2)

	Final scope	Company submission (CS)	Rationale if CS different from DP
Outcomes	• Relapse rate • Severity of relapse • Disability (e.g. EDSS) • Symptoms of MS (e.g. fatigue, cognition and visual disturbance) • Freedom from disease activity (e.g. lesions on MRI scans) • Mortality • Adverse effects of treatment • Health-related quality of life	• Relapse rate • Disability • Freedom from disease activity • Mortality • Adverse effects of treatment • Health-related quality of life • Brain atrophy (brain volume) • Radiological (MRI) measurements of disease activity (T2 and Gd-E T1 brain lesion)	RADIANCE and SUNBEAM trials of ozanimod did not explore severity of relapse and symptoms of MS

NHS England treatment algorithm and company 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]*

[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.

NHS England treatment algorithm and company positioning[a]

RRMS: 1 relapse in last 2 years & radiological activity	RRMS: 2 significant relapses in last 2 years	Rapidly evolving severe MS (RES)

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• *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

[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.

NHS England treatment algorithm and company positioning[a]

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• *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.

Positioning: Will ozanimod be used 1st and 2nd line?

Company: ozanimod may be used as 2nd line treatment

Company

- Original STA submission
  - Ozanimod likely used as first-line therapeutic
- Response to technical engagement
  - Ozanimod should only be used if a patient has failed or is unsuitable for infusion and injectables treatments
  - Positioned as 1st line therapy for people in whom infusion / injectable therapies not suitable because of administration issues or preference for oral treatments
  - Positioned as 2nd line therapy for people who have 'failed' (i.e. not responded to) one or more of the infusion / injectable therapies

- ***Would ozanimod be used as a 1st or 2nd line therapy? Or both?***
- ***If 2nd line is an option, is there sufficient evidence available to evaluate ozanimod at this position in the pathway?***

Population (1): Narrowed in company STA addendum

Only includes people 'suitable for or requesting oral treatment'

	Population	Notes
Marketing authorisation (May 2020)	• Adults with RRMS with active disease as defined by clinical or imaging features	• Does not exclude HA and RES RRMS, but company and ERG agree ozanimod not likely to be used in these populations
STA submission (Nov 2019)	• Adults with RRMS [a]	• Company described expected use in NHS: active RRMS, not HA and/or RES RRMS
FTA submission (Feb 2020)		
Addendum to STA submission (July 2020)	• Adults with active RRMS **who are suitable for or requesting an oral treatment**	• ERG unclear what is meant by 'suitable for or requesting an oral treatment' • Comparator in ozanimod key trials, interferon β-1a, not an oral treatment

[a] Submitted before marketing authorisation granted. FTA, fast track appraisal; HA, highly active; RES, rapidly evolving severe; STA, single technology appraisal.

Population (2): Stakeholder responses to TE

Unclear whether narrowing of population appropriate

Some stakeholders supportive of company's narrowing of population

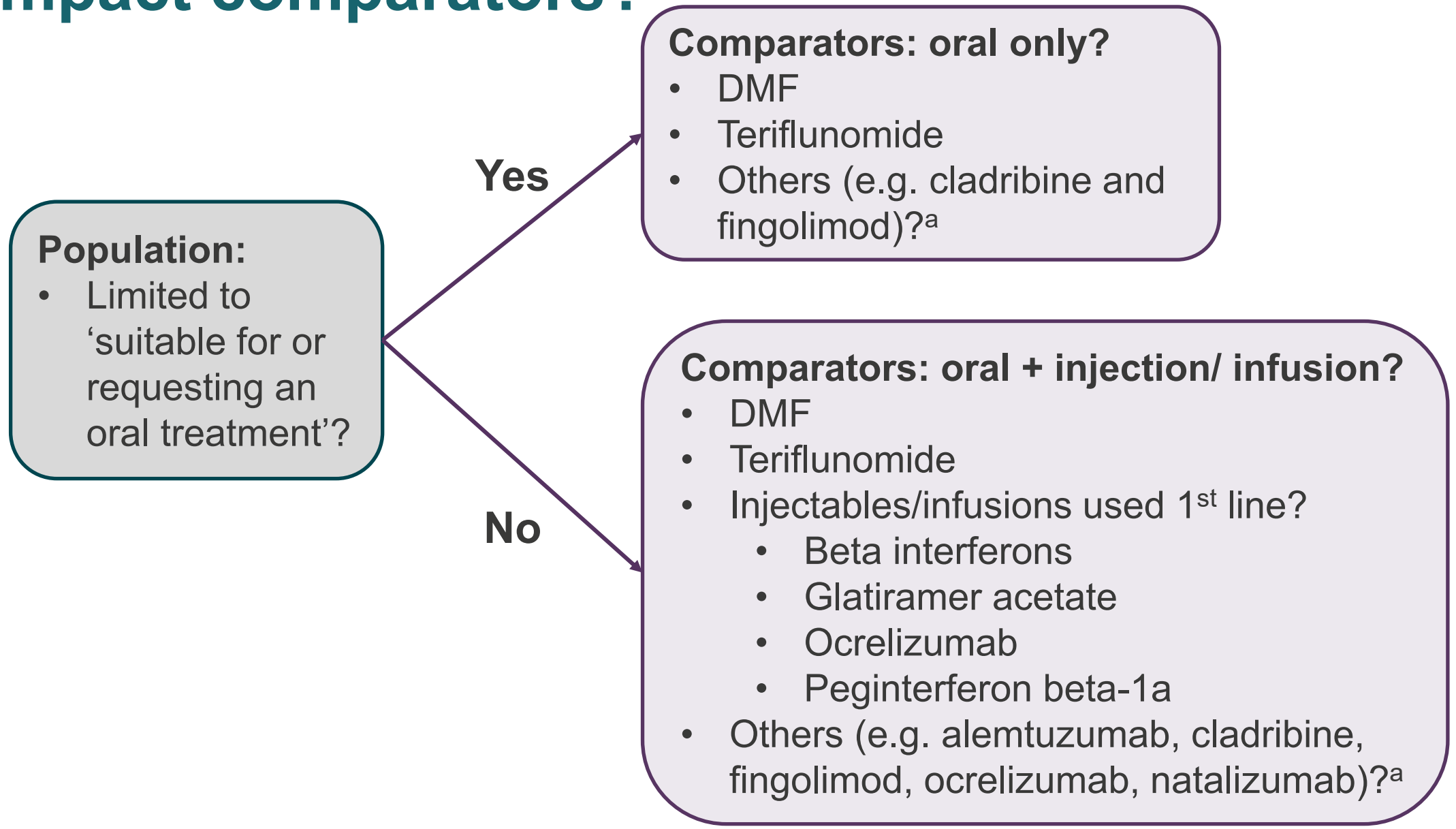
- Some people may have needle-phobia or manual dexterity, visual or cognitive problems – make injectable treatments unsuitable

Others concerned it may be too restrictive

- Not a meaningful subdivision of the population – "there is no clinical subgroup that would only be suitable for oral treatment"
- Could restrict future options – e.g. people who start with ozanimod but need to switch to another treatment taken by a different route of administration
- MS requires a suite of medicines to be available to suit people's different needs
- "Medicine choice is key and may change" – there are other factors that contribute to choice, e.g. risk profile

- ***Is narrowing of population to people 'suitable for or requesting oral treatment' appropriate? How would this population be defined clinically?***

Comparators (1): How does population impact comparators?



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

Comparators (2): Company and ERG disagree

Appropriate to limit comparators to oral treatments for 'active' RRMS?[a]

- Comparators in company's original STA submission: [b]
  - Beta-interferons
  - Dimethyl fumarate
  - Glatiramer acetate
  - Peginterferon beta-1a
  - Teriflunomide
- Comparators in company's STA addendum after narrowing of population to people 'suitable for or requesting an oral treatment':
  - Dimethyl fumarate
  - Teriflunomide
- ERG: all comparators in company's original submission, **and ocrelizumab**, should be comparators

- ***Is ocrelizumab a relevant comparator?***
- ***Are beta-interferons, glatiramer acetate, and peginterferon beta-1a comparators?***
- ***Are treatments used at 2nd line relevant comparators?***

[a] N.B. relates only to 'active' RRMS, and not highly active / rapidly evolving severe RRMS; [b] Ocrelizumab not comparator but comparison was provided in appendix.

Comparators (3): Stakeholder responses to TE

Agreement that DMF and teriflunomide not the only comparators

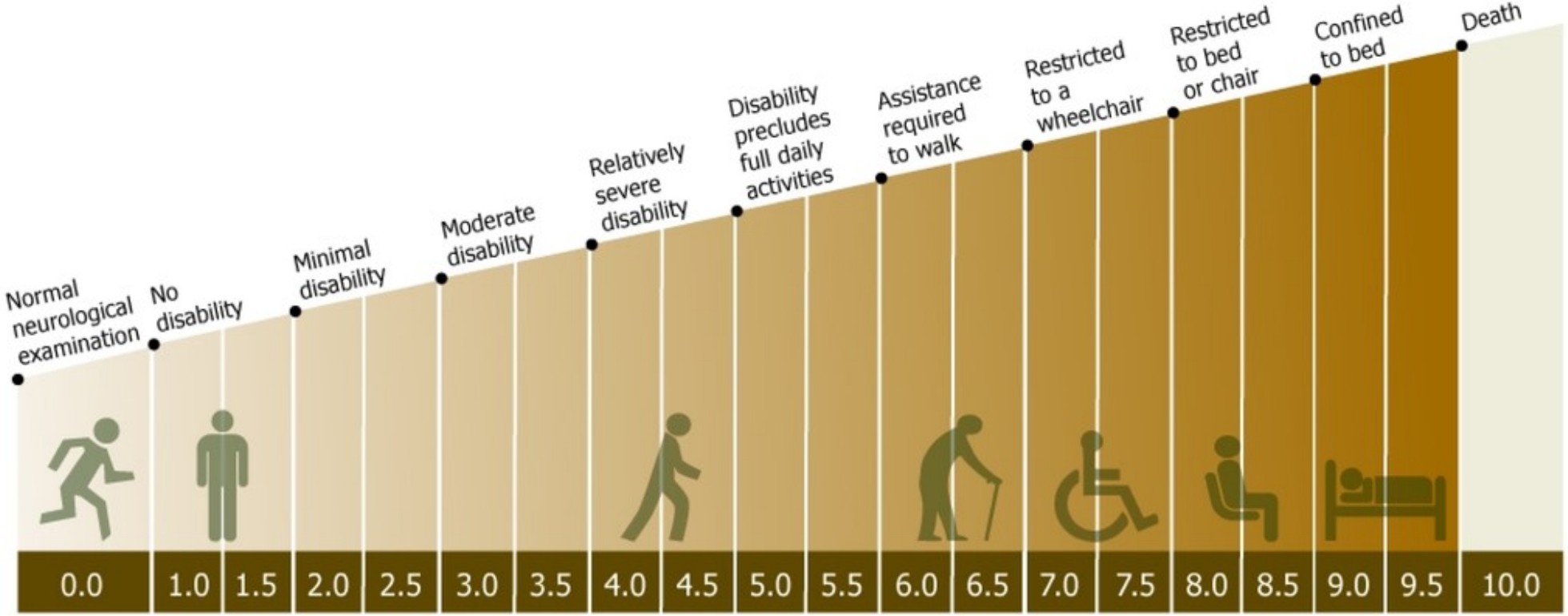
Stakeholders generally support widening group of comparators

- Ocrelizumab would be used in the same population as ozanimod:
  - licensed for active RRMS and NICE appraisal covers adults with active disease defined by clinical or imaging features
  - established therapy, now widely used at 1st and 2nd line
  - doctors are prescribing it in England and Wales
- All 1st line treatments should be relevant comparators
  - interferons, peginterferon beta-1a, glatiramer acetate, ocrelizumab all used 1st line in active RRMS in NHS clinical practice

Clinical effectiveness

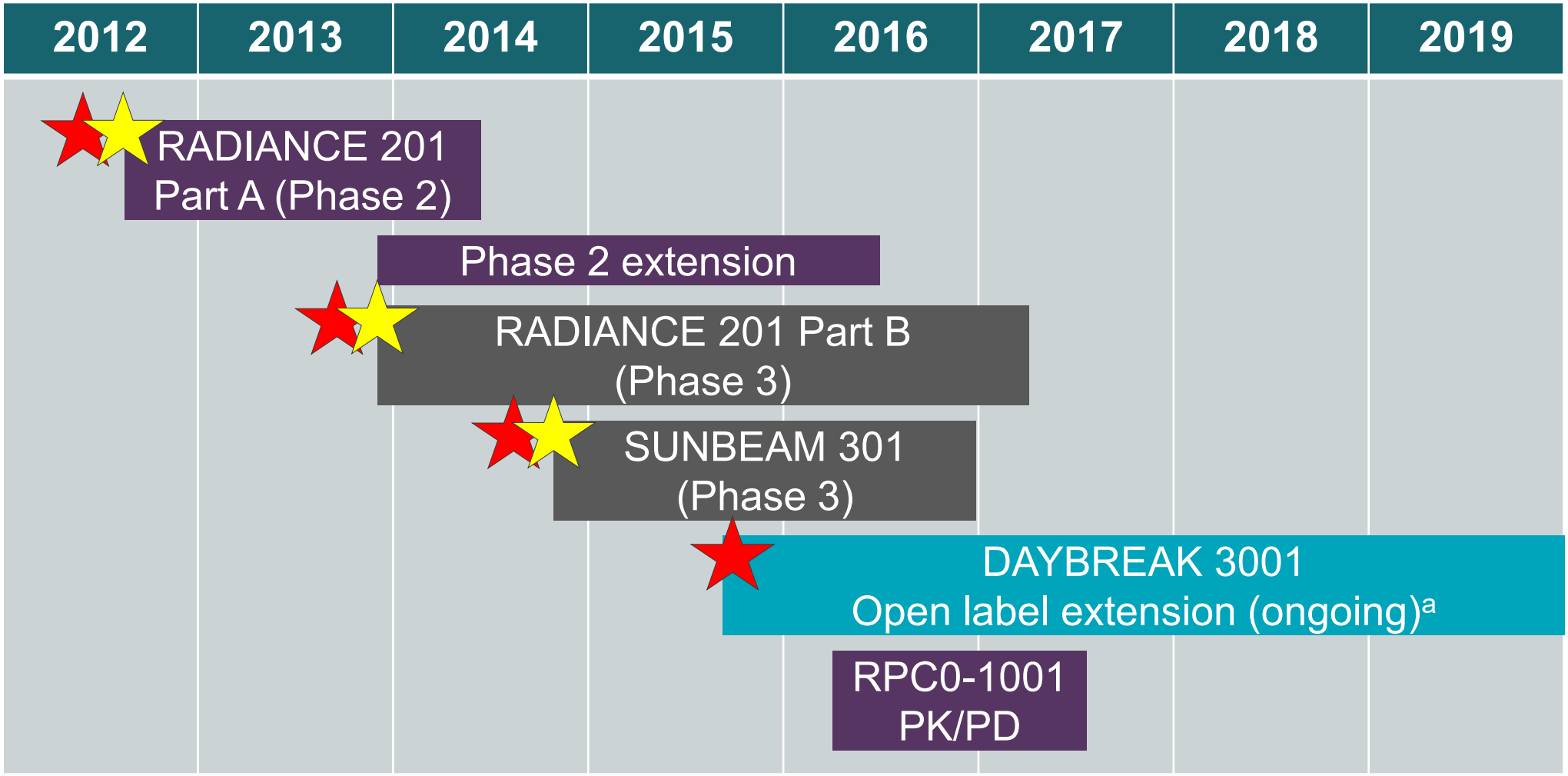
Definition of outcomes in trials

- 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 clinical trial programme in RMS



[a] People completing RADIANCE Part A extension, RADIANCE Part B, SUNBEAM, or PK/PD study were eligible for DAYBREAK. NMA, network meta-analysis; PK/PD, pharmacokinetics and pharmacodynamics; RMS, relapsing MS. Figure adapted from company submission, document B, Figure 3.

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

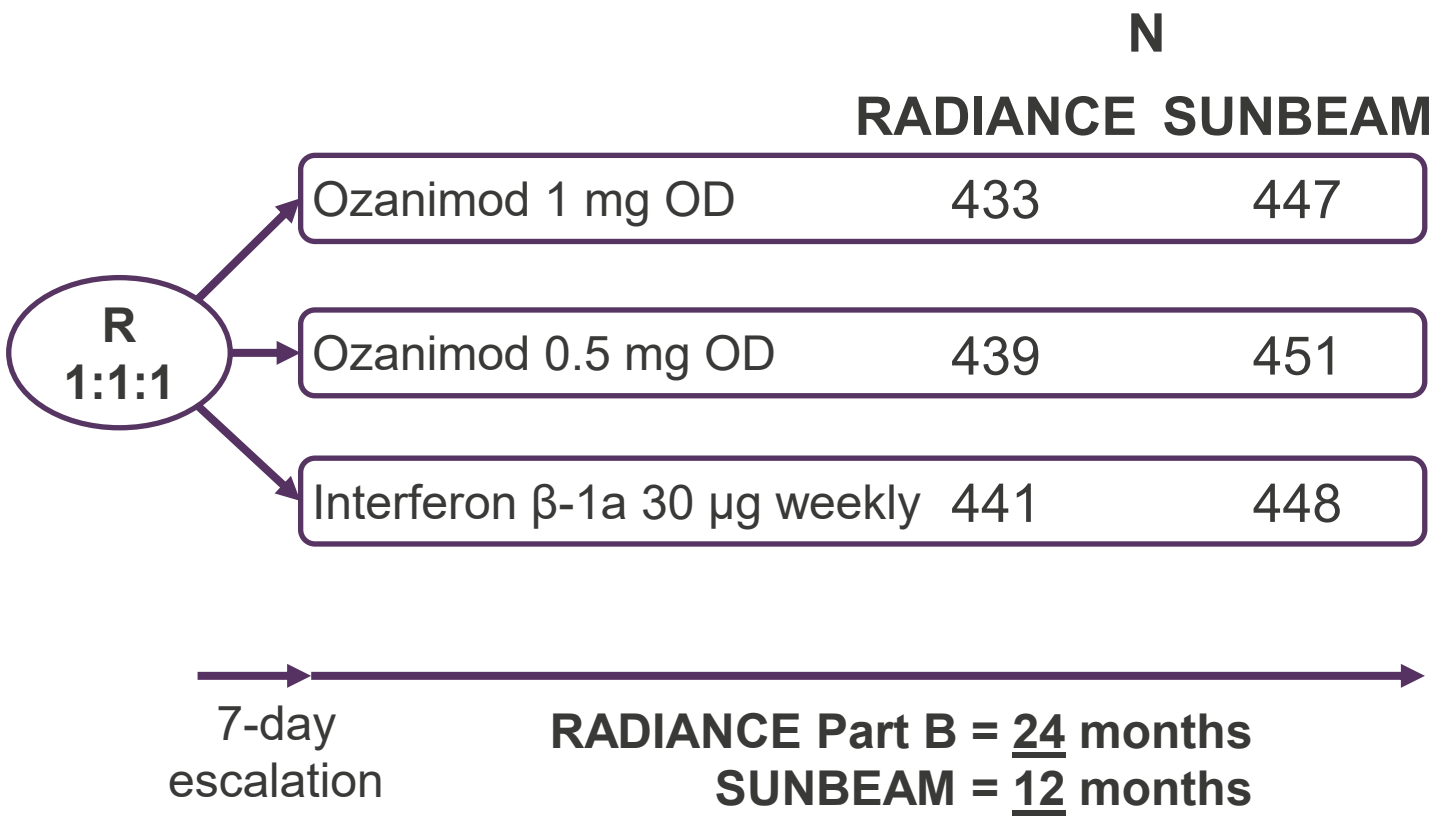
NICE

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

RADIANCE Part B and SUNBEAM: study designs

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

Trials had similar designs and outcomes, but different durations



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.

Baseline characteristics in Phase 3 trials

	RADIANCE Part B (24 months)		SUNBEAM (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)
Age, years	35 (9.1)	36 (8.9)	36 (9.1)	35 (9.2)
Female, n (%)	304 (68.9)	291 (67.2)	300 (67.0)	283 (63.3)
White, n (%)	432 (98.0)	428 (98.8)	447 (99.8)	446 (99.8)
Eastern Europe, n (%)	379 (85.9)	374 (86.4)	419 (93.5)	415 (92.8)
Rest of world, n (%)	62 (14.1)	59 (13.6)	29 (6.5)	32 (7.2)
EDSS score	2.5 (1.2)	2.6 (1.2)	2.6 (1.1)	2.6 (1.2)
No. of relapses in last year	1.3 (0.6)	1.3 (0.6)	1.3 (0.6)	1.3 (0.6)
No. with high disease activity,[a] n (%)	104 (23.6)	90 (20.8)	103 (23.0)	102 (22.8)

RADIANCE Part B and SUNBEAM pooled data		
	IFN β-1a 30 µg	Ozanimod 1 mg
No prior use of any DMT	XXXXXXX	XXXXXXX
Prior treatment with a DMT	XXXXXXX	XXXXXXX

Source: Company document B, Table 6 and ERG report, Table 6. Data are mean (standard deviation) unless otherwise stated. DMT, disease-modifying treatment; EDSS, Expanded Disability Status Scale; IFN, interferon.

[a] Includes more active types of RRMS comparable to highly active and rapidly evolving severe RRMS.

Generalisability of trials

ERG and stakeholders satisfied trials broadly generalisable

ERG

- Clinical advice: baseline characteristics from RADIANCE Part B and SUNBEAM trials reflective of NHS practice
- Some characteristics of trials may limit generalisability:
  - ~25% of people had HA/RES RRMS – not aligned with ozanimod expected use
  - ~30% of people received prior DMT – unclear whether aligned with positioning
  - People with cardiovascular conditions excluded, but unclear if they would receive ozanimod in clinical practice
  - High proportion of white and Eastern European people – NHS more diverse

Stakeholder responses to technical engagement

- Baseline characteristics in trials broadly comparable to people in NHS practice
- Majority white and from Eastern Europe, but this population likely to have similar course of RRMS compared to people in NHS practice

DMT, disease-modifying therapy; HA, highly active; RES, rapidly evolving severe.

Key results from Phase 3 trials (1)

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)	XXXX XXXXXXX	XXXX XXXXXXX
Rate ratio (95% CI)	**0.62 (0.51, 0.77)**		**0.52 (0.41, 0.66)**		XXXXXXX	
Key endpoints associated with disability (secondary outcomes)						
CDP at 3 months, n (%)	50 (11.3)	54 (12.5)	XXXXXXX	XXXXXXX	69 (7.8)	67 (7.6)
HR vs IFN (95% CI)	1.05 (0.71, 1.54)		XXXXXXX		0.95 (0.68, 1.33)	
CDP at 6 months, n (%)	29 (6.6)	42 (9.7)	XXXXXXX	XXXXXXX	36 (4.0)	51 (5.8)
HR vs IFN (95% CI)	1.44 (0.89, 2.31)		XXXXXXX		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.

Key results from Phase 3 trials (2)

Company: CDP benefits of ozanimod underestimated

Company

- RADIANCE part B + SUNBEAM trials: rates of CDP low in each treatment arm
  - Resulted in high variability and wide statistical range
  - Reduced ability to detect a meaningful difference
- CDP should be considered within the context of other outcomes (e.g. ARR and MRI[a])
- Implausible interferon beta-1a could have lower CDP rate compared with ozanimod

[a] MRI results available as back up slide.

ARR, annualised relapse rate; CDP, confirmed disability progression; MRI, magnetic resonance imaging.

Safety profile in Phase 3 trials

Company and ERG agree ozanimod has favourable safety profile

Company

- Ozanimod demonstrated consistent safety profile across RADIANCE Part B and SUNBEAM
  - Lower incidence of adverse events (AEs) compared with interferon beta-1a
  - Incidence of serious treatment-emergent AEs (TEAEs) infrequent with ozanimod and similar to interferon beta-1a
  - Incidence of TEAEs and AEs of special interest (AESIs)[a] also similar
  - No clinically meaningful cardiac AEs or findings considered related to ozanimod reported during dose escalation

ERG

- Agrees with company that ozanimod demonstrated favourable safety profile
- Very little difference between ozanimod and interferon beta-1a for most AEs
  - Influenza-like illness more common with interferon beta-1a than ozanimod

[a] Safety risks associated with administration of S1P1R modulators (such as ozanimod and fingolimod), e.g. infections, malignancies, bradycardia and heart conduction abnormalities, pulmonary function abnormalities, ophthalmic abnormalities, hepatic abnormalities and dermatological abnormalities.

Indirect treatment comparison (1)

ERG generally considers company's methods appropriate

Company

- Bayesian network meta analysis to establish relative effectiveness versus comparators
- Outcomes: ARR, CDP-3M, CDP-6M, CDP-6M combined (see below), discontinuation, AEs, SAEs
- CDP-6M committee's preferred definition of disability progression in previous appraisals but older studies may not report this outcome
  - Company analysed CDP-3M and -6M combined within single model so CDP-6M can be estimated for treatments with no data

ERG

- Company's approach generally appropriate and any heterogeneity / inconsistency present does not have important impact on results
  - Some outstanding areas of uncertainty and variability remain [a]
- Company's combined CDP-6M analysis requires assumption that HR of CDP-6M between treatments is proportional to the hazard ratio of CDP-3M – assumption for ozanimod may have been violated
- Potential data extraction error for glatiramer acetate 40 mg CDP-3M data

[a] Trial duration, dates trials conducted, prior treatment and disease severity. AEs, adverse events; ARR, annualised relapse rate; CDP-3M/6M, confirmed disability progression at 3/6 months; HR, hazard ratio; SAEs, serious AEs.

Indirect treatment comparison (2)

Choice of full or reduced NMA depends on comparators

Company

- Submitted 2 NMAs (results on next slides):
  - Original STA submission (Nov 2019): 'Full' NMA, including data from trials of all comparators in original submission
  - FTA submission (Feb 2020): 'Reduced' NMA, including data from trials of ozanimod, DMF and teriflunomide only
- Used 'full' NMA even when only DMF and teriflunomide considered comparators
- Impact of selecting one NMA in favour of another is very small

ERG

- If injectables / infusions are comparators use 'full' NMA
- If only teriflunomide and DMF are comparators use reduced NMA – including data from other comparators introduces uncertainty

N.B. Company also conducted matching-adjusted indirect comparison (MAIC) to validate results from NMA and support claim that ozanimod is similar to DMF or teriflunomide. Results not shown because company and ERG in agreement that MAIC assumptions violated.

Company's full 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)**	XXXXXXXXX	XXXXXXXXX	XXXXXXXXX	XXXXXXXXX
Glatiramer acetate					
20 mg	**0.7 (0.6, 0.9)**	XXXXXXXXX	XXXXXXXXX	XXXXXXXXX	XXXXXXXXX
40 mg[b]	**0.7 (0.6, 0.9)**	–	–	XXXXXXXXX	XXXXXXXXX
Interferons					
★ **Beta-1a, 30µg**	**0.6 (0.5, 0.7)**	XXXXXXXXX	XXXXXXXXX	XXXXXXXX	XXXXXXXXX
Beta-1a, 22µg	**0.7 (0.5, 0.9)**	XXXXXXXXX	XXXXXXXXX	XXXXXXXX	XXXXXXXXX
Beta-1a, 44 µg	**0.7 (0.6, 0.9)**	XXXXXXXXX	XXXXXXXXX	XXXXXXXXX	XXXXXXXXX
Beta-1b, 250µg	**0.7 (0.6, 0.9)**	XXXXXXXXX	XXXXXXXXX	XXXXXXXXX	XXXXXXXXX
Others					
DMF	0.9 (0.7, 1.1)	XXXXXXXXX	XXXXXXXXX	XXXXXXXXX	XXXXXXXXX
Ocrelizumab[c]	**1.3 (1.0, 1.7)**	XXXXXXXXX	XXXXXXXX	XXXXXXXXX	XXXXXXXXX
Peg-IFN β-1a	0.7 (0.6, 1.01)	XXXXXXXXX	–	XXXXXXXXX	XXXXXXXXX
Teriflunomide	**0.7 (0.6, 0.9)**	XXXXXXXXX	XXXXXXXXX	XXXXXXXXX	XXXXXXXXX

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

○ ***Is ozanimod similar to comparators in terms of key outcomes (e.g. CDP-6M)?***

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; [a] Assumes HR of CDP-6M between treatment arms proportional to HR of CDP-3M – conducted so estimates of CDP-6M relative efficacy can be generated 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 reduced NMA: results versus ozanimod

Little difference in results between the 2 NMAs

	NMA network	ARR, Rate ratio (95% CrI)	CDP-3M, Annualised HR (95% CrI)	CDP-6M, Annualised HR (95% CrI)	Discontinuation Annualised HR (95% CrI)
Used in model		**Base case**	**Scenario**	**Base case**	**Base case**
Placebo	Original	XXXX XXXXXXXXXX	XXXX XXXXXXXXXX	XXXX XXXXXXXXX	XXXX XXXXXXXXX
	Reduced	**0.47 (0.21, 0.98)**	0.75 (0.45, 1.24)	0.97 (0.57, 1.64)	0.27 (0.01, 2.33)
IFN beta-1a 30µg (Avonex)	Original	XXXX XXXXXXXXX	XXXX XXXXXXXXX	XXXX XXXXXXXXX	XXXX XXXXXXXXX
	Reduced	**0.57 (0.48, 0.66)**	0.99 (0.70, 1.38)	1.46 (0.96, 2.26)	**0.73 (0.54, 0.98)**
DMF	Original	XXXX XXXXXXXXX	XXXX XXXXXXXXX	XXXX XXXXXXXXX	XXXX XXXXXXXXX
	Reduced	0.84 (0.36, 1.78)	1.20 (0.68, 2.12)	1.41 (0.77, 2.58)	0.28 (0.01, 2.44)
Teriflunomide	Original	XXXX XXXXXXXXX	XXXX XXXXXXXXX	XXXX XXXXXXXXX	XXXX XXXXXXXXX
	Reduced	0.71 (0.31, 1.48)	1.02 (0.58, 1.77)	1.19 (0.65, 2.16)	0.27 (0.01, 2.35)

Statistically significant results in bold. In favour of ozanimod highlighted green (N.B. no results statistically significantly in favour of comparator).

Cost effectiveness

Cost minimisation or cost utility analysis (1)

NICE reference case stipulates cost–utility analysis

NICE Guide to the methods of technology appraisal (2013), section 5.1.11

- "cost-effectiveness (specifically cost–utility) analysis is the preferred form of economic evaluation. This seeks to establish whether differences in expected costs between options can be justified in terms of changes in expected health effects"

	Measurement of costs	Measurement of benefits	Results
Cost minimisation	Money (£)	Benefits assumed to be the same	Difference in costs between interventions – pick cheapest
Cost utility	Money (£)	Quality-adjusted life-years (QALYs)	Incremental cost-effectiveness ratio (£/QALY) – apply decision rules

Cost minimisation or cost utility analysis (2)

Company previously submitted FTA, but NICE re-routed to STA

NICE Addendum to the Guide to the methods of technology appraisal

- "A cost comparison[a] case can be made if a health technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication"
- Suitable topics can enter the fast track appraisal (FTA) process – shorter timeline than STA
- Cost minimisation (rather than cost–utility) analysis can be submitted

Background to FTA process for ozanimod

- Company originally submitted via FTA process and made a cost minimisation case
- ERG critiqued the company's FTA submission
- NICE overall judgement: FTA high risk because unclear whether ozanimod offers 'similar or greater benefits' compared with DMF and teriflunomide
- Higher level of scrutiny required – re-routed to STA process

NICE

[a] Note 'cost comparison' terminology used by NICE – same meaning as 'cost minimisation'.

Cost minimisation or cost utility analysis (3)

Company and ERG disagree on whether cost comparison suitable

Company: STA addendum, July 2020

- **Cost minimisation analysis comparing ozanimod with teriflunomide and DMF should be used for this appraisal**
  - 3 treatments have similar efficacy, supported by lack of statistically significant differences for CDP-3M and CDP-6M in NMA
- Conducted cost-minimisation analysis, including the following:
  - differences in drug list prices over 1 year
  - differences in monitoring costs over 1 year
- No administration costs included because all included treatments are oral

ERG critique of company's STA addendum

- Insufficient evidence that ozanimod similar to DMF or teriflunomide
- Showing ozanimod is not statistically superior to DMF or teriflunomide not the same as showing there to be no difference, or that they are 'comparable'
- N.B. ERG critique of company's cost-minimisation – all methods appropriate

CDP-3M / 6M; confirmed disability progression at 3 months / 6 months; DMF, dimethyl fumarate; NMA, network meta-analysis.

Company's cost utility model structure

From company's original STA submission, Nov 2019

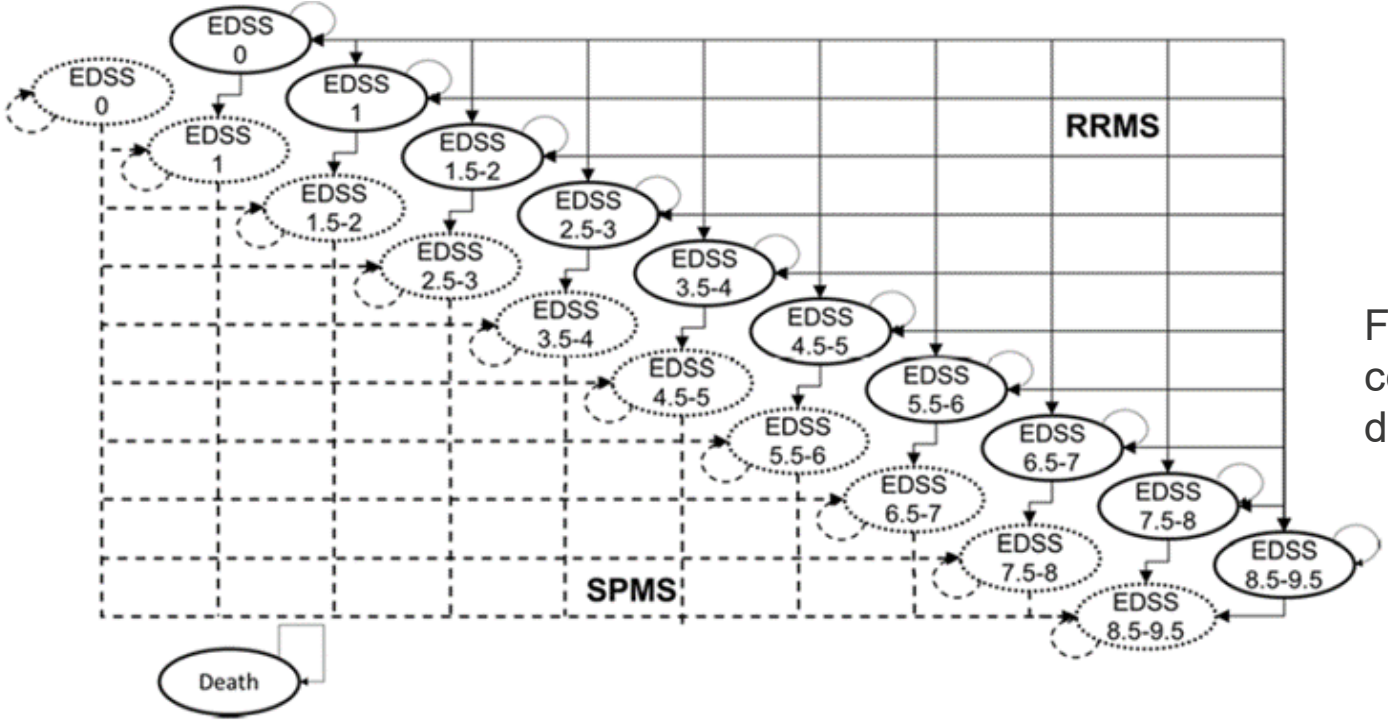
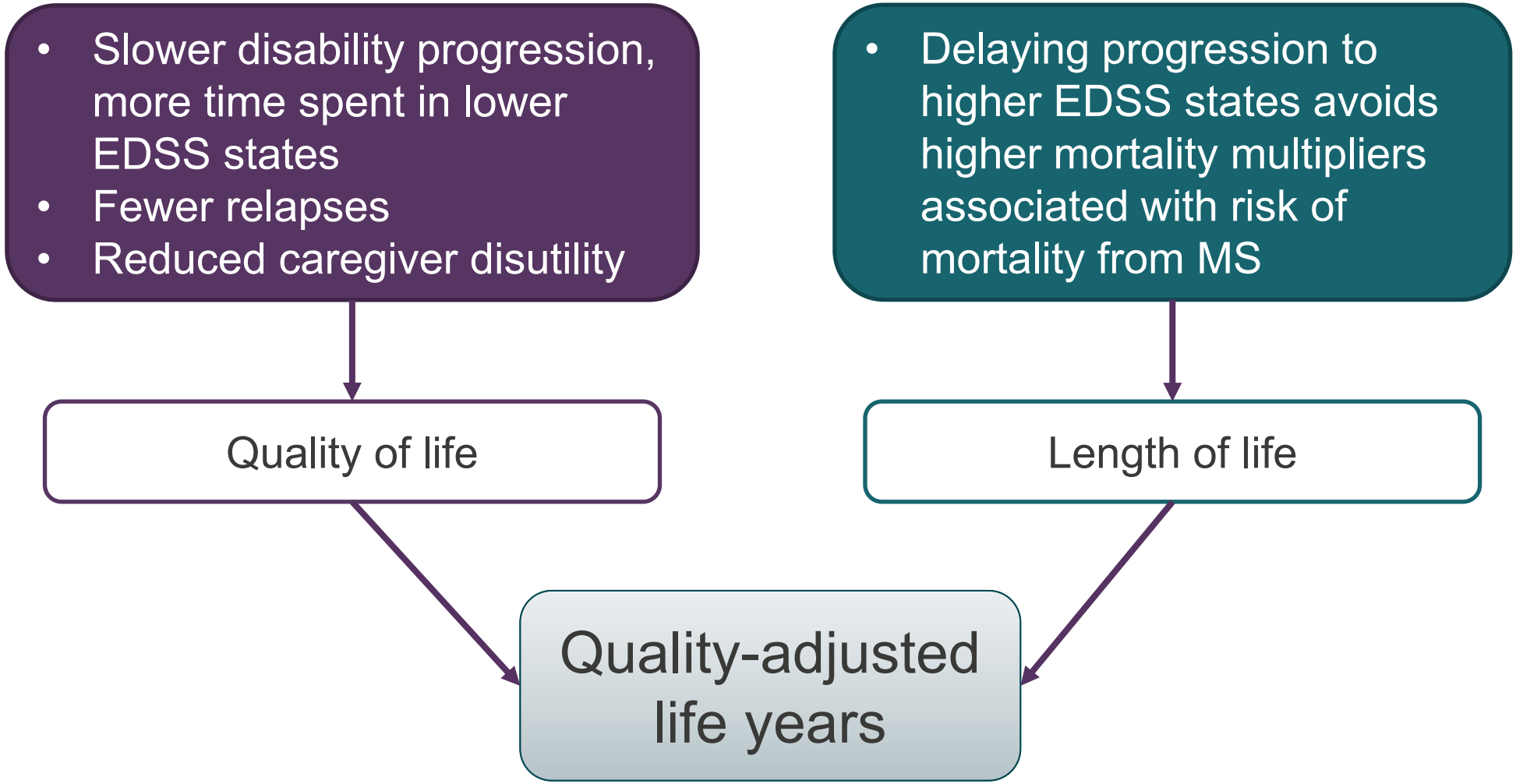


Figure source: company's submission document B, Figure 8

- 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



Company's key model assumptions (1)

	Assumption	Company's justification
Natural history – disability progression	Disability progression modelled assuming a constant transition probability matrix over time	Consistency with other appraisals + shown to accurately predict EDSS status over 10 years
Natural history – relapse	Relapses based on EDSS state	Consistency with other appraisals
Effectiveness of interventions	CDP and relapses modelled independently	Consistency with other appraisals. Some treatments may be more effective in reducing relapses than slowing disease progression
Mortality	Treatment has indirect effect on the risk of mortality	Using EDSS-dependent standardised mortality ratios assumes an indirect effect of treatment on mortality (by delaying progression to higher EDSS states)

Adapted from company's submission document B, Tables 57 and 58.
CDP, confirmed disability progression; DMT, disease-modifying treatment; EDSS, Expanded Disability Status Scale.

Company's key model assumptions (2)

	Assumption	Company's justification
Discontinuation of DMT or cessation of treatment effect	People who discontinue treatment then follow natural history progression of disease	Consistency with other appraisals
	People discontinue treatment after transitioning to SPMS, and after progressing to EDSS ≥7	Lack of data on the effects of DMT in people with EDSS ≥7.0
Treatment waning effect	In base case, all treatments 100% effective for 2 years, 75% effective from Years 3 to 5, 50% effective thereafter	Consistency with other appraisals
HRQoL	HRQoL source: ocrelizumab NICE submission TA533 with SPMS adjustment from Orme et al.	Patient characteristics of ocrelizumab trials used in TA533 similar to ozanimod Phase 3 trials

Adapted from company's submission document B, Tables 57 and 58.
CDP, confirmed disability progression; DMT, disease-modifying treatment; EDSS, Expanded Disability Status Scale; HRQoL, health-related quality of life; SPMS, secondary progressive MS.

Company: benefits of ozanimod underestimated

Affects CDP hazard ratio for ozanimod in company's NMA

Recap of company's CDP issues in clinical trials

- RADIANCE part B + SUNBEAM trials: rates of CDP low in each treatment arm
  - Resulted in high variability and wide statistical range
  - Reduced ability to detect a meaningful difference

Company: using CDP results from NMA underestimates ozanimod's benefits

- CDP should be considered within the context of other outcomes
- In RADIANCE Part B and SUNBEAM, ozanimod significantly better than interferon β-1a in terms of relapse rates, MRI endpoints[a] and other exploratory endpoints
- Implausible interferon β-1a could have lower CDP rate compared with ozanimod

In model (cost utility, Nov 2019), company set CDP-6M (combined[b]) HR for ozanimod equal to interferon β-1a 30 µg HR rather than using ozanimod's own HR, which was worse than interferon β-1a 30 µg

- ***Is it appropriate for the company to have set the CDP-6M HR for ozanimod equal to the CDP-6M HR for interferon β-1a 30 µg in the model?***

CDP, confirmed disability progression; HR, hazard ratio; MRI, magnetic resonance imaging. [a] Total number of new or enlarging T2 lesions, number of Gd-E brain lesions. [b] Assumes HR of CDP-6M between treatment arms proportional to HR of CDP-3M.

Modelling treatment discontinuation

Company: original submission [a]

- No treatment switching included in model
- Original approach to treatment discontinuation in model:
  - Rates of discontinuation for each treatment taken from NMA
  - Rates constant over entire model horizon

ERG [a]

- Clinical advice: if no switching allowed, people would only discontinue treatment if they were no longer benefitting, even if they still had relapses
- Should use trial treatment discontinuation rates where available, then assume everybody stays on treatment while they are benefitting

Company: response to technical engagement

- Accept ERG's approach to modelling discontinuation

- ***In a hypothetical scenario in which treatment switching was not allowed:***
  - ***Would people stay on treatment even if they continued to have relapses?***

[a] In company and ERG approaches, people also discontinue if they reach EDSS state ≥7, enter SPMS state or die.

Innovation and equalities

Innovation: company considers ozanimod innovative

- Ozanimod addresses unmet need for more options and can represent a meaningful addition to the NHS's treatment algorithm for RRMS
- Key innovations relate to mechanism of action and safety
- Modulator of the S1P1R pathway – better 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

No equality issues identified

Abbreviations: QALY, quality-adjusted life-year; S1P, sphingosine 1-phosphate.

Key issues

- 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?
- At what position(s) in the pathway will ozanimod be used – 1st line, 2nd, or both?
  - If relevant, has enough evidence been presented to consider ozanimod at multiple lines of therapy?
- Are RADIANCE Part B and SUNBEAM trials generalisable to NHS practice?
- 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?
- How should treatment discontinuation be applied in the model?

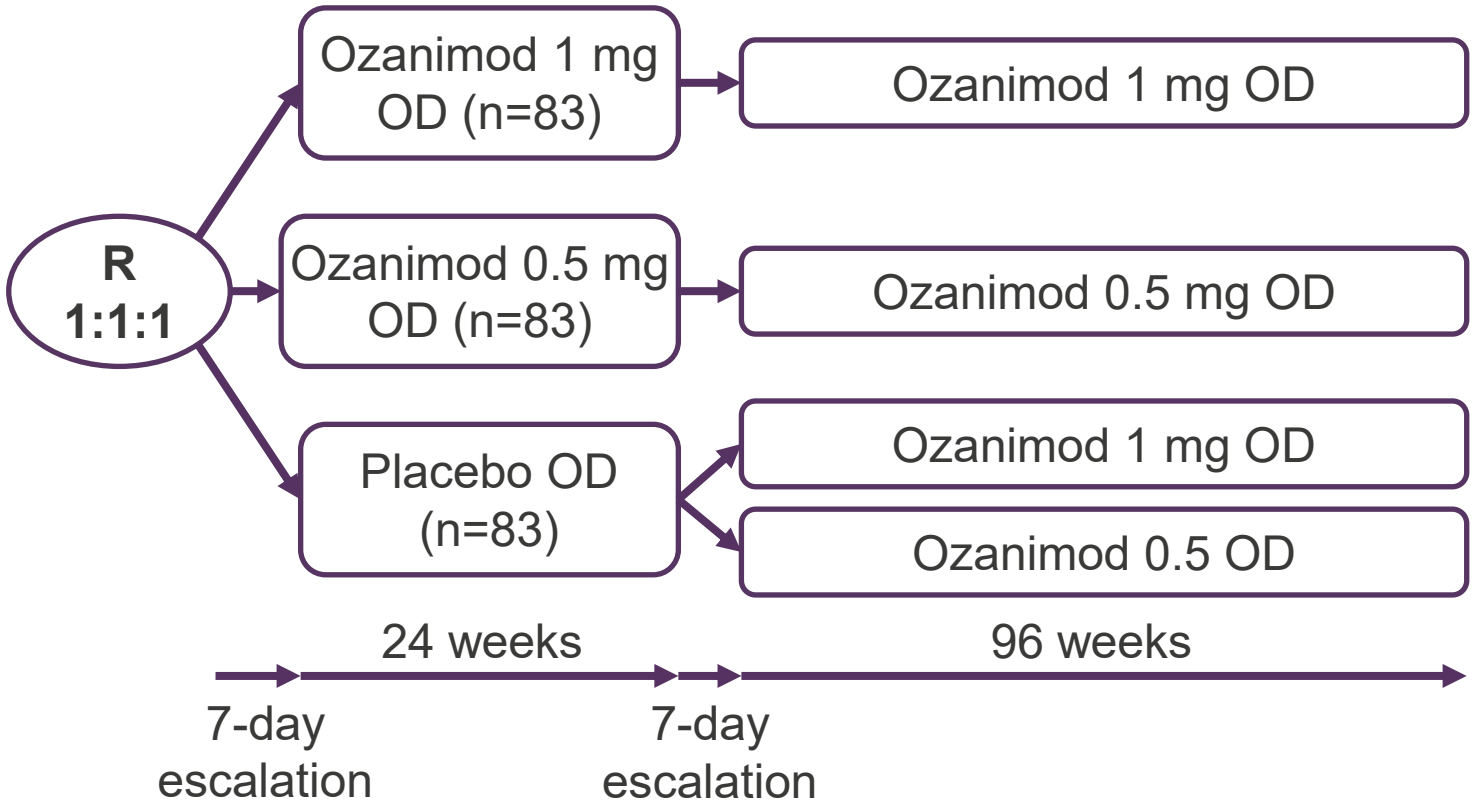
Cost-effectiveness results

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

Back up slides

RADIANCE Part A: study design

24-week, phase 2, multi-centre, randomised, double-blind, placebo-controlled trial with a blinded extension of 24 months (RADIANCE Part B)



Primary endpoint

- Total number of GdE lesions on MRI (weeks 12–24)

Secondary outcomes

- ARR
- Discontinuation
- Adverse events

- RADIANCE Part A trial data used in economic model (included in NMA)

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

Key results from Phase 3 trials: MRI outcomes

Improvements compared with IFN β-1b

	RADIANCE Part B (24 months)		SUNBEAM (12 months)		Pooled analysis	
	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)
New or enlarging hyperintense T2-weighted MRI lesions (secondary outcome)						
Percentage reduction (95% CI)[a]	XXXX XXXXXXXXXXXXX		XXXX XXXXXXXXXXXXX		XXXX XXXXXXXXXXXXX	
Rate ratio (95% CI)[a]	**0.6 (0.5 to 0.7)**		**0.5 (0.4 to 0.6)**		XXXX XXXXXXXXXXXX[b]	
Number of Gd-E T1 brain MRI lesions (secondary outcome)						
Percentage reduction (95% CI)[a]	XXXX XXXXXXXXXXXXX		XXXX XXXXXXXXXXXXX		XXXX XXXXXXXXXXXXX	
Rate ratio (95% CI)[a]	**0.5 (0.3 to 0.7)**		**0.4 (0.2 to 0.5)**		XXXX XXXXXXXXXXXX[b]	

Statistically significant results in bold. N.B. MRI outcomes on slide not included in model.

[a] Rate ratio and percent reduction of brain MRI lesions are expressed as ozanimod / IFN β-1a. Rate ratio < 1 and percent reduction > 0 favours ozanimod over IFN β-1a; [b] Estimated by the ERG based on the reported percentage reduction of new or enlarging hyperintense T2-weighted brain MRI lesions and 95% CI.