NICE National Institute for Health and Care Excellence

Public observer slides

Ponesimod for treating multiple sclerosis [ID1393]

Chair's presentation

2nd appraisal committee meeting

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Evidence Review Group (ERG): PenTAG

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Company: Janssen

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Appraisal history

ACD preliminary recommendation:

Ponesimod is not recommended, within its marketing authorisation, for treating relapsing forms of multiple sclerosis with active disease defined by clinical or imaging features in adults.

DMT: disease modifying therapies

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

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

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

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[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

ACD conclusions and uncertainties (1)

To discuss: updated network meta-analysis

Topic	Committee conclusion	Area for discussion?	ACD section
New treatment option	Despite many available treatments, would welcome new treatment options for RRMS	No	3.1
Treatment pathway	Likely to be used as first- or second-line treatment for active RRMS	No	3.2
Comparators	All first- and second-line treatments for active RRMS were relevant comparators	No	3.3
Disability progression (3m vs 6m)	Differences seen in 3- and 6 month confirmed disability accumulation were uncertain	No	3.4
Baseline characteristics	Studies broadly aligned with other populations in clinical trials; were appropriate for decision making	No	3.5
Fatigue as an outcome measure	Fatigue is an important outcome measure; not explicitly modelled in the cost-effectiveness analysis. Uncertain effect on CE without comparator data	No	3.6
Meta-analysis	Have major limitations; results highly uncertain	Yes	3.7
CDA measure	Using outputs from 6 month CDA appropriate	No	3.8

CDA: confirmed disability accumulation; CE: cost effectiveness; RRMS: relapsing–remitting multiple sclerosis

ACD conclusions and uncertainties (2)

To discuss: hierarchical class-based IFN model, alternative approaches to pooling, movement between EDSS states

Topic	Committee conclusion	Area for discussion?	ACD section
Impact of cladribine 6-month CDA	Anomalous result needs exploring further; particularly if there were any characteristics from the cladribine trials which could explain this	Yes	3.9
Interferons as a class	Hierarchical class-based model may be more appropriate than assuming single, pooled treatment effect; further information on how well alternative approaches to pooling fit the data, and further sensitivity analysis showing effect of different NMA assumptions on cost-effectiveness estimates needed	Yes	3.10
Adverse events	Further data needed to establish safety profile but all appropriate safety evidence incorporated	No	3.11
Model limitations	Model structure/inputs broadly aligned with previous models, but with limitations	No	3.12
EDSS states	Further sensitivity analysis needed to explore numbers of people in high EDSS health states	Yes	3.13

CDA: confirmed disability accumulation; EDSS: extended disability s- scale

ACD conclusions and uncertainties (3)

To discuss: updated mortality data, explanation of inconsistencies between appraisals

Topic	Committee conclusion	Area for discussion?	ACD section
Mortality data	Updated analysis with new mortality data would improve accuracy of model	Yes	3.14
Treatment sequencing	Treatment sequencing not reflective of clinical practice; including only costs but not treatment effect of siponimod not fully consistent; but model simulating treatment sequencing complex to construct	No	3.15
Cost-effectiveness estimates	Above what NICE normally considers an acceptable use of NHS resources; not recommended	Yes	3.16
Impact of model uncertainty	Further analysis needed to understand impact of uncertainty on economic analysis	Yes	3.17
Equalities issues	Recommendation applies equally to all genders; no equality issues identified	No	3.18
Innovation	All benefits captured in economic analysis	No	3.19

ACD 3.17: analysis requests

"The committee considered further analysis was needed to understand the impact of uncertainty on the economic analysis. This would include:

- further summary statistics and sensitivity analysis on the network meta-analyses (**ACD 3.7**), and particularly for interferons:
  - model fit statistics and analysis of inconsistency in the pooled analyses, including trials that compare different interferons with each other in the network, to make direct comparisons between different models possible (**ACD 3.10**)
  - a hierarchical class-based model for the interferons, assuming individual treatment effects within a class come from a distribution of effects with a class mean and between treatment variance within class
- analysis using updated mortality assumptions informed from new evidence (**ACD 3.14**)
- further sensitivity analysis that produces more likely modelled outputs, including rate of secondary progressive multiple sclerosis progression (**ACD 3.13**) and explanation of any inconsistencies of modelled outputs with previous appraisals."

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ACD consultation

ACD consultation responses

Responses received from:

- Company: Janssen-Cilag
  - Provide summary statistics for the pooled interferon NMA
  - Provide updated hierarchical model for interferon class within NMA
  - Provide analysis with more recent mortality data
  - Updated PAS discount
- Comparator companies: Novartis, Merck
- Patient groups: MS Society, MS Trust
- Web comments

New evidence

Model fit statistics and analysis of inconsistency of pooled IFN class-based NMA

ERG considers pooled IFN NMA was appropriate for decision making

Background (ACD 3.10):

- Interferons pooled into single node of the network due to treatment effect heterogeneity
- **Committee**: *"…not been presented with goodness-of-fit statistics and inconsistency assessments for the network meta-analysis that pooled interferons. It also understood that the company had excluded several trials that compared interferons with each other from the pooled network, and noted that it would be helpful to include these"*

Company response:

- Provided; 4 IFN vs IFN studies excluded as no comparative data between IFN and another comparator provided, and cannot be included where IFN is a single node
  - "good fit and is appropriate for decision making"
  - ARR, 3-month/6-month CDA: fixed effect best fit
  - Treatment discontinuation: random effects best fit
- Unrelated means effect model based on NICE TSD4 assessed potential inconsistency
  - ARR, 3-month/6-month CDA, treatment discontinuations: generally good consistency

ERG response:

- Used global approach to evaluating inconsistency; usually recommended to use local approach too due to how challenging detecting inconsistency can be
- Heterogeneity increases uncertainty, and decreases change of detecting inconsistency
- However, company have conducted analyses based on best available evidence

ARR: annualised relapse rate; CDA: confirmed disability accumulation; IFN: interferon; NMA: network meta-analysis; TSD: technical support document

Updated NMA based on a hierarchical class

NMA with hierarchical class based effect for interferon assumes some 'exchangeability' between interferon treatments

Updated NMA based on a hierarchical class

Point estimates broadly align to original pooled IFN class-based NMA

Background (ACD 3.10):

- IFN NMA initially presented as pooled NMA
- **Committee**: "*… a hierarchical class-based model may be more appropriate than assuming single, pooled treatment effect. Further information on how well alternative approaches to pooling fit the data, and further sensitivity analysis showing the effect of different NMA assumptions on the cost-effectiveness estimates would be needed*"

Company response:

- Class effect hierarchical NMA model: extension of standard NMA model from TSD2
  - All treatment effects within class must be exchangeable; 4 IFN trials excluded
- Results broadly aligned to original pooled IFN class-based NMA (total residual deviance)
- Large credible intervals expected due to between-trial heterogeneity across network
- **Model fit statistics**: hierarchical class-based NMA model appropriate for decision-making

ERG response:

- Methods broadly appropriate; trial exclusions in line with prior approaches
- Class-based hierarchical model resembled results from model considering IFNs as separate treatments; but more imprecise
- IFNs as class model favoured ponesimod more than hierarchical/separate IFNs

IFN: interferon; NMA: network meta-analysis; TSD: technical support document

Updated NMA based on a hierarchical class: ARR

Class-based NMA results for ARR, including ADVANCE and INCOMIN (Fixed effects) (company Technical Engagement response, figure 4)

Hierarchical class-based NMA results for ARR, excluding ADVANCE and INCOMIN (company ACD response, figure 5)

ARR: annualised response rate; NMA: network meta-analysis

Updated NMA based on a hierarchical class: CDA

Class-based NMA results for 6-month CDA, including ADVANCE and INCOMIN (Fixed effects) (company Technical Engagement response, figure 6)

Hierarchical class-based NMA results for 6-month CDA, excluding ADVANCE and INCOMIN (fixed effects) (company ACD response, figure 7)

- Why do credible intervals become more uncertain, including for treatments that do not include interferon in the network?

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CDA: confirmed disability accumulation; NMA: network meta-analysis

Updated mortality data: Harding et al., 2018

Improves QALY outputs, aligned closer to outputs expected by committee

Background (ACD 3.14):

- Company used data from Pokorski (1997) to model mortality of each EDSS health state
- Clinical experts: data outdated; managing acute infection/nursing has reduced mortality
- New standardised mortality rates by EDSS state recently published: Harding et al., 2018
- Committee: *"unclear how this would interact with implausibly high number of people in high EDSS states to affect the cost effectiveness results… an updated analysis with the new mortality data would improve the accuracy of the model"*

Company response:

- Pokorski data used as inputs for EDSS 0-3; Harding for EDSS 4-9 (as didn't capture 0-3)

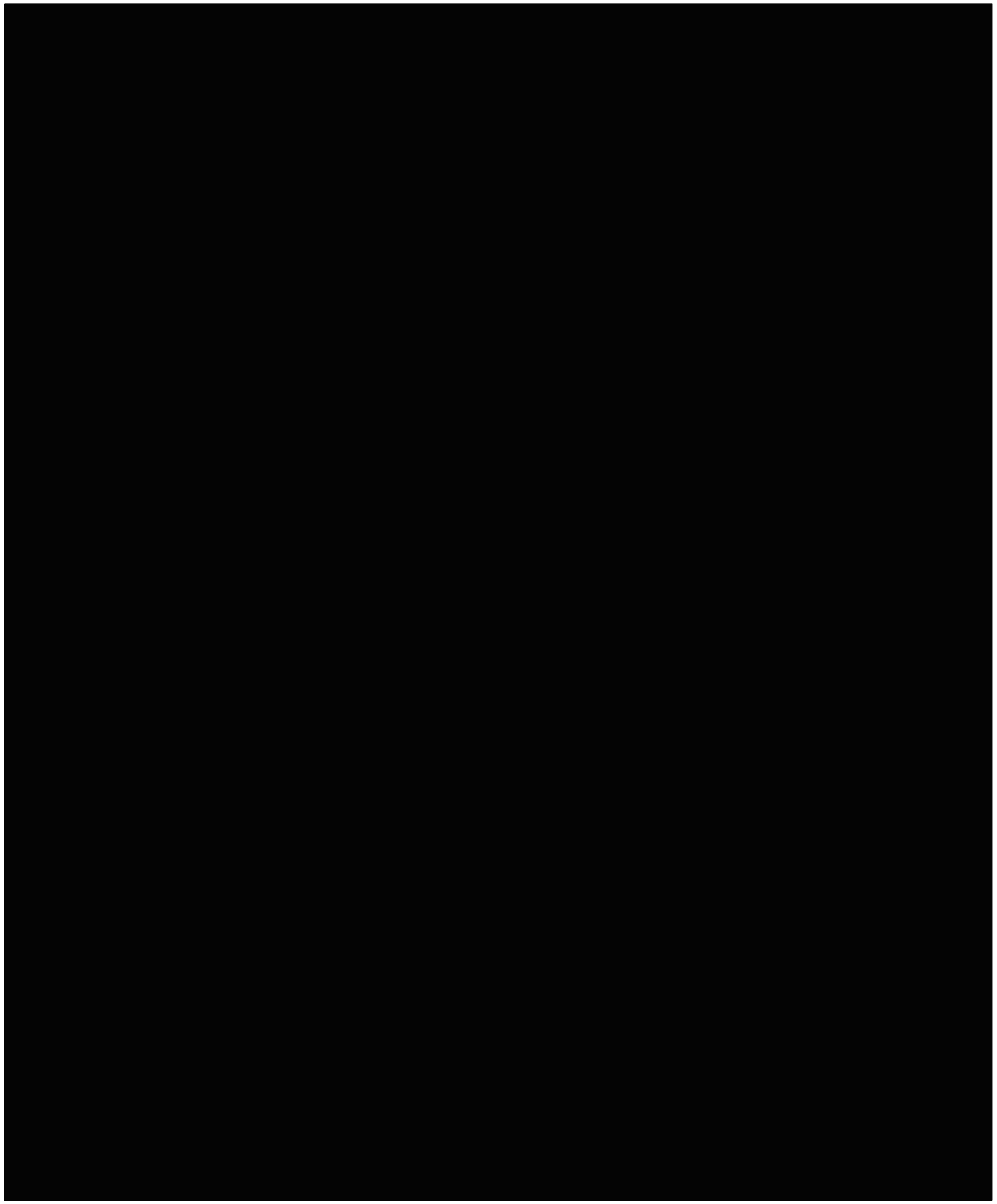
ERG response:

- Higher mortality rates in Harding et al. resulted in reduction in life years in updated model
- Had anticipated improved mortality due to recent nature of data/advances in MS treatment
- Estimation of mortality risk by EDSS score based on few patient deaths; limit robustness
  - Time constraints precluded seeking clinical opinion on disparity in morbidity estimates
- Harding may be more appropriate (more generalisable to UK, large cohort of patients)
- May be more appropriate sources available, however literature search not possible due to time constraints

Updated mortality data: mortality risk

Modelled relative risk of mortality (Harding., EDSS 4-9, Pokorski EDSS 1-3)

EDSS state	Relative risk (company revised base case)	Relative risk (company original base case)
EDSS 0	1	1
EDSS 1	1.3	1.3
EDSS 2	1.60	1.6
EDSS 3	1.68	1.68
EDSS 4	2.02	1.76
EDSS 5	2.02	1.84
EDSS 6	3.86	2.71
EDSS 7	4.76	3.57
EDSS 8	22.17	4.44
EDSS 9	60.74	5.31



Updated mortality data: overall survival

[redacted]

	Ponesimod	Teriflunomide	Dimethyl Fumarate	Glatiramer Acetate	Interferon Class	Ocrelizumab	Ofatumumab
Pokorski et al 1997 data							
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Caregivers	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Harding et al 2018 data							
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Caregivers	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

QALY outputs and time spent in RRMS/SPMS

Those produced by ponesimod model consistent with peg-interferon model TA624

Background (ACD 3.13):

- Committee: *"modelled outputs, including total quality adjusted life year (QALY) gain, from the company's model were inconsistent with other appraisals… queried why the company analysis modelled that people would spend a greater amount of time in SPMS state"*

Company response:

- Reviewed ofatumumab (TA699), pegIFN (TA624) and beta IFNs/GA (TA527); unable to review ozanimod (TA706) and ocrelizumab (TA533) due to redaction
- Ofatumumab and pegIFN: 3.5-6 QALYs, beta IFNs/GA: much higher at 8-10 QALYs
- Scenario analysis done using appraisal with most visible inputs: pegIFN (TA624)
  - Aligned on all model inputs except treatment effects and life tables (redacted)
- Inputs from peginterferon appraisal inputted into ponesimod model to replicate results in original submission

Treatment	QALYs (company model)	QALYs (pegIFN model inputs)	Difference
Teriflunomide	[redacted]	[redacted]	[redacted]
DMF	[redacted]	[redacted]	[redacted]
GA 20	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]

- QALYs for comparators common to both appraisals: [redacted] and [redacted] – very comparable
- Inputs with most notable changes in QALY values included removal of caregiver disutility (as done in TA527) and baseline characteristics from trials

DMF: dimethyl fumarate; GA: glatiramer acetate; IFN: interferon; RRMS: relapsing remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis

QALY outputs and time spent in RRMS/SPMS

Those produced by ponesimod model consistent with peg-interferon model TA624

- Conducted review of time spent in SPMS reported from pegIFN appraisal (TA624) and a scenario analysis putting pegIFN inputs into ponesimod model to test outputs
  - Outputs consistent with pegIFN model; models highly aligned for time in SPMS
- Time spent in SPMS calculated using undiscounted life years e.g. time spent in SPMS for terifluromide is [redacted] **TLYs –** [redacted] **years spent SPMS free /** [redacted] **TLYs)**

Treatment	% Time spent in SPMS (company base case analysis a)	% Time spent in SPMS (company model with PegIFN inputs b)	% Time spent in SPMS (pegIFN model c)	Difference (column b – column c)
GA	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide	[redacted]	[redacted]	[redacted]	[redacted]
DMF	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]

Avg. time in SPMS
PegIFN: 65%
Ponesimod: [redacted]

Order (most time to least time) same for both models

ERG response:

- QALYs for TA527 higher as preferred base case incorporated risk sharing scheme data; compared against natural history without matching or adjustment – considered outlier
- Company model adequate for decision making; outputs vary with respect to QALY gain due to differences in model inputs (inc. treatment effect estimates/baseline characteristics)
- Time in SPMS slightly higher for ponesimod vs PegIFN model, outputs broadly in line
- When using PegIFN inputs in ponesimod model, both models produced similar SPMS time outputs with minimal difference between comparators

DMF: dimethyl fumarate; GA: glatiramer acetate; IFN: interferon; SPMS: secondary progressive multiple sclerosis; TLY: total life years

Updated company base case: model inputs and outputs

Updated model outputs following changes to model inputs

Treatment	QALYs (company ACM1 base case)	QALYs (company revised base case)	Difference in QALYs	% time in SPMS (company ACM1 base case)	% time in SPMS (company revised base case)	Difference in % time
Ponesimod	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DMF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFN class	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ofatumumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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DMF: dimethyl fumarate; GA: glatiramer acetate; IFN: interferon; SPMS: secondary progressive multiple sclerosis

Recap: 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;

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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

Cladribine: 6-month CDA result in NMA

Reason for anomalous result remains unknown

Background (ACD 3.9):

- Committee: *"Cladribine had a substantially higher treatment effect for 6-month confirmed disability accumulation than other treatments in the network meta-analysis for the highly active subgroup… anomalous result needs exploring further, particularly if there were any characteristics from the cladribine trials which could explain this"*
- Clinical experts at committee agreed that this high value did not reflect clinical practice

Company response:

- Unable to determine the rationale for the higher treatment effect in cladribine trial
- Cladribine is an induction therapy and may be used differently to ponesimod

Stakeholder response:

- Merck: manufacturer of cladribine
- Ponesimod NMA effects were not calculated using meta-regression to provide sub-population specific estimates, therefore homogeneity has been assumed
- Berardi et al. 2019; alternative indirect treatment comparison (without ponesimod) adjusted for population characteristics when estimating treatment effect
  - Does not align with anomalous result for cladribine in ponesimod NMA

CDA: confirmed disability accumulation

Stakeholder responses to ACD

MS Society, MS Trust

- ***Ponesimod would be a valuable additional oral treatment***
  - Patients would prefer more oral options over injectables; simplicity/less complications
    - "*so easy, so unobtrusive … just a simple pill taken every day*"
    - less frequent administration and increased efficacy compared to other oral treatments
    - Same mechanism as fingolimod
    - Ponesimod more selective; expected to cause fewer side effects than fingolimod
  - Currently no oral drugs routine available as first-line treatments for 1 relapse/2 years
- ***Ponesimod's effect on progression of disability***
  - Those on trial reported reduced relapses (in 10+ years), no progression of EDSS state
    - "*my MS does not stop me doing anything I wish to do*"
  - Patients report being "*essentially unchanged … in some ways improved*" from diagnosis
  - Emphasise relapse reduction as a treatment aim; ponesimod effective at this
- ***Impact on carers and wider society***
  - My MS My Needs survey: 40% of respondents relied on unpaid care from family/friends
- ***Value of reducing fatigue in MS***
  - Most commonly reported invisible symptom of MS; may not be reflected in EDSS score
  - Ponesimod significantly better than teriflunomide in scores of MS-related fatigue
- ***Family planning in MS***
  - Most common disabling condition of young adults; many diagnosed in twenties/thirtles
  - Women with RRMS considering future pregnancy prefer to use DMTs with more favourable reproduction-related attributes even when not actively trying to conceive

CDA: confirmed disability accumulation; DMF: dimethyl fumarate; DMT: disease modifying treatment

Stakeholder responses to ACD (2)

Novartis, Merck

- ***NMA and modelling challenges***
  - Principle of pooling IFN data in NMA can be explored, but important to separately analysis cost-effectiveness of each IFN using confidential net prices to NHS
  - Agreed with committee that constructing model to simulate treatment sequencing and variable treatment waning would be "*complex and difficult to populate*" (ACD 3.12)
  - Support for well-established model structure for assessing RRMS DMTs
  - Using costs of siponimod without including benefits is fundamentally biased and methodologically inappropriate

DMT: disease modifying treatment; EDSS: Extended Disability Status Scale; NMA: network meta-analysis; RRMS: relapsing remitting multiple sclerosis

Web responses to ACD

Disagreement with negative recommendation for ponesimod – trial participants

- ***Impact on patients***
  - Those on trial report reduction in relapses and symptoms across 10+ years
  - Minimal side effects to treatment; easy to administer
  - Many continue to work and live life as normal, *'with no restriction whatsoever'*
  - Important to consider personal experience of participants alongside clinical evidence
  - General fear/concern around stopping treatment with ponesimod
- ***Pharmacokinetics***
  - Short half-life; unlike other treatments it is eliminated from the body quickly, with normal immunity returning within 7-8 days
    - Beneficial for family planning, change in medication
  - No active metabolites; less interactions with other medications
- ***Fatigue***
  - Ponesimod first DMT to suggest significant reduction in fatigue levels
    - MS-related fatigue has implications for patients of working age; direct financial impact on patients and the state
    - Limited methods and medications used to manage fatigue; those used are off license and have poor efficacy/poor data supporting their use
- ***Disease progression***
  - Difficult to gain data on disability progression in short period of time
    - Possible changes to EDSS at 12/24 weeks due to relapse, not disease progression
    - Teriflunomide post marketing real world data proves efficacy; ponesimod had similar efficacy in trials

DMT: disease modifying therapy; EDSS: Extended Disability Status Scale

Cost-effectiveness results

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