Public observer slides - Redacted

# Lead team presentation

## Ocrelizumab for treating primary progressive multiple sclerosis (ID938)

1st Appraisal Committee meeting

Committee B, 6th June 2018

Lead team: David Chandler, Richard Hoddes and Sanjeev Patel

Chair: Amanda Adler

Assessment Group: Warwick Evidence

NICE technical team: Thomas Walker, Rebecca Albrow

# Summary of evidence and key issues

**ICERs**
***'MRI active' population***
**Company's base case:**
- Modified* PAS price: Over £75,000 per QALY

**ERG's base case:**
- Modified* PAS price: Over £125,000 per QALY

*Updated PAS provided after initial submission

**Innovation**
Company submission:
Only disease modifying therapy to delay disability progression in PPMS

**Clinical effectiveness**
***'MRI active' population***
- Significant positive impact on time to **disease progression that is sustained for 12 weeks (CDP-12)**
- Significant positive impact of ocrelizumab on measure of **upper limb function**
- Figure provided suggests ocrelizumab has no effect on **fatigue** (based on mean change in MFIS)

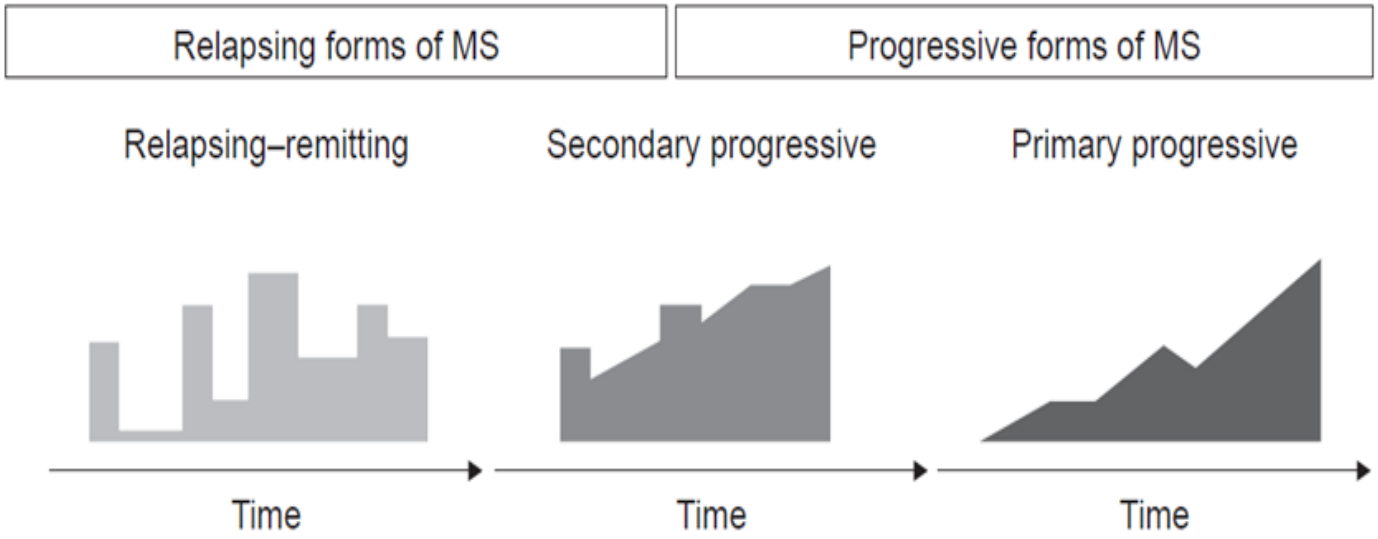
Ocrelizumab for PPMS

**Issues**
Should the model:
- Use CDP-12 or CDP-24 for treatment effect
- Include a disutility based on upper limb dysfunction
- Include a disutility based on fatigue
- Include a treatment waning effect

**Uncertainties**
- Does EDSS adequately capture disutility associated with PPMS?
- Does treatment discontinuation adequately represent any waning of treatment effect?

# Multiple sclerosis

- Multiple sclerosis (MS) is a chronic autoimmune disease characterised by inflammation of the central nervous system
- Disease progression results in disability and cognitive impairment
- 3 main types, depending on whether it is ‘relapsing’ or ‘progressive’:




**~14% people with MS**
**Median age onset 40 years**

*Reference: Company submission, section B.1.3.2*

# Primary-progressive MS (PPMS)

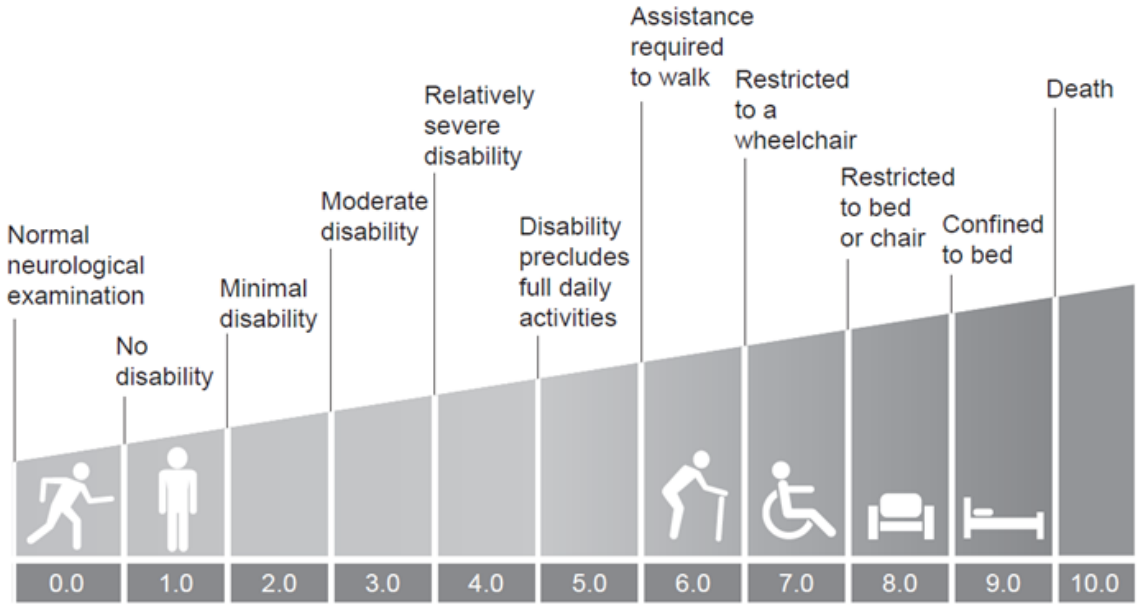
- Characterised by gradual, unpredictable disability progression from onset
- No disease-modifying treatments; diagnosed, although not necessarily managed, by a MS specialist; care focusses on managing symptoms
- Different phenotypes have been proposed, based on:
  - clinical and subclinical (detected using MRI*) activity
  - progression of condition
- People may already have lower limb disability at PPMS diagnosis
  - so, company says preserving upper limb function is an important endpoint
  - treatment for RRMS** stops when people are unable to walk
  - ERG notes aim of treatment for both PPMS and RRMS is to preserve functional independence for as long as possible, which includes upper arm function
- Disability in MS traditionally measured using the **Expanded Disability Status Scale** (**EDSS**)

** magnetic resonance imaging; ** relapsing remitting MS*

# Expanded Disability Status Scale to measure disability progression

*Company criticises EDSS's emphasis on walking*

"…*not adequate as a measure to capture disability progression in PPMS*"




*Reference: Company submission, section B.1.3.2*

**ERG:**

- EMA advocates use of additional secondary measures of disability
- Company's trial uses a measure based on EDSS as primary endpoint
  - Upper limb function and fatigue assessed as exploratory endpoints

# Ocrelizumab (Ocrevus)

*License is more restricted than population in key trial*
*NICE must appraise within marketing authorisation*

| | |
|---|---|
| **Marketing authorisation** | Ocrelizumab is indicated for the treatment of adult patients with **early** primary progressive multiple sclerosis in terms of disease duration and level of disability, and with **imaging characteristic of inflammatory activity** |
| **Mechanism** | Humanised monoclonal antibody; selectively depletes CD20+ B cells |
| **Administration and dose** | Intravenous (IV) infusion<br>• First 600 mg dose administered as two 300 mg infusions 2 weeks apart<br>• Subsequent doses as a single 600 mg infusions every 6 months<br>Minimum interval of 5 months between each dose |
| **Cost** | List price: £4,790 per 300 mg vial<br>A simple discount PAS has been approved |
| **Average cost of a course of treatment** | £19,160 per patient per year (based on twice yearly 600 mg infusions at list price) |

**ERG:** Marketing authorisation is 'vague and subjective'

# Patient and professional feedback (1)

Submissions from MS Society, Multiple Sclerosis Trust, Association of British Neurologists, NHS England, clinical and patient expert statements

- Symptoms, notably incontinence and fatigue, disrupt daily activities
  - slowing disability progression would allow people to work and engage in everyday activities for longer
- Frustrating to patients that no disease modifying treatment is available (unlike relapsing MS) and that the best that can be done is to treat symptoms only
- Living with MS is hard and expensive
  - *"I've been to the depths of despair …knowing the drugs I'm taking can only lessen the pain, discomfort and reduced mobility"*
  - an estimated 85% of people who need care receive unpaid care, support or assistance from a friend or family member
  - many people diagnosed with PPMS have young children and may become dependent on help to look after them
- Upper limb function is important for self-care
  - *"Three limbs are totally lifeless and the fourth.. is virtually useless…"*

# Patient and professional feedback (2)

- People with PPMS often have limited contact with specialist MS services
- Patients will require further investigation to find out who is eligible for ocrelizumab
- No precedent for treating PPMS; so no consensus on what would constitute a clinically significant effect
- EMA is unclear in its criteria for who is eligible for ocrelizumab
  - too vague to be useful in clinical practice
  - clinicians will inconsistently interpret marketing authorisation
- A stopping rule for treatment – based on advanced disability - is difficult
  - disease modifying therapies for RRMS are stopped at EDSS 7.0; however there is an argument for continued use in PPMS to preserve upper limb function

# NICE scope vs. company's decision problem

| | NICE scope | Company submission | Rationale | ERG comments |
|---|---|---|---|---|
| **Population** | Primary progressive multiple sclerosis (PPMS) | Restricted to:<br>• early PPMS<br>• imaging characteristic of inflammatory activity - 'MRI active' | Consistent with marketing authorisation granted by the EMA | • ERG disagree with definition of 'early PPMS'<br>• 'MRI active' does **not** reflect NHS practice<br>• No evidence for people >55 years old |
| **Outcomes** | • Disability<br>• Disease activity<br>• Patient-reported outcomes<br>• Cognition<br>• Visual disturbance<br>• Mortality<br>• Adverse effects<br>• Health-related quality of life | Per scope | - | Generally matches scope – although visual disturbance not measured as a separate outcome |

# Key issues: Clinical effectiveness

- ORATORIO (key trial) population broader than marketing authorisation
  - company provides post-hoc subgroup ('MRI active') to match
  - ERG concerned about how company defines this subgroup; NHS clinicians may interpret this inconsistently in practice
- "Statistically significant" improvement in time to 'confirmed disability progression sustained for 12 weeks' (1∘ outcome; CDP-12) relies on imputing unconfirmed events
  - ERG prefer CDP sustained for 24 weeks (2∘ outcome, CDP-24)
- Company presents several exploratory endpoints
    - upper limb function
    - fatigue
    - Multiple Sclerosis Functional Composite (MSFC) score
    - composite endpoints
  - ERG concerned that company selectively reports and models exploratory endpoints

# Clinical evidence: ORATORIO trial

*Trial finished; open label extension continues*

| | WA25046 (ORATORIO) | In model? |
|---|---|---|
| **Design** | Phase III, multicentre, randomised, parallel-group, double blinded, placebo controlled | |
| **Pop'n** | • Diagnosis of PPMS (per revised McDonald criteria)<br>• **18 to 55** years<br>• EDSS at screening: **3.0 to 6.5**<br>• From onset of MS symptoms, disease duration of:<br>− <15 years if EDSS at screening >5.0<br>− <10 years if EDSS at screening ≤5.0 | No, instead:<br>**Base case**: only 'MRI active'<br>**Scenario:** 'MRI active <50 years' |
| **Inter'n** | Ocrelizumab 600 mg (n=488; 24 from UK)<br>• 2x 300 mg infusions 14 days apart, every 24 weeks | |
| **Control** | Placebo (n=244; 5 from UK) | |
| **Out-comes** | • Confirmed disability progression:<br>− sustained for 12 weeks (CDP-12) [1∘outcome]<br>− sustained for 24 weeks (CDP-24) [2∘outcome]<br>• Change in timed 25 foot walk<br>• Change in T2 lesion volume and total brain volume<br>• SF-36 physical component summary score | 1∘ outcome (company also modelled 'exploratory' endpoints not listed here) |
| **Treat** | • No stopping rule | Stop at EDSS 8 |

# Summary
## Populations in the company's submission

| Population | |
|---|---|
| **ITT (intention to treat)** | • Entire enrolled population from ORATORIO<br>• Does not match marketing authorisation<br>• Power calculations for the planned analyses were calculated for this population |
| **'MRI active'** | • Post-hoc subgroup to match marketing authorisation population ("…*imaging features characteristic of inflammatory activity*")<br>  − Includes people with:<br>  − gadolinium-enhancing T1 lesions at screening or baseline, *or*<br>  − new T2 lesions between screening and baseline<br>• Company states that inclusion/exclusion criteria for enrolment in ORATORIO meet 'early PPMS' criteria in marketing authorisation<br>• Used in economic model (base case) |
| **'MRI active ≤50 years'** | • Post-hoc subgroup analysis<br>• Used in economic model (scenario analysis) |

# ORATORIO baseline characteristics and subgroup

*Marketing authorisation includes **early disease** and **radiographic inflammation***

| Characteristic | | ORATORIO *ITT* | | ORATORIO post hoc *'MRI active'* | |
|---|---|---|---|---|---|
| | | Placebo (n=244) | Ocrelizumab (n=488) | Placebo (n=104) | Ocrelizumab (n=189) |
| **Years since onset symptoms** | Mean (SD) | 6.1 (3.6) | 6.7 (4.0) | [redacted] | [redacted] |
| **Years since diagnosis** | Mean (SD) | 2.8 (3.3) | 2.9 (3.2) | [redacted] | [redacted] |
| **No previous use of DMTs** | | 87.7% | 88.7% | [redacted] | [redacted] |
| **EDSS** | Mean (SD) | 4.7 (1.2) | 4.7 (1.2) | [redacted] | [redacted] |
| **Gd-enhancing lesions on T1** | | 24.7% | 27.5% | [redacted] | [redacted] |

**ERG: *Early disease*:** ERG's clinical experts disagreed with company's definition – early disease better defined as <5 years of symptom onset
***Radiographic inflammation***: Scans with gadolinium (Gd) not routinely done in NHS and not done repeatedly (needed for T2 lesions)

- *Does this population reflect what NHS clinicians would define as 'early disease' and 'radiographic evidence of inflammation'? How would NHS clinicians define early disease? How widely used are T1 gadolinium and T2 MRI ?*

# Clinical effectiveness results: ORATORIO (1)

**Disability progression**

| Population | Hazard ratio (95% CI) Ocrelizumab versus placebo | |
|---|---|---|
| | CDP-12 (Primary outcome) | CDP-24 (Secondary outcome) |
| Whole (intention-to-treat) | 0.76 (0.59 to 0.98) | 0.75 (0.58 to 0.98) |
| 'MRI active' | 0.68 (0.46 to 0.99) | 0.71 (0.47 to 1.06) |
| 'MRI active ≤50 years' subgroup | 0.55 (0.36 to 0.85) | 0.54 (0.35 to 0.85) |

**Treatment effect applied in company base case**

**Treatment effect applied in company scenario analysis/ERG base case**

**ERG:**

- Significance is lost without imputing disability events
- **CDP-24** is a more clinically relevant and meaningful outcome of a sustained effect on disease progression
- No evidence that treatment effect is the same for all EDSS transitions

⊙ *Committee has previously preferred longer CDP for RRMS. For PPMS, which is more appropriate CDP-12 or CDP-24?*

# Clinical effectiveness results **upper limb function**: ORATORIO (2)

**Exploratory endpoints**

- **Upper limb function:** 9-hole peg test (9-HPT)

| Population | | | Hazard ratio (95% CI) Ocrelizumab versus placebo | P-value |
|---|---|---|---|---|
| **ITT** | 20% increase in 9-HPT confirmed after: | 12 weeks | 0.56 (0.41 to 0.78) | 0.0004 |
| | | 24 weeks | 0.55 (0.38 to 0.77) | 0.0006 |
| **'MRI active'** | 20% increase in 9-HPT confirmed after: | 12 weeks | 0.52 (0.32 to 0.85) | 0.0083 |

- *Note*: 9-HPT data included in model; ocrelizumab treatment effect reduces proportion of people with upper limb impairment (and associated utility decrement) in model

**ERG**:
- ERG questioned clinical relevance of this outcome
- Increase confirmed at 24 weeks more appropriate than at 12 weeks

- No statistically significant results for **Multiple Sclerosis Functional Composite score (MSFC)** or **Cognitive impairment** (Paced Auditory Serial Addition Test)

# Clinical effectiveness results **fatigue**: ORATORIO (3)

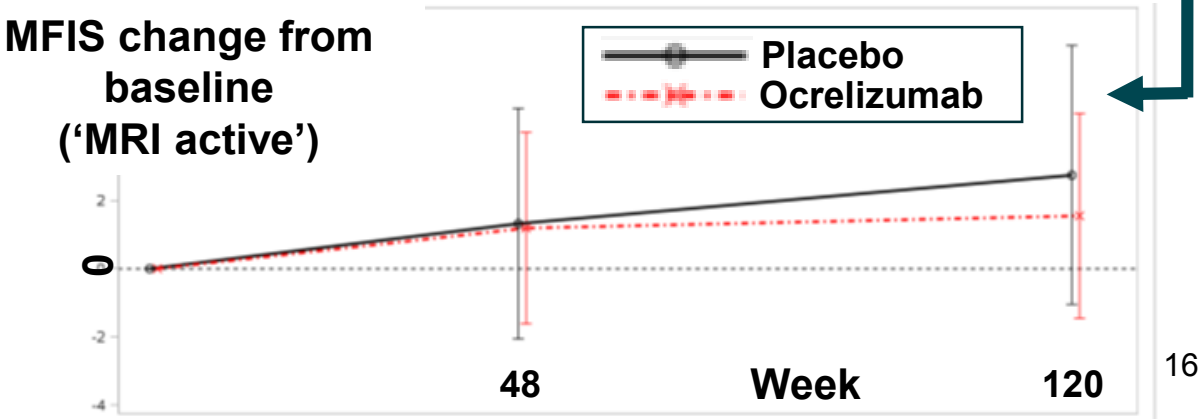
- **Modified Fatigue Impact Scale (MFIS)**

| Population | Change in fatigue from baseline to week 120 | | Difference in means |
|---|---|---|---|
| | Placebo | Ocrelizumab | |
| ITT | 2.99 (0.66 to 5.33) | -0.46 (-2.15 to 1.22) | -3.46 (-6.05 to -0.86) |

**ERG**:

- Company uses MFIS data in economic model; but not change from baseline, rather the **proportion of people** with clinically meaningful fatigue (MFIS>38)
  - ocrelizumab treatment effect reduces proportion of people with fatigue (and associated utility decrement) in model
- **'MRI active'** subgroup: No numerical data provided, but provided figure suggests ocrelizumab has no impact on fatigue compared to placebo
  - at odds with effect of ocrelizumab on fatigue applied in economic model

⊙ *What is the 'clinically meaningful difference' in MFIS? Does ocrelizumab have an effect on fatigue in the 'MRI active' group?*



# Clinical effectiveness results – company's **exploratory endpoints**: ORATORIO (4)

**ERG**: **General comments on exploratory endpoint data**

- Company should use exploratory endpoints (9-HPT, MFIS and others measured) only to generate hypotheses for further research and not to draw formal conclusions
- Incorporating outcomes from these analyses into the cost-effectiveness model should be viewed cautiously

- Some **risk of bias** as selected exploratory endpoint data presented in company submission
  - several pre-defined exploratory outcomes not presented

# ORATORIO: Adverse events (AEs)

*Rounded to nearest percentage (with exception of death)*

| Event | Ocrelizumab (n=486) | Placebo (n=239) |
|---|---|---|
| Any AE | 95% | 90% |
| Serious AE | 20% | 22% |
| AE leading to withdrawal from treatment | 4% | 3% |
| Death | 0.8% | 0.4% |
| **Infusion related reactions (IRRs; ≥1)** | **40%** | **26%** |
| Serious IRRs | 1% | 0.0% |
| Infection | 70% | 68% |
| **Upper respiratory tract infection** | **11%** | **6%** |
| **Malignancy** | **2%** | **1%** |
| Relapses | 5% | 11% |

- AEs in **bold** included in economic model

**ERG**: Rate of events appears to be similar in general

Relapses should have been included in the clinical effectiveness section

Slight but plausible benefit for ocrelizumab in reducing **relapses** (adjusted annualised rate of **0.35** (95% CI 0.19 to 0.65)

- *What about progressive multifocal leukoencephalopathy (PML)?*
  - *ACD for ID937:* PML is a possible adverse event with ocrelizumab / model should include risk of PML

# Key issues: cost effectiveness

- Should the company use CDP-12 or CDP-24 in its model to represent the effect of ocrelizumab on disability progression?
- Should the company include a **treatment waning** effect in the model?
- How should time to stopping treatment be modelled:
  - *Company*: Model time to stopping (extrapolated with Gompertz distribution) + stopping rule at EDSS 8.0
  - *ERG*: Model time to stopping (extrapolated with Gompertz distribution) with an increased rate after 5 years + stopping rule at EDSS 8.0
- Should the company include or exclude from the model:
  - disutilities from **upper limb dysfunction** and **fatigue**?
  - costs/utilities associated with **relapses**?

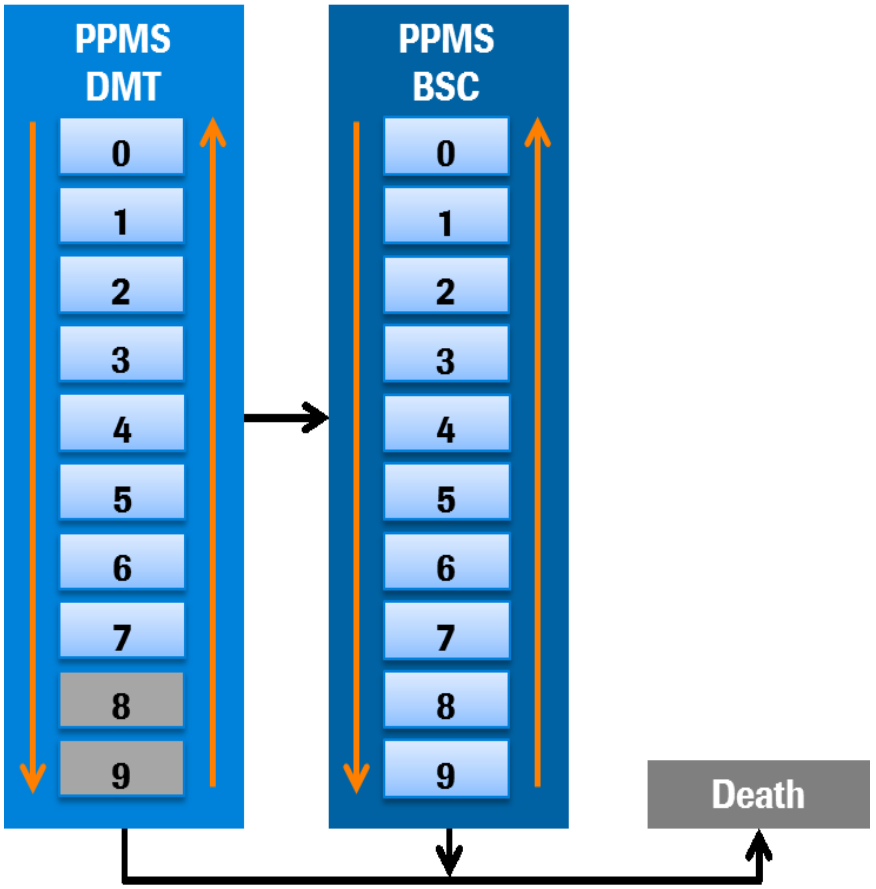
**Equality**

- Potential equality issue associated with 'MRI active ≤50' analyses

# Company's model

- Cohort Markov model, 1 year cycle length
- **Base case population**: 'MRI active'
- **Scenario population**: 'MRI active ≤50'
- Health states defined by EDSS
- Patients transition between EDSS states and can withdraw from active treatment (to best supportive care)
- Transition probabilities between EDSS states from natural history data (MSBase registry)
  - Patients can improve

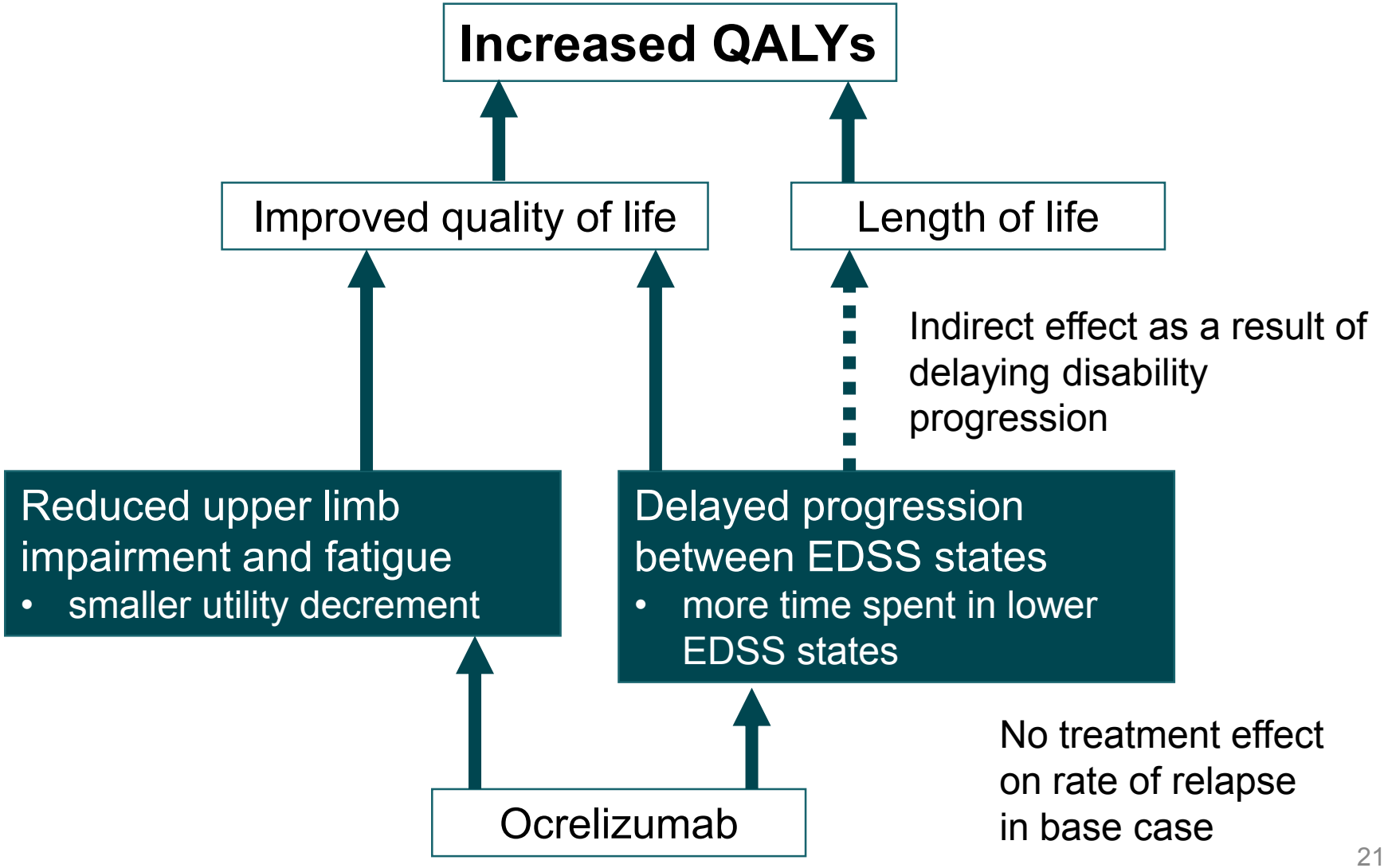
⊙ *Is there a clinical justification to support a subgroup based on age?*




DMT: disease modifying therapy
BSC: best supportive care

# How QALYs accrue

## Company base case



# Company's model assumptions (1)

| Factor | Company base case | Company's justification | ERG preferred |
|---|---|---|---|
| Upper limb function not adequately captured by EDSS | Apply lower utility to EDSS states for **upper limb impairment** | 'Clinically meaningful' upper limb dysfunction (20% increase in 9-hole peg test) impacts utility independent of EDSS | Exclude utility decrement |
| Fatigue not adequately captured by EDSS | Apply lower utility to EDSS states for **fatigue** | 'Clinically meaningful' fatigue (MFIS score >38) impacts utility independent of EDSS | Exclude utility decrement |
| Disability progression endpoint | CDP-12 used for treatment effect | • 1◦ endpoint ORATORIO<br>• Company assumes 12-week values stable (not impacted by relapse/remit dynamics) | CDP-24: More relevant and meaningful |

EDSS, Expanded disability status scale; MFIS, Modified fatigue impact scale; CDP, Confirmed disability progression

# Company's model assumptions (2)

| Factor | Company base case | Company's justification | ERG preferred |
|---|---|---|---|
| Treatment waning | Ocrelizumab does not wane | Waning of treatment effect lacks clinical plausibility<br><br>Expected that people would stop if no longer any treatment effect | Implausible assumption:<br>• Fluctuation in treatment effect<br>• No evidence of long-term sustained effect.<br>Included treatment waning in model |
| Stopping treatment | Gompertz model<br><br>Everyone stops at EDSS≥8.0 | Fit to ORATORIO data + clinical opinion - rate expected to increase over time | Increase in yearly stopping rate after 5 years.<br>Everyone stops at EDSS≥8.0 |
| Treatment effect on relapses | Not in base case<br>Included in scenario | Goal of treatment is to slow disability progression and maintain patients' independence – not relapses | Costs, disutilities, and treatment effect associated with relapses included |

# Disability progression in absence of treatment

*Company chose not to use trial control group*

- Company used **MSBase** registry PPMS patient data to estimate annual probability of transition between EDSS states **in absence of treatment**
  - international registry for MS (73 countries)
- Company preferred registry data to placebo arm from ORATORIO trial
  - longer follow-up, larger population
- Company considers London Ontario data not reliable - few with PPMS
- Limited MRI data available in MSBase; therefore transition probabilities for 'MRI active' subgroup **not** possible
  - people with 'MRI active' disease expected to progress faster
  - scenario analyses apply 5% and 10% 'acceleration factor' to MSBase data
- **Treatment effect** (CDP-12/CDP-24 hazard ratio) applied to natural history transitions

**ERG:** MSBase registry includes people with and without inflammatory disease and <3% people were from UK

⊙ *Is MSBase a valid reflection of the natural history of early/radiographic inflammatory disease? Does committee prefer this or trial data?*

# Treatment waning

## *Company does not model waning of treatment while taking drug*

- Company considers ocrelizumab treatment effect won't wane because it:
  - generates negligible neutralising antibodies
  - has a 'sustained effect' in RRMS
    - *n.b. Appraisal consultation document (ACD) for ID937 (ocrelizumab for RRMS): treatment efficacy is likely to wane over time with ocrelizumab*
  - decreases inflammation which may reduce waning effect
- Company has modelled rates of stopping ocrelizumab for any reason from ORATORIO
  - expects that patients will stop if no longer benefitting from treatment

**ERG:** Lack of waning is implausible

- Most relevant way to apply a waning of treatment effect is to:
  - worsen the hazard ratio for ocrelizumab CDP over time, while
  - increasing the rate of stopping treatment to reflect waning effectiveness

⊙ *Should a treatment waning effect be included in the model?*

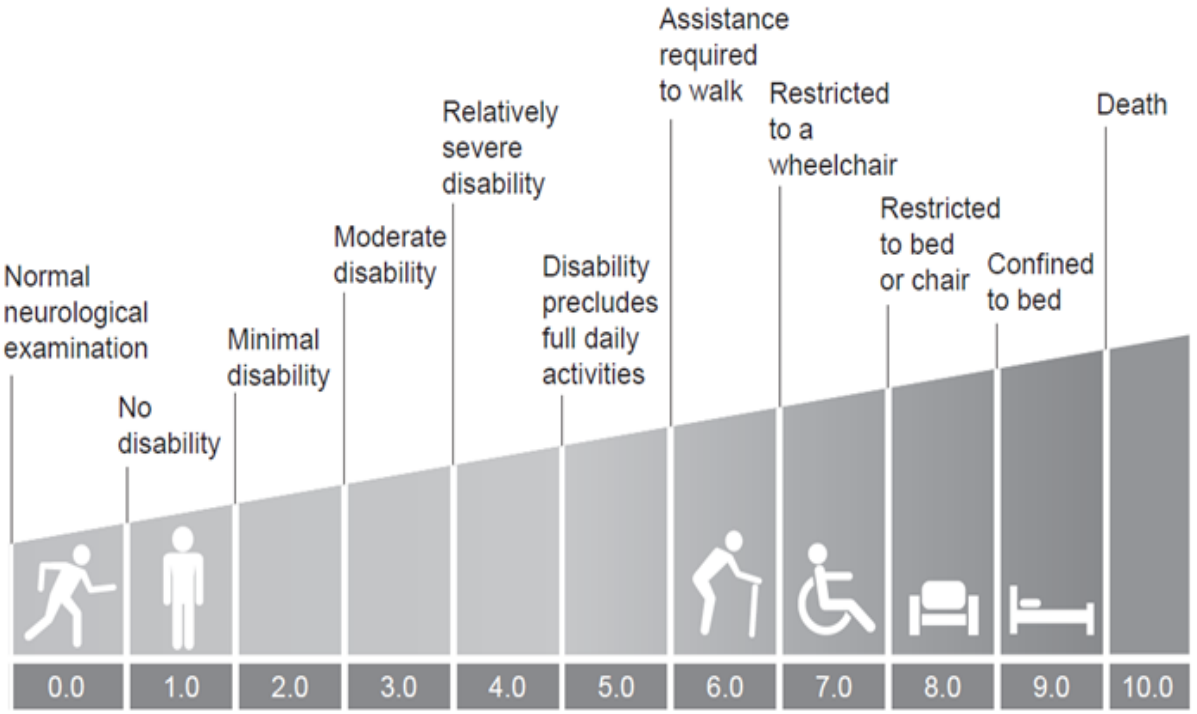
# Stopping treatment (1)
## Company approach

- Parametric models fitted to observed data for all-cause discontinuation (adverse events + no efficacy) from ORATORIO ITT population
- Company chose Gompertz distribution – based on model fit and clinical opinion that withdrawal rates would increase
- Assumed that all patients stop when progress to EDSS 8.0
- Company considered that predicted average treatment duration too high (~7 years)
  - so, in a scenario, company used a higher, **constant**, treatment withdrawal rate (gave average treatment duration ~4.5 years)

**ERG comments:**
Company:
- did not provide Kaplan-Meier plots
- did not consider generalised gamma distribution
- did not use 'MRI active' subgroup
- chose a higher EDSS state to stop compared to other MS submissions

⊙ *Why not based on subgroup data?*

# Stopping rule




*Reference: Company submission, section B.1.3.2*

- Association of British Neurologists clinical guideline recommends treatment in RRMS to cease once patients are non-ambulatory (i.e. EDSS 7.0)

⊙ *Is stopping at EDSS 8.0 too late? Is there reason to treat longer than in RRMS (EDSS 7.0)?*

*Clinicians envisage treatment most beneficial for people 'who retain some independence, i.e. are mobile and / or retain good upper limb function' (clinical expert statement)*

- *Note*: Company provide model scenario analyses with stopping rule at EDSS 7.0 and at 9.0

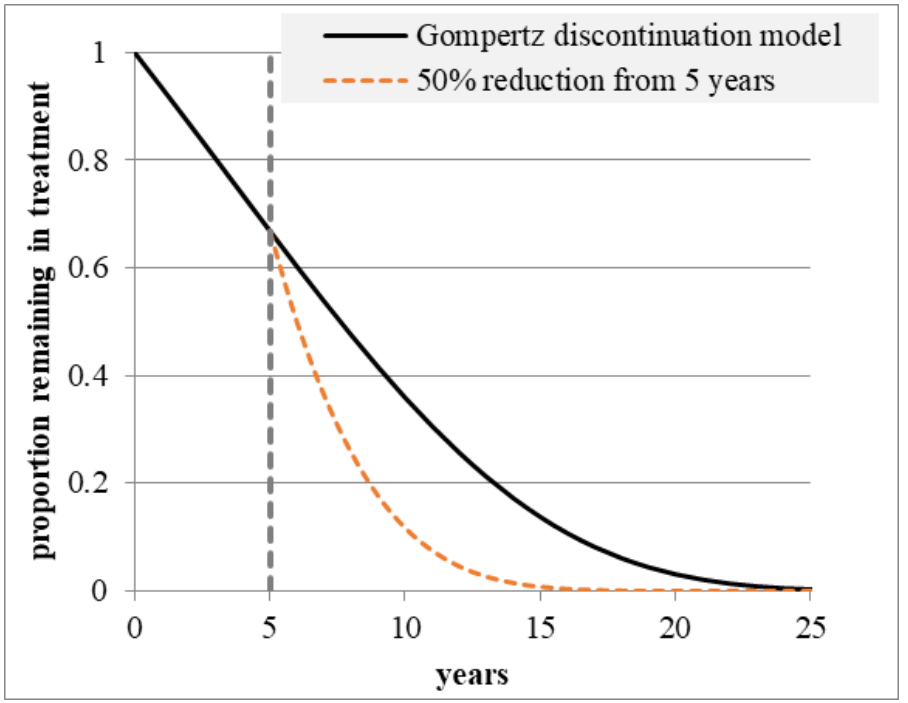
# Stopping treatment (2)
## ERG approach

**ERG approach to modelling treatment discontinuation**

Additional increase in annual discontinuation rate so that the average time spent in treatment beyond 5 years was reduced by 50%

- Because treatment effect wanes after 5 years (ERG model), increased treatment discontinuation as well

- *How should treatment discontinuation be modelled:*
- *Gompertz*
- *Gompertz (with higher rate after 5 years)*
- *constant withdrawal rate (company scenario analysis; gave average treatment duration ~4.5 years)*




*ERG report, section 5.3.1*

# Adverse events in economic model

*Company did not use subgroup data*

- Company included
  - adverse events that occurred more frequently in the ocrelizumab arm of ORATORIO with a difference >3%
  - malignancies
- Company assumed rates adverse events constant over time
- Company calculated probability of adverse events from ITT population and used these for 'MRI active' and 'MRI active ≤50' in model

| Adverse event | Ocrelizumab | Placebo |
|---|---|---|
| | Yearly probability | Yearly probability |
| Infusion related reaction | 15.6% | 0% |
| Malignancy | 0.8% | 0.3% |
| Upper respiratory tract infection | 3.8% | 2.0% |

**ERG:** Assumption of constant adverse event rates appropriate. Not stated why 3% was used as a threshold for selecting adverse events for the model

# Health related quality of life patients and caregivers (1)

*Company in base case used trial-based EQ-5D and literature-based values*

- Company pooled EQ-5D-3L from ORATORIO between trial arms to derive values for each health state
- Company took utility values for low and high EDSS states not captured in ORATORIO from literature (Orme et al.)
  - scenario analysis used only utility values from Orme et al.
- Utility values from ORATORIO higher than those in 2 other identified studies
  - suggested to be because of lower age in ORATORIO
- Company included disutility for caregivers from TA127 (natalizumab for RRMS)

| EDSS | Utility values ORATORIO | Utility values Orme et al. | Carer disutility |
|---|---|---|---|
| **0** | See ORME | 0.837 | 0.000 |
| **1** | See ORME | 0.766 | -0.001 |
| **2** | 0.791 | 0.672 | -0.003 |
| **3** | 0.738 | 0.541 | -0.009 |
| **4** | 0.678 | 0.577 | -0.009 |
| **5** | 0.665 | 0.485 | -0.020 |
| **6** | 0.605 | 0.425 | -0.027 |
| **7** | 0.428 | 0.264 | -0.053 |
| **8** | See ORME | -0.082 | -0.107 |
| **9** | See ORME | -0.228 | -0.140 |

# Health related quality of life (2)

*Company included disutility for upper arm impairment and fatigue*

- Company used the same disutilities for adverse events as used in daclizumab and alemtuzumab technology appraisals (for RRMS)

**ERG:** Company considered relapse an adverse event; but did not model its disutility (or costs) in base case

⊙ *Should costs/utilities associated with relapses be included in the model?*

- Company modelled utility decrements to % of people in each EDSS state with:
  - upper limb impairment (**-0.064**) in EDSS stage 5 and above
  - clinically meaningful fatigue (**-0.150**) in each EDSS stage
- Proportions of patients with upper limb impairment and fatigue determined by clinical opinion (for BSC)
- Treatment effect from ORATORIO data; proportion of people with:
  - upper limb dysfunction (20% increase in 9-HPT sustained over 12 weeks)
  - clinically meaningful fatigue (MFIS score >38)

# Health related quality of life (3)

*ERG opposes including extra utility decrements for upper limb impairment and fatigue*

**ERG notes:**

- Lack of transparency in how company chose outcomes
  - 9-hole peg test included in other outcome measures
  - company selected exploratory outcomes post-hoc (should only be used to generate hypotheses)
- Potential double counting of utilities; EQ-5D may adequately capture health related quality of life for people with MS:

| |
|---|
| 'Usual activities' and 'self-care' related questions in both MFIS (fatigue) and EQ-5D |
| MFIS asks if people have been 'clumsy and uncoordinated' which may assess upper limb function |
| MFIS questions are linked to progression through EDSS stages (asking about muscle weakness and impaired walking) |
| Utility decrements for caregivers may double count the impact of upper limb impairment and fatigue |

# Health related quality of life (4)
## ERG comments

- Proportion (best supportive care) with fatigue/upper limb impairment based solely on clinical expert opinion
- These utility decrements are not used in other (RRMS) appraisals
- Upper limb impairment treatment effect inappropriately applied (hazard ratio was used as relative risk)
- Use of MFIS score >38 to indicate clinically meaningful fatigue:
  - cut-offs not commonly used with fatigue scales
  - on average people already fatigued when they entered ORATORIO (baseline mean score 41.6)
  - based on mean change in MFIS, ocrelizumab has no effect on fatigue in 'MRI active' group

⊙ *Is it appropriate to include utility decrements for:*
- *Upper limb impairment*
- *Fatigue*

# Costs

- Company used health state costs associated with RRMS from Tyas et al. (2007; based on MS Trust survey)
  - PPMS costs considered too low
  - adjusted to include direct medical costs and 25% direct non-medical costs
  - inflated to 2016/17 prices using Personal Social Services Research Unit (PSSRU) 2017 inflation index
  - *Company*: Robust and used in previous appraisals
  - *ERG*: No issues raised

- 3 ocrelizumab prices:
  - List price – not shown
  - PAS price ('modified PAS': PAS has changed since original company submission/ERG report)
  - Managed access agreement (with a different discount to the 'modified PAS') also proposed – part 2 (confidential)

# Company's base case results with patient access scheme discount (PAS)

*ICERs exceed those generally considered to be cost effective*

| Population | Deterministic ICER (£/QALY) | Probabilistic ICER (£/QALY) |
|---|---|---|
| | Modified PAS price | Modified PAS price |
| MRI active | £78,316 | £84,249 |
| MRI active ≤50 years | £47,857 | £54,341 |

*ICER = incremental cost effectiveness ratio*

**ERG:** Company does not comment on discrepancy between deterministic and probabilistic ICERs

**Sensitivity analyses**

***Deterministic***

- Results most sensitive to CDP-12 treatment effect and discount rates

# Company's scenario analyses
## ('MRI active')

| Scenario | | 'MRI active' ICER (£/QALY) |
|---|---|---|
| | | Modified PAS price |
| **Base case** | | **£78,316** |
| Increase in transition rates between EDSS states (MSBase with 'acceleration factor'): | 5% | £75,764 |
| | 10% | £73,479 |
| Only progression between EDSS states allowed (no improvement) | | £68,143 |
| Treatment discontinuation set to constant withdrawal rate (gave average treatment duration ~4.5 years) | | £75,520 |
| Stopping rule set to EDSS at: | 7.0 | £77,739 |
| | 9.0 | £80,679 |
| EDSS utilities all from Orme et al. | | £87,194 |
| Combination:<br>• Progression only transitions<br>• 5% increase in transition rates between EDSS states<br>• Treatment discontinuation set to constant withdrawal rate<br>• Stopping rule at EDSS 7.0 | | £61,606 |

# ERG's scenario analyses in company's model
('MRI active')

| Scenario | | 'MRI active' ICER (£/QALY) |
|---|---|---|
| | | Modified PAS price |
| - | **Base case** | **£78,316** |
| SA1 | CDP-24 used for treatment effect | £86,824 |
| SA2 | Treatment waning: 50% decrease in treatment effect from year 5 | £103,923 |
| SA3 | Increase in rate of people stopping treatment (year 5+) | £74,707 |
| SA4 | SA2+SA3 | £93,197 |
| SA5 | Utility decrement for upper limb impairment ***excluded*** | £87,038 |
| SA6 | Utility decrement for fatigue ***excluded*** | £84,959 |
| SA7 | Alternative relative risk for 20% increase in 9-HPT* | £79,749 |
| SA8 | Relapses: Costs, disutilities and treatment effect included | £78,155 |

*ERG consider treatment effect inappropriately applied (hazard ratio was used as relative risk). ERG would have preferred to use 20% increase in 9-HPT sustained for 24 weeks, but the data was not available

# ERG's base case

| | Company's base case | ERG's base case |
|---|---|---|
| Treatment effect | CDP-12 | CDP-24 |
| Treatment waning effect | Not included | Included<br>(50% reduction in treatment effect from year 5 onwards) |
| Stopping treatment – extrapolating beyond trial | Gompertz | Additional increase in annual discontinuation rate so that the average time spent in treatment beyond 5 years was reduced by 50% |
| Stopping rule | EDSS 8 | EDSS 8 (rather than earlier) |
| Utility decrement for upper limb impairment | Included | Excluded |
| Utility decrement for fatigue | Included | Excluded |
| Costs, disutilities and treatment effect associated with relapses | Excluded | Included |

- *Is it appropriate to apply both a treatment waning effect and increased treatment discontinuation?*

# ERG's base case using PAS

| Population | Deterministic ICER (£/QALY) | Probabilistic ICER (£/QALY) |
|---|---|---|
| | Modified PAS price | Modified PAS price |
| MRI active | £129,877 | £145,161 |
| MRI active ≤50 years | £67,813 | £77,022 |

***One-way sensitivity analyses***

- CDP-24 treatment effect had greatest impact on the ICER

# Exploratory analyses in ERG's base case

| | | ICER (£/QALY) |
|---|---|---|
| | | PAS price |
| **ERG base case** | | **£129,877** |
| ***Exploratory analyses:*** | | |
| Efficacy set to CDP-12 | | £116,022 |
| No treatment waning | | £101,540 |
| 50% decrease in effectiveness from 5 years | | £147,266 |
| Increase in annual discontinuation rate | | £101,540 |
| MRI active ≤50 years subgroup | | £67,813 |
| Utility values from Orme et al. (2007) | | £147,321 |
| Including utility decrements for: | Upper limb impairment | £116,105 |
| | Fatigue | £116,051 |
| Including utility decrements for limb impairment and fatigue | | £104,929 |
| Excluding relapse costs and disutility | | £130,184 |

# Innovation

Company

- Only disease modifying therapy (DMT) to delay disability progression (including deterioration of upper limb function) in PPMS
- Single infusion every 6 months, less than most DMTs
- Safety profile similar to placebo; expected to require less monitoring than other DMTs for treating other forms of MS
- Low probability of treatment waning

⊙ *Are there any additional QALY benefits that have not been captured in the health economic modelling?*

# Equality and diversity

- Potential equality issue associated with subgroup analyses based on age

# Key issues: cost effectiveness

- Should the company use CDP-12 or CDP-24 in its model to represent the effect of ocrelizumab on disability progression?
- Should the company include a **treatment waning** effect in the model?
- How should time to stopping treatment be modelled:
  - *Company*: Model time to stopping (extrapolated with Gompertz distribution) + stopping rule at EDSS 8.0
  - *ERG*: Model time to stopping (extrapolated with Gompertz distribution) with an increased rate after 5 years + stopping rule at EDSS 8.0
- Should the company include or exclude from the model:
  - disutilities from **upper limb dysfunction** and **fatigue**?
  - costs/utilities associated with **relapses**?

**Equality**

- Potential equality issue associated with 'MRI active ≤50' analyses