Slides for projector, committee and public observers [noACIC]

# Chair's presentation

# Ocrelizumab for treating relapsing multiple sclerosis

2nd Appraisal Committee meeting

Committee B

Chair: Sanjeev Patel

Lead team: Mark Chapman, Richard Hoddes and Nigel Westwood

ERG: Southampton Health Technology Assessments Centre

NICE technical team: Jessica Cronshaw, Frances Nixon

Company: Roche

10th May 2018

# ACD: preliminary recommendation

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

  - No analyses that reflected the committee's preferred assumptions
  - Company and ERG ICERs that were closest to the committees preferred assumptions > £30,000 per QALY, but expected to be underestimates

# Ocrelizumab (Ocrevis)

| | |
|---|---|
| **Marketing authorisation** | For ‘adult patients with relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features’ |
| **Mechanism** | Humanised monoclonal antibody that 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. Subsequent doses administered as a single 600 mg infusion every **6 months**. |
| **Cost** | List price £4,790 per 300 mg vial.<br>Simple discount PAS* for ocrelizumab |
| **Cost of a course of treatment** | Per patient per year £19,160 based on twice yearly 600 mg infusions (list price) |

*PAS – patient access scheme

# Clinical evidence: OPERA trials

| | WA21092 (OPERA I) n=821 | WA21093 (OPERA II) n=835 |
|---|---|---|
| **Design** | Phase III, randomised-controlled, active comparator, double-blind, double-dummy | |
| **Population** | 18–55 years with a diagnosis of RMS ≥2 documented relapses within the previous two years or one relapse within the year before screening. | |
| **Intervention** | Ocrelizumab 600 mg n=410<br>Licensed dose | Ocrelizumab 600 mg n=417<br>Licensed dose |
| **Comparator** | IFNB-1α 44 µg n=411 | IFNB-1α 44 µg n=418 |
| **Outcomes** | • Annualised relapse rate (primary outcome)*<br>• Confirmed disability progression at 3 months*<br>• Confirmed disability progression at 6 months *<br>• No evidence of disease activity<br>• Number of gadolinium-enhancing T1 leisons<br>• Number of T2 hyperintense lesions<br>• Number of T1 hypointense lesions<br>• Brain volume change<br>• Multiple sclerosis functional composite score<br>• SF-36 physical component summary score<br>• EuroQOL five dimensions Health-Related Quality of Life Questionnaire EQ-5D-3L* | |

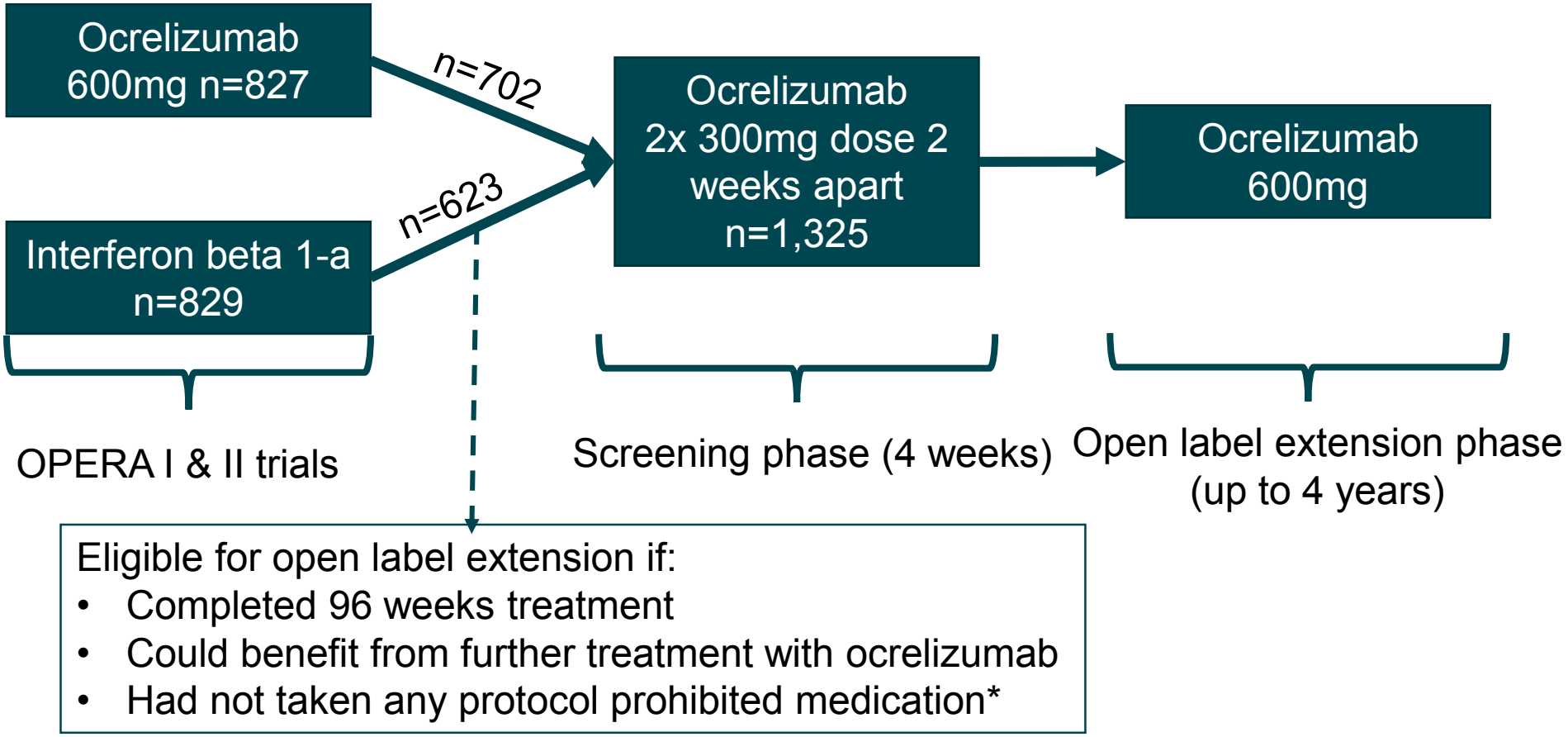
***used in company economic model**

**WA21493** Phase II study with primary endpoint gd-enhancing lesions. No disease progression endpoint. Not included in mixed treatment comparison or economic model

# Open label extension OPERA I & II

OPERA I & II patients entered in to open label extension trial (n=1,325)

- To evaluate long term safety, tolerability and efficacy




Eligible for open label extension if:

- Completed 96 weeks treatment
- Could benefit from further treatment with ocrelizumab
- Had not taken any protocol prohibited medication*



**in open label extension dalfampridine was allowed, if indicated by the treating physician*

# ACD consultation responses

- Consultees
  - Roche
  - MS society
  - MS trust
  - Association of British Neurologists
  - Clinical experts
- Commentators
  - Novartis
  - Sanofi Genzyme
- 8 web comments
- Company new evidence
  - Revised PAS
  - Post hoc disability analysis from the OPERA studies
  - Updated mixed treatment comparison
  - Updated economic model assumptions

# Committee's conclusions (I)

| Issue | Committee's conclusion | Company adjustment | Match committee's preference? |
|---|---|---|---|
| **Blended comparator (3.4 ACD)** | Appropriate to compare ocrelizumab with each individual treatment | Compared ocrelizumab with each individual interferon and glatiramer acetate | Yes |
| **Mixed treatment network (3.11 ACD)** | Jointly modelled outcomes for confirmed disability progression at 3 months and 6 months | Updated Mixed treatment comparisons using 2 models. **Model 1** – uses CDP 3 month data when 6 month data missing **Model 2** – jointly models 3 month and 6 month data to infer missing values | Partially – only model 1 used for RES and HA subgroups |
| **Source of EDSS cost (3.14 ACD)** | UK MS Survey 2007 updated to 2015/16 costs<br>• Daclizumab committee considerations | UK MS Survey 2007 updated to 2015/16 costs | Yes |

# Committee's conclusions (II)

| Issue | Committee's conclusion | Company adjustment | Match committee's preference? |
|---|---|---|---|
| **Measure of disability progression (3.16 ACD)** | Preferred confirmed disability progression at 6 months<br>• more robust measure<br>• long episodes of relapse less likely | Confirmed disability at 6 months | Yes |
| **PML possible adverse event with ocrelizumab (3.18 ACD)** | Risk of PML for ocrelizumab is likely to be less than with natalizumab (2.1%), but more than 0 | Included risk for PML informed by proxy data from rituximab in rheumatoid arthritis (0.00028%) | Partially |
| **Treatment waning effect (3.20 ACD)** | Treatment discontinuation rates can be used as a proxy for treatment waning | None needed, same as original company base case | Yes |

# Consultation comments – confirmed disability progression

**Committee discussion**
Appropriate to use a mixed treatment network to jointly model the outcomes for continued disease progression at 3 months and 6 months

**Roche**

- Agree that longer confirmation periods are generally better measures
- But, precision in the effect size and quality of indirect comparisons is also a function of the size and quality of the trials and available evidence

**Novartis**

- Ratio of 3:6 month data is not likely to be consistent between trials

**Sanofi Genzyme**

- Agree that confirmed disability at 6 months data preferred
- Only two studies (OPERA I and II) to validate a correlation between confirmed disability progression 3 months and 6 months

# Consultation comments – mixed treatment comparison subgroups

**Committee discussion:**

- Mixed treatment comparison results are highly uncertain in the highly active and rapidly evolving severe subgroups
- Prefer only subgroup data included in subgroup mixed treatment comparisons (company included whole population data to 'link' network)

**Roche**

- Agree considerable uncertainty in subgroups
- Not much published subgroup data for IFNB-1a (avonex and rebif) which connects ocrelizumab to the network of comparators
- Updated analyses using joint modelling introduces more uncertainty
  - should 'not detract from making a decision about ocrelizumab within its marketing authorisation'

**Sanofi Genzyme**

- All relevant evidence considered apart from annualised relapse rate in highly active subgroup, 0.18 for alemtuzumab (Krieger S *et al.* Neurology Apr 2016)

# Consultation comments – treatment waning

**Committee discussion:**
Treatment efficacy is likely to wane over time with ocrelizumab and stopping treatment can be considered a proxy for treatment waning.

**Roche**

- Negligible proportion of ocrelizumab patients developing anti-drug antibodies
- Open label extension data demonstrating durable effects up to 4 years
- All-cause discontinuation rates are a conservative assumption
  - patients withdrawing no longer accrue a treatment benefit in the model.

**Sanofi Genzyme**

- Agree that same waning effect is applied to all comparators as in previous submissions

**Clinical experts, MS Society and MS Trust**

- No clear evidence for treatment waning

**Clinical expert**

- Observational study suggests sustained efficacy of rituximab compared with other DMTs such as natalizumab (Swedish MS registry; Granquist et al 2018)

# Consultation comments – adverse events

**Committee discussion:**
Adverse events with ocrelizumab are broadly similar to those with other disease-modifying therapies and are likely to be less frequent with ocrelizumab than with other similar therapies.

**Roche**

- Do not agree with the ACD statement *'adverse events with ocrelizumab are broadly similar to those with other disease-modifying therapies.'*
  - Needs to specify broadly similar to moderate-efficacy therapies, but less frequent and less severe than those associated with other high-efficacy treatments

**Clinical experts and Association of British Neurologists**

- Adverse events for ocrelizumab are not broadly similar to other therapies
  - The risk of auto immune disease is much less than alemtuzumab
  - Risk of PML is much less than with natalizumab

# Consultation comments – adverse events risk of progressive multifocal leukoencephalopathy (PML)

**Committee discussion:**

- PML is a possible adverse event with ocrelizumab
- The risk is likely to be lower than that associated with natalizumab (2.1%).

**Roche**

- Included a risk of PML in the updated model (annualised rate 0.00028%, based on rituximab data) , but this remains a potential, rather than actual, risk
- No reported cases of PML causally attributed to ocrelizumab to date

**Association of British Neurologists**

- Rituximab is a more legitimate comparator [for PML risk than natalizumab]. Clifford et al 2011 reported estimating a risk of 1 in 25,000 for PML

# Consultation comments - innovation

**Committee discussion:**
- ocrelizumab is not innovative compared with other recent treatment options
- not the first B-lymphocyte antigen
- better safety profile than some other high-efficacy treatments
- less frequent monitoring compared with other treatments

**Roche**
- Ocrelizumab is innovative, it offers unique efficacy, safety, tolerability and convenience
  - Low frequency of infusions, less frequent monitoring
  - Demonstrates an effect on confirmed disability improvement

**Association of British Neurologists, Clinical experts, MS society and MS trust**
- Ocrelizumab is innovative provides unique benefits compared with other treatment options
  - Improved quality of life because of less onerous treatment schedule
  - Likely to reduce additional costs to the NHS
  - Lower level of monitoring and frequency of treatment

⊙ *Is innovation fully captured in the economic model?*

# Company new evidence – confirmed disability progression 8 months and 11 months

**Roche**

- Post hoc analyses of disability progression in OPERA studies at 36 and 48 weeks, direct comparison to IFNB-1a
  - Appears to be a trend for increasing effect sizes with longer confirmatory periods
  - Confirmed disability progression not reported for other comparators at 36 and 48 weeks, so an indirect comparison could not be done
- "Directional effect could be expected to result in more favourable ICERs for ocrelizumab"

| | Pooled analysis (HR, 95% CI) | OPERA I (HR, 95% CI) | OPERA II (HR, 95% CI) |
|---|---|---|---|
| **CDP 3 months** | 0.60 (0.45, 0.81) | 0.57 (0.37, 0.90 | 0.63 (0.42, 0.92) |
| **CDP 6 months** | 0.60 (0.43, 0.84) | 0.57 (0.34, 0.95) | 0.63 (0.40, 0.98) |
| **CDP 8 months** | 0.50 (0.34, 0.76) | 0.47 (0.25, 0.87) | 0.53 (0.31, 0.91) |
| **CDP 11 months** | 0.43 (0.26, 0.69) | 0.51 (0.25, 1.03) | 0.36 (0.19, 0.71) |

Abbreviations: CDP, confirmed disability progression

**ERG comment**: agree company conclusion reasonable

- The analyses were post hoc (but risk of bias appears to be low);
- Only hazard ratios are reported, without the corresponding CDP estimates per trial arm so unable to check veracity of the results.

# Company new evidence – mixed treatment comparison whole relapsing remitting population

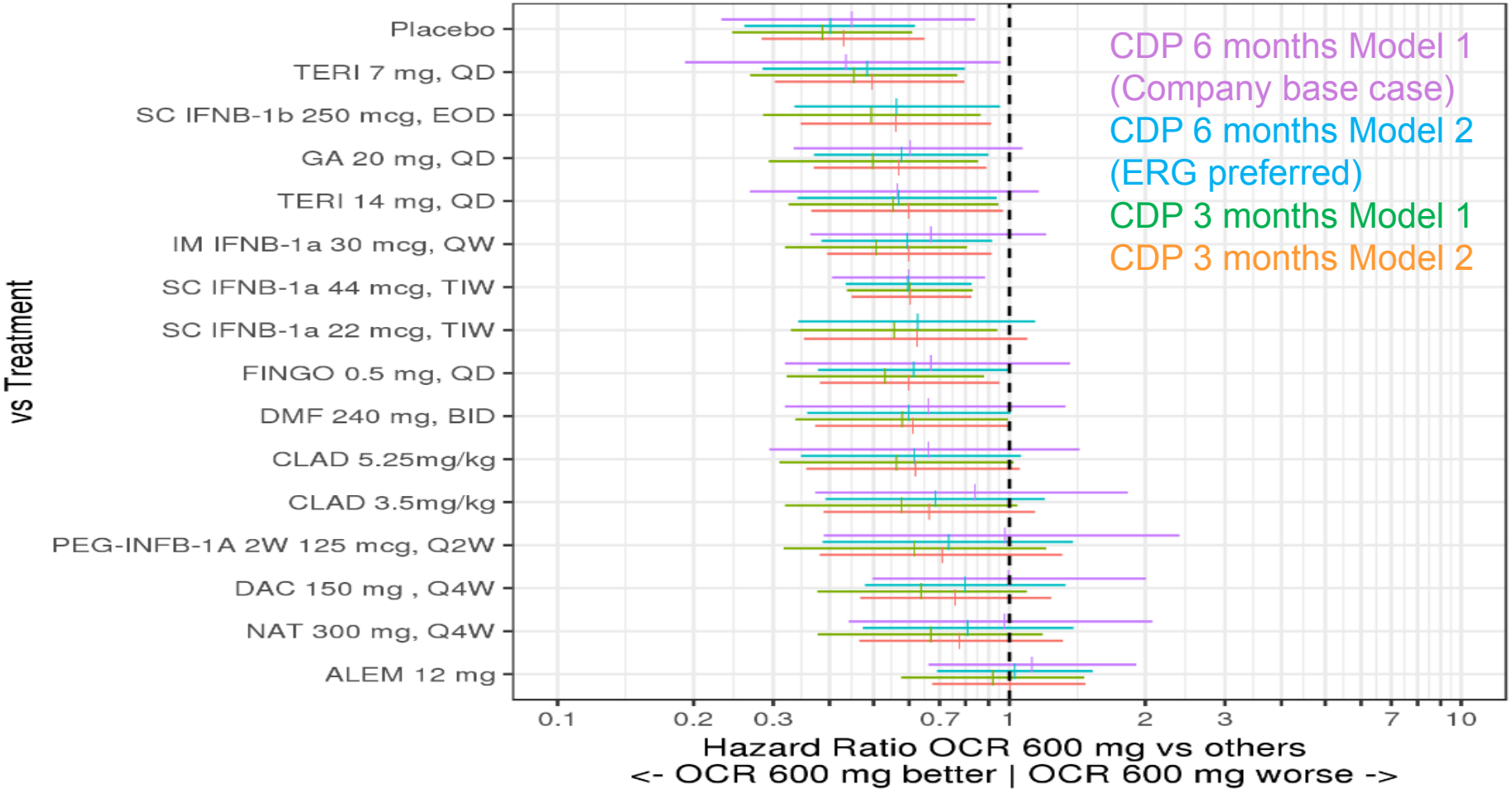
| | Model 1 | Model 2 |
|---|---|---|
| | Company base case | Company scenario analysis |
| **Description** | Confirmed disability progression 3 month data used where 6 month data not reported | Multivariate model – estimates missing 6 month data based on 3 month data |
| **Results** | Confidence intervals narrower than MTC in company original submission, point estimates generally improved | |
| **Ocrelizumab more effective than** | • IFNB-1a (avonex and rebif)<br>• IFN1-b (betaferon)<br>• glatiramer acetate<br>• teriflunomide | • IFNB-1a (avonex and rebif)<br>• IFN1-b (betaferon)<br>• glatiramer acetate<br>• teriflunomide<br>• dimethyl fumarate<br>• fingolimod |
| **No statistically significant difference compared with** | • dimethyl fumarate<br>• fingolimod<br>• natalizumab<br>• alemtuzumab<br>• pegIFNB-1a | • natalizumab<br>• alemtuzumab<br>• pegIFNB-1a |

Company justification model 1: Credible and conservative approach

- Used by Cochrane and the Institute for Clinical and Economic Review
- Model 1 and 2 presented for whole relapsing remitting population
- Only model 1 presented for subgroups

# Company new evidence mixed treatment comparison total relapsing remitting population confirmed disability progression

- Updated MTC confidence intervals narrower than MTC in company original submission, point estimates generally improved in favour of ocrelizumab
- Model 2 generally smaller confidence intervals than model 1



# Company new evidence – mixed treatment comparison highly active and rapidly evolving severe subgroups

- Model 1 only: Confirmed disability progression 3 month data used where 6 month data not reported
- Wider confidence intervals than whole relapsing remitting population
- No statistical difference between ocrelizumab and fingolimod and alemtuzumab in the HA subgroup, or between ocrelizumab and natalizumab and alemtuzumab in the RES subgroup
- Data from the whole relapsing remitting population is used to join glatiramer acetate and INFB-1a to the networks

# ERG comments company updated mixed treatment comparison

ERG prefer model 2

- Model 2 makes best use of the available CDP 3 months and CDP 6 months data
- Should provide more accurate and precise estimates of CDP 6 months
- Lack of clarity of methods of analysis used, however company's overall modelling approach likely to be generally appropriate
- Main concern is credible intervals for CDP 6 months outcome may underestimate the uncertainty

New subgroup MTC analyses do not resolve:

- Use of data for the total relapsing remitting population to join interferon β and glatiramer acetate to the network
  - Assumes the treatment effect in the total relapsing remitting population is the same as in the subgroups
- New models do not change conclusion that subgroup results should be interpreted with caution

# Company new evidence - comparators

**Committee discussion:**

Individual comparisons of ocrelizumab with beta interferons and glatiramer acetate are appropriate

**Roche**

- Applying efficacy from trial comparator IFNB-1a (Rebif) to all beta-interferons and glatiramer acetate reflect the committee's conclusion that these treatments are clinically equivalent
- Updated MTC suggest pegIFN-1a is more effective than other beta-interferons and glatiramer acetate, and treatments like natalizumab
  - Contrary to clinical experience
  - Excluded in company's base incremental analyses because outlier
  - The definition of CDP in the pegIFN-1a study is unconventional

Roche include base case fully incremental analyses for:

1. All relevant comparators
2. Excluding pegIFNB-1a because it seems to be an outlier
3. Excluding pegIFNB-1a and alemtuzumab to allow for patient choice

# Cost-effectiveness results

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

# Company new base case

- Mixed treatment comparison estimates for confirmed disability progression at 6 months, with missing data imputed based on 3-month data (MTC Model 1)
- Includes potential risk of PML for ocrelizumab (0.00028%) informed by proxy data from rituximab in rheumatoid arthritis
- Provides cost-effectiveness estimates for each beta interferon and glatiramer acetate compared with ocrelizumab
- Uses UK MS Survey as the source of EDSS costs (from TA320 inflated to 2015/16)
- Uses treatment stopping rates for ocrelizumab and all comparators from the mixed treatment comparison in the absence of evidence for a treatment waning effect (same as in previous base case)

# Company new scenario analyses

1. MTC Model 2 for CDP 6 month efficacy
2. Assumes clinical equivalence between beta-interferons and glatiramer acetate
   i. Applies IFNB-1a (Rebif) efficacy (Model 1) to all beta-interferons and glatiramer acetate